Maternal and Child Nutrition 2

Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost?

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Maternal undernutrition contributes to 800 000 neonatal deaths annually; stunting, wasting, and micronutrient deficiencies are estimated to underlie nearly 3·1 million child deaths annually. Progress has been made with many interventions implemented at scale and the evidence for effectiveness of nutrition interventions and delivery strategies has grown since *The Lancet* Series on Maternal and Child Undernutrition in 2008. We did a comprehensive update of interventions to address undernutrition and micronutrient deficiencies in women and children and used standard methods to assess emerging new evidence for delivery platforms. We modelled the effect on lives saved and cost of these interventions in the 34 countries that have 90% of the world's children with stunted growth. We also examined the effect of various delivery platforms and delivery options using community health workers to engage poor populations and promote behaviour change, access and uptake of interventions. Our analysis suggests the current total of deaths in children younger than 5 years can be reduced by 15% if populations can access ten evidence-based nutrition interventions at 90% coverage. Accelerated gains are possible and about a fifth of the existing burden of stunting can be averted using these approaches, if access is improved in this way. The estimated total additional annual cost involved for scaling up access to these ten direct nutrition interventions in the 34 focus countries is Int$9·6 billion per year. Continued investments in nutrition-specific interventions to avert maternal and child undernutrition and micronutrient deficiencies through community engagement and delivery strategies that can reach poor segments of the population at greatest risk can make a great difference. If this improved access is linked to nutrition-sensitive approaches—ie, women's empowerment, agriculture, food systems, education, employment, social protection, and safety nets—they can greatly accelerate progress in countries with the highest burden of maternal and child undernutrition and mortality.

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This is the second in a **Series** of four papers about maternal and child nutrition

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Introduction

Stunting prevalence has been decreasing slowly and 165 million children were stunted in 2011.[1] Undernutrition, consisting of fetal growth restriction, stunting, wasting, and deficiencies of vitamin A and zinc, along with suboptimum breastfeeding, underlies nearly 3·1 million deaths of children younger than 5 years annually worldwide, representing about 45% of all deaths in this group.[2] Maternal and child obesity have also increased in many low-income and middle-income countries.[3]

In a comprehensive review of nutrition interventions, we previously assessed 43 nutrition-related interventions in detail and reported estimates of efficacy and effect for 11 core interventions.[4] Much progress has been made since with many interventions implemented at scale, assessments of promising new interventions, and new delivery strategies. We used standard methods to do a comprehensive review of potential nutrition-specific interventions to address undernutrition and micronutrient deficiencies in women and children. We modelled the potential effect of delivery of these interventions on lives saved in the 34 countries with 90% of the global burden of stunted children, and estimated the effect of various delivery platforms that could enhance equitable scaling up of nutrition-specific interventions.

Selection of interventions for review

We selected several nutrition-specific interventions across the lifecycle for assessment of evidence of benefit (figure 1); these interventions included those affecting adolescents, women of reproductive age, pregnant women, newborn babies, infants, and children. We also reviewed the evidence for delivery platforms for nutrition interventions and other emerging interventions of interest for nutrition of women and children.

We identified and relied on the most recent reviews with good quality methods for all interventions and updated the evidence by incorporating newer studies, when available. For other identified interventions, when we did not find any relevant review, we did a de-novo review using the methodology described in panel 1.[5] Additionally, we consulted the electronic library on nutrition actions (eLENA) for existing evidence used by WHO for development of guidelines and policies for action (appendix p 2).

See **Online** for appendix

Interventions to address adolescent health and nutrition

There is growing interest in adolescent health as an entry point to improve the health of women and children, especially because an estimated 10 million girls younger than 18 years are married each year.[6] A range of interventions exist in relation to adolescent health and

Key messages

- Globally, 165 million children are stunted; undernutrition underlies 3·1 million deaths in children younger than 5 years.
- A clear need exists to introduce promising evidence-based interventions in the preconception period and in adolescents in countries with a high burden of undernutrition and young age at first pregnancies; however, targeting and reaching a sufficient number of those in need will be challenging.
- Promising interventions exist to improve maternal nutrition and reduce fetal growth restriction and small-for-gestational-age (SGA) births in appropriate settings in developing countries, if scaled up before and during pregnancy. These interventions include balanced energy protein, calcium, and multiple micronutrient supplementation and preventive strategies for malaria in pregnancy.
- Replacement of iron-folate with multiple micronutrient supplements in pregnancy might have additional benefits for reduction of SGA in at-risk populations, although further evidence from effectiveness assessments might be needed to guide a universal policy change.
- Strategies to promote breastfeeding in community and facility settings have shown promising benefits on enhancing exclusive breastfeeding rates; however, evidence for long-term benefits on nutritional and developmental outcomes is scarce.
- Evidence for the effectiveness of complementary feeding strategies is insufficient, with much the same benefits noted from dietary diversification and education and food supplementation in food secure populations and slightly greater effects in food insecure populations. Further effectiveness trials are needed in food insecure populations with standardised foods (pre-fortified or non-fortified), duration of intervention, outcome definition, and cost effectiveness.
- Treatment strategies for severe acute malnutrition with recommended packages of care and ready-to-use therapeutic foods are well established, but further evidence is needed for prevention and management strategies for moderate acute malnutrition in population settings, especially in infants younger than 6 months.
- Data for the effect of various nutritional interventions on neurodevelopmental outcomes are scarce; future studies should focus on these aspects with consistency in measurement and reporting of outcomes.
- Conditional cash transfers and related safety nets can address the removal of financial barriers and promotion of access of families to health care and appropriate foods and nutritional commodities. Assessments of the feasibility and effects of such approaches are urgently needed to address maternal and child nutrition in well supported health systems.
- Innovative delivery strategies, especially community-based delivery platforms, are promising for scaling up coverage of nutrition interventions and have the potential to reach poor populations through demand creation and household service delivery.
- Nearly 15% of deaths of children younger than 5 years can be reduced (ie, 1 million lives saved), if the ten core nutrition interventions we identified are scaled up.
- The maximum effect on lives saved is noted with management of acute malnutrition (435 000 [range 285 000–482 000] lives saved); 221 000 (135 000–293 000) lives would be saved with delivery of an infant and young child nutrition package, including breastfeeding promotion and promotion of complementary feeding; micronutrient supplementation could save 145 000 (30 000–216 000) lives.
- These interventions, if scaled up to 90% coverage, could reduce stunting by 20·3% (33·5 million fewer stunted children) and can reduce prevalence of severe wasting by 61·4%.
- The additional cost of achieving 90% coverage of these proposed interventions would be Int$9·6 billion per year.

nutrition, which could also affect the period before first pregnancy or between pregnancies. Evidence supporting reproductive health and family planning interventions in this age group suggests that it might be possible to reduce unwanted pregnancies and optimise age at first pregnancy. These aims might be important to reduce the risk of small-for-gestational age (SGA) births in populations in which a substantial proportion of births occur in adolescents. Opportunities might also exist to address micronutrient deficiencies and emerging issues of overweight and obesity in adolescents through community and school-based education platforms. Although evidence from robust randomised controlled trials is scarce, we identified a range of interventions in the adolescent period affecting maternal, newborn, and child health and nutrition outcomes (panel 2[7–18]).

Interventions in women of reproductive age and during pregnancy

Folic acid supplementation

Neural tube defects can be effectively prevented with periconceptional folic acid supplementation. A review[19] of five trials of periconceptional folic acid supplementation suggested a 72% reduction in risk of development of neural tube defects and a 68% reduction in risk of recurrence compared with either no intervention, placebo, or micronutrient intake without folic acid (table 1[19–26]). A review[20] of folic acid supplementation during pregnancy showed that folic acid supplementation improved mean birthweight, with a 79% reduction in the incidence of megaloblastic anaemia (table 1[19–26]). Furthermore no evidence of adverse effects was noted from folic acid supplementation in programme settings. Despite

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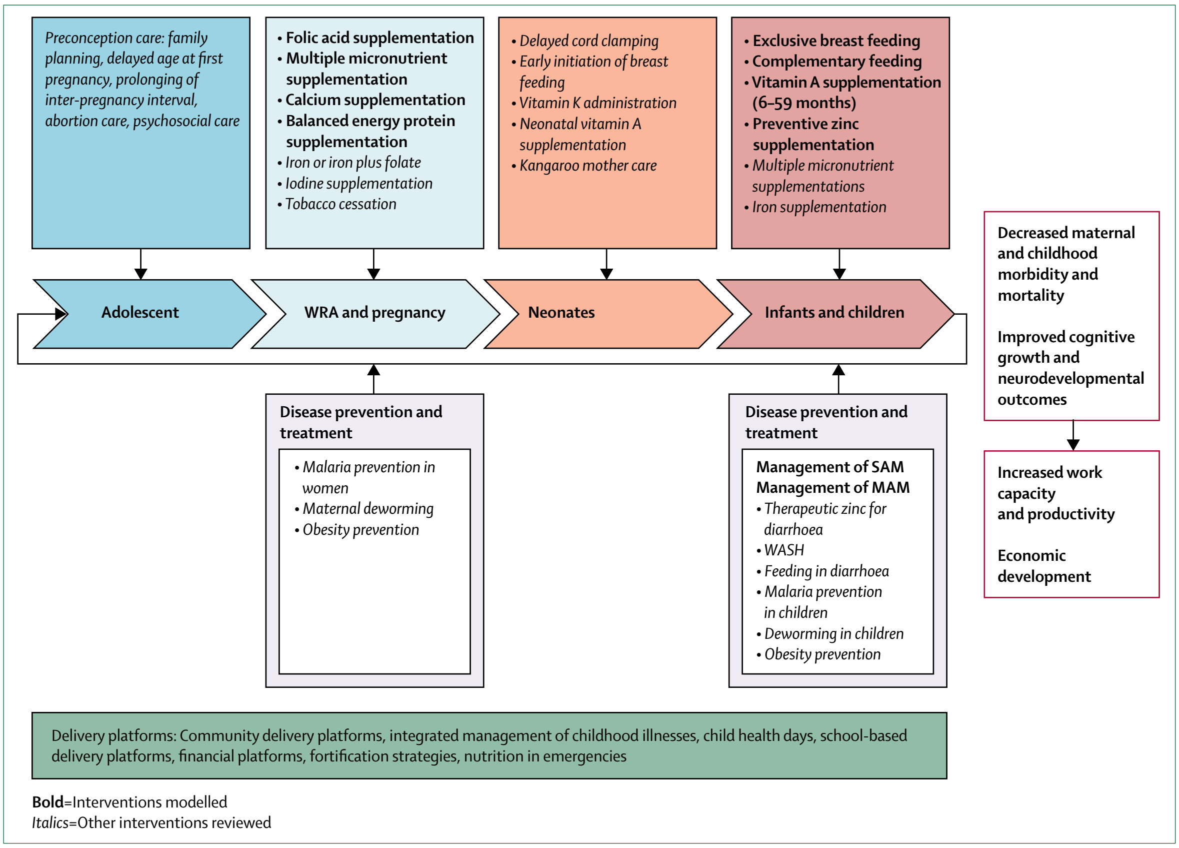

***Figure 1:* Conceptual framework**
WRA=women of reproductive age. WASH=water, sanitation, and hygiene. SAM=severe acute malnutrition. MAM=moderate AM.

strong evidence of benefit, reaching women of reproductive age in the periconceptual period to provide folic acid supplements through existing delivery platforms remains a logistical challenge. Fortification of cereals and other foods might be a feasible way to reach the population in need.

Iron or iron and folic acid supplementation

A review[21] of iron supplementation in non-pregnant women of reproductive age showed that intermittent iron supplementation (alone or with any other vitamins and minerals) reduced the risk of anaemia by 27% (table 1[19–26]). A Cochrane review[22] of daily iron supplementation to women during pregnancy reported a 70% reduction in anaemia at term, a 67% reduction in iron deficiency anaemia (IDA), and 19% reduction in the incidence of low birthweight. Another review[27] further suggests that the effects were much the same in women receiving intermittent iron supplementation, or daily iron, or iron and folic acid supplementation. Although some evidence suggests that side-effects are fewer with intermittent iron therapy in non-anaemic populations, WHO recommends daily iron supplementation during pregnancy as part of the standard of care in populations at risk of iron deficiency.[28]

Panel 1: Methods, search strategy, and selection criteria

As per the Child Health Epidemiology Reference Group (CHERG) systematic review guidelines,[5] we searched PubMed, Cochrane libraries, electronic library on evidence on nutrition actions (eLENA), and WHO regional databases and included publications in every language available in these databases. We used Medical Subject Heading Terms (MeSH) and keyword search strategies with various combinations of relevant terms. We made every effort to gather unpublished data when reports were available for full abstraction. Inclusion and exclusion criteria were established for each area of review, and studies meeting these criteria were double data extracted and categorised according to outcome. Evidence was then summarised by outcome and study design, including study quality, generalisability, and summary outcome measures. We did meta-analyses for each outcome containing more than one study, using either the Mantel-Haenszel or the Der Simonian-Laird pooled relative risks (RR, with 95% CIs), when there was unexplained heterogeneity of effect. Heterogeneity was assessed by visual inspection of forest plots and by the χ^2 p value ($p<0 \cdot 10$). The binary measure for individual studies and pooled statistics was reported as the RR between the experimental and control groups with 95% CIs. For the outcome of interest for each intervention, we applied the CHERG Rules for Evidence Review[5] to generate a final estimate.

Maternal multiple micronutrient supplementation

Multiple-micronutrient deficiencies often coexist in low-income and-middle-income countries (LMICs) and can be exacerbated in pregnancy with potentially adverse

Panel 2: **Interventions to address adolescent nutrition and preconception care**

Women of lower socioeconomic status and young age are at risk of being undernourished and underweight. Ronnenberg and colleagues[7] assessed the association between preconception anaemia and poor fetal and neonatal outcomes. They showed that the risk of being born low birthweight was significantly greater with moderate preconception anaemia (odds ratio [OR] 6·5, 95% CI 1·6–26·7) and fetal growth restriction (4·6, 1·5–13·5).

Important factors indirectly related to maternal, fetal, and neonatal nutritional status and pregnancy outcomes include young age at first pregnancy and repeated pregnancies. Young girls who are not physically mature might enter pregnancy with depleted nutrition reserves and anaemia.[8] Adolescent pregnancy is associated with a 50% increased risk of stillbirths and neonatal deaths, and increased risk of preterm birth, low birthweight, and asphyxia.[9–11] Adolescents are especially prone to complications of labour and delivery, such as obstructed and prolonged labour, vesico-vaginal fistulae, and infectious morbidity.[11] In societies in which most births are within a marital relationship, interventions to increase the age at marriage and first pregnancy are important.[12] Evidence suggests that programmes for adolescent mothers can reduce repeat adolescent pregnancies by 37% (95% CI 12–51%) when they teach parenting skills through home visitation and provide young mothers with education and vocational or job support.

Two reviews by Conde-Agudelo and colleagues[13,14] assessed the association between inter-pregnancy intervals with maternal, newborn, and child health outcomes and found a J-shaped dose-response association for perinatal outcomes. Short inter-pregnancy intervals (<6 months) were associated with a higher probability of maternal anaemia (32%) and stillbirths (40%) whereas longer intervals (>60 months) were associated with an increased risk of pre-eclampsia.[15] Both short and long birth intervals increase the risk for preterm births (OR 1·45 [95% CI 1·30–1·61] for short term; OR 1·21 [95% CI 1·12–1·30] for long intervals), low birthweight (OR 1·65 [95% CI 1·27–2·14] for short intervals; relative risk [RR] 1·37 [95% CI 1·21–1·55] for long intervals), and neonatal mortality (OR 1·31 [95% CI 0·96–1·79] for short interval; RR 1·15 [95% CI 1·06–1·25] for long intervals). With repeated pregnancies and advanced maternal age there is increased risk of chromosomal abnormalities, and increased risks of gestational diabetes and hypertension, stillbirths (RR 1·62, 95% CI 1·50–1·76), perinatal mortality (RR 1·44, 95% CI 1·10–1·89), and low birthweight (RR 1·61, 95% CI 1·16–2·24).[16,17] These findings support the need to optimise age at first pregnancy and family size and inter-pregnancy intervals. A global unmet need exists for family planning with more than 100 million unmarried women in developing countries not using contraception.[18] Optimisation of age at first pregnancy must be coupled with promotion of effective contraceptive use and exclusive breastfeeding, so that women can ideally space their pregnancies 18–24 months apart.

maternal outcomes. A Cochrane review[23] of multiple micronutrient supplementation in pregnant women assessed 23 trials and reported an 11–13% reduction in low birthweight and SGA births, whereas effects on anaemia and IDA were much the same when compared with iron and folic acid supplements (table 1). Despite earlier concerns about potential excess neonatal mortality with multiple micronutrient use,[29] present analyses suggest no adverse effects on maternal mortality, stillbirths, perinatal, and neonatal mortality with insufficient data for neuro-developmental outcomes. Although scarce, there are interesting data for benefits of maternal multiple micro-nutrient supplementation on growth in early childhood.[30] Preliminary data from a large trial[31] comparing multiple micronutrient with iron-folate supplementation in pregnancy in Bangladesh show a significant reduction in preterm births with no adverse effects. Inclusion of this study in our meta-analysis confirms the reduction in low birthweight (relative risk [RR] 0·88, 95% CI 0·85–0·91) and SGA (0·89, 0·83–0·96) and is also indicative of a small effect on preterm births (0·97, 0·94–0·99). These findings support the potential replacement of iron-folate supplements in pregnancy with multiple micronutrient supplements in populations at risk.

Maternal calcium supplementation

Gestational hypertensive disorders are the second leading cause of maternal morbidity and mortality and are associated with increased risk of preterm birth and fetal growth restriction.[32,33] Calcium supplementation during pregnancy in women at risk of low calcium intake has been shown to reduce maternal hypertensive disorders and preterm birth. A Cochrane review by Hofmeyr and colleagues[34] assessed 13 trials and showed that calcium supplementation during pregnancy reduced the incidence of gestational hypertension by 35%, pre-eclampsia by 55%, and preterm births by 24% (table 1). These estimates have been updated in a review[24] of 15 randomised controlled trials, which also showed a 52% reduction in the incidence of pre-eclampsia and confirmed that these effects were only noted in populations at risk of low calcium intake.

Maternal iodine supplementation or fortification

In nearly all regions affected by iodine deficiency, use of iodised salt is the most cost-effective way to avert deficiency. A Cochrane review[35] suggests that although iodised salt is an effective means to improve iodine status, no conclusions can be drawn about physical and mental development in children and mortality. In some regions of the world with severe iodine deficiency, salt iodisation alone might not be sufficient for control of iodine deficiency in pregnancy; in these circumstances iodised oil supplementation during pregnancy can be a viable option (table 1). A review[25] of five randomised trials of iodised oil supplementation in pregnancy in iodine-deficient populations showed a 73% reduction in cretinism and a 10–20% increase in developmental scores in children. Existing evidence supports continued focus on effective universal salt iodisation for women of reproductive age and those who are pregnant. Further high-quality controlled studies are needed to address dosage and alternative strategies for iodine supplementation in different population groups and settings.

Addressing maternal wasting and food insecurity with balanced energy and protein supplementation

Maternal undernutrition is a risk factor for fetal growth restriction and adverse perinatal outcomes.[1] Several nutritional interventions have been assessed in such situations, including dietary advice to pregnant women,

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	Evidence reviewed	Setting	Estimates
Folic acid supplementation			
Women of reproductive age	Systematic review of five trials[19] of periconceptual folic acid supplementation	Developing and developed countries	Significant effects: NTDs (RR 0·28, 95% CI 0·15–0·52), recurrence of NTDs (RR 0·32, 95% CI 0·17–0·60) Non-significant effects: other congenital abnormalities, miscarriages, still births
Pregnant women	Systematic review of 31 trials[20]	Mostly developed countries	Significant effects: mean birthweight (MD 135·75, 95% CI 47·85–223·68), incidence of megaloblastic anaemia (RR 0·21, 95% CI 0·11–0·38) Non-significant effects: preterm birth, still births, mean predelivery haemoglobin, serum folate, red cell folate
Iron and Iron-folate supplementation			
Women of reproductive age	Systematic review of 21 RCTs and quasi-experimental studies[21]	Developing and developed countries. Intervention mostly given in school settings. Mostly effectiveness studies	Intermittent iron supplementation Significant effects: anaemia (RR 0·73, 95% CI 0·56–0·95), serum haemoglobin concentration (MD 4·58 g/L, 95% CI 2·56–6·59), serum ferritin concentration (MD 8·32, 95% CI 4·97–11·66) Non-significant effects: iron deficiency, adverse events, depression
Pregnant women	Systematic review of 43 RCTs and quasi-experimental studies[22] (34 iron alone, eight iron-folate)	Developed and developing countries. Intervention delivered in community or at facility antenatal clinic. Mostly effectiveness studies	Daily iron-alone supplementation Significant effects: low birthweight (RR 0·81, 95% CI 0·68–0·97), birthweight (MD 30·81 g, 95% CI 5·94–55·68), serum haemoglobin concentration at term (MD 8·88 g/L, 95% CI 6·96–10·80), anaemia at term (RR 0·30, 95% CI 0·19–0·46), iron deficiency (RR 0·43, 95% CI 0·27–0·66), iron deficiency anaemia (RR 0·33, 95% CI 0·16–0·69), side-effects (RR 2·36, 95% CI 0·96–5·82) Non-significant effects: premature delivery, neonatal death, congenital anomalies Iron-folate supplementation Significant effects: birthweight (MD 57·7 g, 95% CI 7·66–107·79), anaemia at term (RR 0·34, 95% CI 0·21–0·54), serum haemoglobin concentration at term (MD 16·13 g/L, 95% CI 12·74–19·52) Non-significant effects: low birthweight, premature birth, neonatal death, congenital anomalies
MMN supplementation			
Pregnant women	Systematic review of 21 RCTs[23]	Developed and developing countries. Studies compared MMN with two or fewer micronutrients	Significant effects: low birthweight (RR 0·88, 95% CI 0·85–0·91), SGA (RR 0·89, 95% CI 0·83–0·96), preterm birth (RR 0·97, 95% CI 0·94–0·99) Non-significant effects: miscarriage, maternal mortality, perinatal mortality, stillbirths, and neonatal mortality Insufficient data for neurodevelopmental outcomes
Calcium supplementation			
Pregnant women	Systematic review of 15 RCTs[24]	Developed and developing countries. Mostly effectiveness trials	Significant effects: pre-eclampsia (RR 0·48, 95% CI 0·34–0·67), birthweight 85 g (95% CI 37–133), preterm birth (RR 0·76, 95% CI 0·60–0·97) Non-significant effects: perinatal mortality, low birthweight, neonatal mortality
Iodine through iodisation of salt			
Pregnant women	Systematic review of five RCTs[25]	Mostly developing countries. Mostly effectiveness trials	Significant effects: cretinism at 4 years of age (RR 0·27, 95% CI 0·12–0·60), developmental scores 10–20% higher in young children, birthweight 3·82–6·30% higher
Maternal supplementation with balanced energy protein			
Pregnant women	Systematic review of 16 RCTs and quasi-experimental studies[26]	Developing and developed countries	Significant effects: SGA (RR 0·66, 95% CI 0·49–0·89), stillbirths (RR 0·62, 95% CI 0·40–0·98, birthweight (MD 73g, 95% CI 30–117) Non-significant effects: Bayley mental scores at 1 year

NTD=neural tube defects. RR=relative risk. MD=mean difference. RCT=randomised controlled trial. MMN=multiple micronutrient. SGA=small-for-gestational age.

Table 1: **Review of nutrition interventions for women of reproductive age and during pregnancy**

provision of balanced energy protein supplements, and high protein or isocaloric protein supplementation. In other contexts, prescription and promotion of low energy diets to pregnant women who are either overweight or exhibit high weight gain in early gestation have been assessed.[36] Balanced energy protein supplementation, providing about 25% of the total energy supplement as protein, is deemed an important intervention for prevention of adverse perinatal outcomes in malnourished women.[26,37] A Cochrane review[38] concluded that balanced energy protein supplementation reduced the incidence of SGA by 32% and risk of stillbirths by 45% (table 1). An updated meta-analysis showed that balanced energy protein supplementation increased birthweight by 73 g (95% CI 30–117) and reduced risk of SGA by 34%, with more pronounced effects in malnourished women.[26]

Nutrition interventions in neonates

Delayed cord clamping

Early clamping of the umbilical cord after birth is a common practice and permits immediate transfer of the baby for care as required, whereas delaying of clamping allows continued blood flow between the placenta and the baby for a longer duration. A Cochrane review[39] suggested that delayed cord clamping in term neonates led to significant increase in newborn haemoglobin and higher serum ferritin concentration at 6 months of age (table 2[39–45]). Another review[40] of studies in preterm neonates concluded that delayed cord clamping was associated with 39% reduction in need for blood transfusion and a lower risk of complications after birth. Although promising, these strategies have as yet not been assessed for effect or feasibility of implementation at scale in health systems.

	Evidence reviewed	Setting	Estimates
Delayed cord clamping			
Term neonates	Systematic review of 11 RCTs[39]	Developing and developed countries. 24 and 36 weeks' gestation at birth	Significant effects: increased newborn haemoglobin conentration (MD 2·17 g/dL, 95% CI 0·28–4·06) Non-significant effects: postpartum haemorrhage, severe postpartum haemorrhage Delayed cord clamping was associated with an increased requirement for phototherapy for jaundice
Preterm neonates	Systematic review of 15 RCTs[40]	Developing and developed countries	Significant effects: reduced need for blood transfusion (RR 0·61, 95% CI 0·46–0·81), decrease in intraventricular haemorrhage (RR 0·59, 95% CI 0·41–0·85), reduced risk of necrotising enterocolitis (RR 0·62, 95% CI 0·43–0·90) Peak bilirubin concentration was higher for delayed cord clamping group (MD 15·01 mmol/L, 95% CI 5·62–24·40)
Neonatal vitamin K administration			
Neonates	Systematic review of two RCTs for intramuscular vitamin K and 11 RCTs for oral vitamin K[41]	Developing and developed countries	Significant effects: One dose of intramuscular vitamin K reduced clinical bleeding at 1–7 days and improved biochemical indices of coagulation status. Oral vitamin K also improved coagulation status
Vitamin A supplementation			
Very low birthweight infants	Systematic review of nine RCTs[42]	Developed countries	Significant effects: reduced number of deaths and oxygen requirement at 1 month of age. Non-significant effects: one large trial showed no significant effect on neurodevelopment assessment at 18–22 months of age
Term neonates	Systematic review of five RCTs and quasi-experimental studies[43]	Developing countries	Significant effects: reduction in infant mortality at 6 months (RR 0·86, 95% CI 0·77–0·97) Non-significant effects: infant mortality at 12 months (RR 1·03, 95% CI 0·87–1·23) Little data available for cause specific mortality, morbidity, vitamin A deficiency, anaemia, and adverse events
Kangaroo mother care for promotion of breastfeeding and care of preterm and SGA infants			
Healthy neonates	Systematic review of 34 RCTs[44]	Developing and developed countries	Significant effects: increase in breastfeeding at 1–4 months after birth (RR 1·27, 95% CI 1·06–1·53), increased breastfeeding duration (MD 42·55 days, 95% CI 1·69–86·79)
Preterm neonates	Systematic review of 16 RCTs[45]	Developing and developed countries	Significant effects: reduction in the risk of mortality (RR 0·60, 95% CI 0·39–0·93), reduction in nosocomial infection and sepsis (RR 0·42, 95% CI 0·24–0·73), reduction in hypothermia (RR 0·23, 95% CI 0·10–0·55), reduced length of hospital stay (MD 2·4 days, 95% CI 0·7–4·1)

RCT=randomised controlled trial. MD=mean difference. RR=relative risk. SGA=small-for-gestational age.

Table 2: **Review of nutrition interventions in neonates**

Neonatal vitamin K administration

Vitamin K deficiency can result in bleeding in the first weeks of life and vitamin K is commonly given prophylactically after birth for prevention of bleeding. In the absence of vitamin K prophylaxis there is a 0·4–1·7% risk of development of clinically significant bleeding. A Cochrane review[41] suggested that one dose of intramuscular vitamin K, when compared with placebo, reduced clinical bleeding at 1–7 days of life, including bleeding after circumcision (table 2). Oral and intramuscular vitamin K had much the same effects on improved biochemical indices of coagulation status at 1–7 days. Currently, vitamin K administration after birth is largely restricted to births in health facilities; no information is available on the public health significance of vitamin K deficiency-related bleeding in LMICs or population-based programmes for prevention.

Neonatal vitamin A supplementation

A Cochrane review[42] of oral or intramuscular vitamin A supplementation to very low birthweight infants showed reduced mortality and oxygen requirement at 1 month of age compared with placebo (table 2).[42] Although neonatal vitamin A supplementation has also been shown to be effective in reduction of all-cause mortality by 6 months of age, evidence is conflicting, and might be related to maternal vitamin A status.[46] Although a Cochrane review[43] did report a 14% reduction in the risk of infant mortality at 6 months of age, four more trials are currently underway in Asia and Africa, and researchers agree that these additional data will be needed before development of recommendations for neonatal vitamin A supplementation.

Kangaroo mother care

Kangaroo mother care denotes early skin-to-skin contact between mother and baby at birth or soon thereafter, plus early and continued breastfeeding, parental support, and early discharge from hospital. A Cochrane review[44] of 34 randomised controlled trials of early skin-to-skin care in healthy neonates showed a significant 27% increase in breastfeeding at 1–4 months of age and increased duration of breastfeeding (table 2). In a Cochrane review[45] of 16 randomised trials, kangaroo mother care in preterm neonates was associated with a 40% reduction in the risk of mortality, a 58% reduction in nosocomial infection or sepsis, and a 77% reduction in prevalence of hypothermia. The trials included in these analyses were done in health facilities; although kangaroo mother care might also be useful for home deliveries, there is not yet evidence of effectiveness in community settings. Kangaroo mother care was also shown to increase some measures of infant growth, breastfeeding, and mother-infant attachment,[45] but few studies provide objective evidence of any effect on early child development.

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Nutrition interventions in infants and children

Promotion of breastfeeding and supportive strategies

WHO recommends initiation of breastfeeding within 1 h of birth, exclusive breastfeeding of infants till 6 months of age, and continued breastfeeding until 2 years of age or older.[47] However, global progress on this intervention is both uneven and suboptimum.[48] The exact scientific basis for the absolute early time window of feeding within the first hour after birth is weak.[49,50] A systematic review[51] suggests that breastfeeding initiation within 24 h of birth is associated with a 44–45% reduction in all-cause and infection-related neonatal mortality, and is thought to mainly operate through the effects of exclusive breastfeeding. We updated the previous review by Imdad and colleagues,[52] which assessed the effect of promotion interventions on occurrence of breastfeeding, and concluded that counselling or educational interventions increased exclusive breastfeeding by 43% at day 1, by 30% till 1 month, and by 90% from 1–5 months. Significant reductions in occurrence of mothers not breastfeeding were also noted; 32% reduction at day 1, 30% till 1 month, and 18% for 1–5 months[53] (table 3[53–62]). Combined individual and group counselling seemed to be better than individual or group counselling alone. Although these results show the potential for scaling up, none of these trials address the issues of barriers around work environments and supportive strategies such as maternity leave provision. A Cochrane review[63] of interventions in the workplace to support breastfeeding for women found no trials. Although some trials are underway, much more needs to be done to assess innovations and strategies to promote breastfeeding in working women, especially in underprivileged communities.

Promotion of dietary diversity and complementary feeding

Complementary feeding for infants refers to the timely introduction of safe and nutritionally rich foods in addition to breast-feeding at about 6 months of age and typically provided from 6 to 23 months of age.[64] Different approaches have been used to create indicators of dietary diversity and to study its association with child malnutrition. In seven Latin American surveys, Ruel and Menon[65] noted significant associations between complementary feeding practices and height-for-age *Z* scores (HAZ). Similarly, analysis of Demographic Health Survey data to create a dietary diversity score based on seven food groups showed that increased dietary diversity was positively associated with height-for-age HAZ in nine of 11 countries.[66] More recently, WHO infant and young child feeding indicators were studied in 14 Demographic Health Survey datasets from low-income countries;[67] consumption of a minimum acceptable diet with dietary diversity reduced the risk of both stunting and underweight whereas minimum meal frequency was associated with lower risk of underweight only.

In an update of a previous review of complementary feeding,[68] we assessed 16 randomised and non-randomised controlled trials and programmes of moderate quality (table 3).[54] We identified ten studies that assessed the effect of nutrition education and seven studies that assessed the effect of provision of additional complementary foods (one trial with three intervention groups was in both these categories). Studies of nutrition education in food secure populations showed a significant increase in height (standard mean difference [SMD] 0·35, 95% CI 0·08–0·62, four studies), and HAZ (0·22, 0·01–0·43, four studies), whereas the effect on stunting was not statistically significant (RR 0·70, 95% CI 0·49–1·01, four studies). We identified a significant effect on weight gain (SMD 0·40, 95% CI 0·02–0·78, four studies), whereas no effects were noted for weight-for-age *Z* scores (WAZ; 0·12; 95% CI –0·02 to 0·26, four studies). Studies of nutrition education in food insecure populations (with an average daily per person income of less than US$1·25) showed significant effects on HAZ (SMD 0·25, 95% CI 0·09–0·42, one study), stunting (RR 0·68, 95% CI 0·60–0·76, one study), and WAZ (SMD 0·26, 95% CI 0·12–0·41, two studies). The review[54] did not find any eligible study that provided complementary feeding (with or without education) in a food secure population. Overall, the provision of complementary foods in food insecure populations was associated with significant gains in HAZ (SMD 0·39; 95% CI 0·05–0·73, seven studies) and WAZ (SMD 0·26, 95% CI 0·04–0·48, three studies), whereas the effect on stunting did not reach statistical significance (RR 0·33, 95% CI 0·11–1·00, seven studies).

Vitamin A supplementation in children

A Cochrane review[55] of 43 randomised trials showed that vitamin A supplementation reduced all-cause mortality by 24% and diarrhoea-related mortality by 28% in children aged 6–59 months (table 3). Vitamin A supplementation also reduced the incidence of diarrhoea and measles in this age group but there was no effect on mortality and morbidity related to respiratory infections. Although a large effectiveness study[69] from India assessing the effect of vitamin A supplementation and deworming over several years did not show a significant effect on mortality from vitamin A supplementation (mortality ratio 0·96, 95% CI 0·89–1·03), inclusion of these data with previous results still shows a significant, albeit lower, effect on mortality (RR 0·88, 95% CI 0·84–0·94).[55] We believe that vitamin A supplementation continues to be an effective intervention in children aged 6–59 months in populations at risk of vitamin A deficiency.

Iron supplementation in infants and children

A Cochrane review[56] of 33 studies showed that intermittent iron supplementation to children younger than 2 years reduced the risk of anaemia by 49% and iron

	Setting	Estimates
Breast feeding promotion in infants		
Systematic review of 110 RCTs and quasi-experimental studies[53]	Developing and developed countries	Significant effects: educational or counselling interventions increased EBF by 43% (95% CI 9–87) at day 1, by 30% (19–42) till 1 month, and by 90% (54–134) from 1–6 months. Significant reductions in rates of no breastfeeding also noted; 32% (13–46) at day 1, 30% (20–38) 0–1 month, and 18% (11–23) for 1–6 months. Non-significant effects: predominant and partial breastfeeding
Complementary feeding promotion in children 6–24 months of age		
16 RCTs and quasi-experimental studies[54]	Mostly from food secure populations. Various foods used	Nutrition education in food secure populations Significant effects: increased height gain (SMD 0·35; 95% CI 0·08–0·62), HAZ (SMD 0·22; 95% CI 0·01–0·43), weight gain (SMD 0·40, 95% CI 0·02–0·78) Non-significant effects: stunting, WAZ Nutrition education in food insecure populations Significant effects: HAZ (SMD 0·25, 95% CI 0·09–0·42), stunting (RR 0·68, 95% CI 0·60–0·76), WAZ (SMD 0·26, 95% CI 0·12–0·41) Complementary food provision with or without education in food insecure populations Significant effects: HAZ (SMD 0·39, 95% CI 0·05–0·73), WAZ (SMD 0·26, 95% CI 0·04–0·48) Non-significant effects: stunting (RR 0·33, 95% CI 0·11–1·00)
Preventive vitamin A supplementation in children 6 months to 5 years of age		
Systematic review of 43 RCTs[55]	Developing and developed countries	Significant effects: reduced all-cause mortality (RR 0·76, 95% CI 0·69–0·83), reduced diarrhoea-related mortality (RR 0·72, 95% CI 0·57–0·91), reduced incidence of diarrhoea (RR 0·85, 95% CI 0·82–0·87), reduced incidence of measles (RR 0·50, 95% CI 0·37–0·67) Non-significant effects: measles-related and ARI-related mortality
Iron supplementation in children		
Systematic review of 33 RCTs and quasi-experimental studies[56]	LMICs. Participant's ages ranged from neonates to 19 years	Intermittent iron supplementation Significant effects: decreased anaemia (RR 0·51, 95% CI 0·37–0·72), decreased iron deficiency (RR 0·24, 95% CI 0·06–0·91), increased haemoglobin concentration (MD 5·20 g/L, 95% CI 2·51–7·88), increased ferritin concentration (MD 14·17 mcg/L, 95% CI 3·53–24·81) Non-significant effects: HAZ, WAZ Evidence for mental development, motor skill development, school performance, and physical capacity was assessed by very few studies and showed no clear effect
Systematic review of 17 RCTs[57]	Developing and developed countries. In children aged 6 months to 15 years	Significant effects: increased mental development score (SMD 0·30, 95% CI 0·15–0·46), increased intelligence quotient scores (≥8 years age; SMD 0·41, 95% CI 0·20–0·62) Non-significant effects: Bayley mental development index in younger children (≤27 months old), motor development
MMN supplementation including iron in children		
Systematic review of 18 trials[58]	Mostly developing countries. In children aged 6 months to 16 years	MMN supplementation Significant effects: increased length (MD 0·13, 95% CI 0·06–0·21), increased weight (MD 0·14, 95% CI 0·03–0·25) MMN might be associated with marginal increase in fluid intelligence and academic performance in healthy school children
Systematic review of 17 RCTs[59]	Developing countries. Mostly effectiveness studies. In children aged 6 months to 11 years	Micronutrient powders Significant effects: Reduced anaemia (RR 0·66, 95% CI 0·57–0·77), reduced iron deficiency anaemia (RR 0·43, 95% CI 0·35–0·52), reduced retinol deficiency (RR 0·79, 95% CI 0·64–0·98). Improved haemoglobin concentrations (SMD 0·98, 95% CI 0·55–1·40). MNP was associated with a significant increase in diarrhoea (RR 1·04, 95% CI 1·01–1·06) Non-significant effects: serum ferritin, zinc deficiency, stunting, wasting, underweight, HAZ, WAZ, WHZ, fever, URI
Zinc supplementation in children		
Systematic review of 18 RCTs[60,61]	Mostly developing countries. In children younger than 5 years	Preventive zinc supplementation Significant effects: mean height improved by 0·37 cm (SD 0·25) in children supplemented for 24 weeks, diarrhoea reduced by 13% (95% CI 6–19), pneumonia reduced by 19% (95% CI 10–27) Non-significant effects: mortality (cause specific and all-cause)
Systematic review of 13 trials[62]	Developing and developed countries. In children younger than 5 years	Non-significant effects: Mental developmental index, psychomotor development index

RCT=randomised controlled trial. EBF=exclusive breastfeeding. HAZ=height-for-age *Z* score. WAZ=weight-for-age *Z* score. WHZ=weight-for-height *Z* score. MMN=multiple micronutrient. ARI=acute respiratory infection. URI=upper-respiratory infection. SMD=standard mean difference. MD=mean difference. RR=relative risk.

Table 3: **Review of evidence for nutrition interventions for infants and children**

deficiency by 76% (table 3). The findings also suggested that intermittent iron supplementation could be a viable public health intervention in settings in which daily supplementation had not been implemented or was not feasible. A review[57] of the effect of iron supplementation in children on mental and motor development showed only small gains in mental development and intelligence scores in supplemented school-age children who were initially anaemic or iron-deficient. There was no convincing evidence that iron treatment had an effect on mental development in children younger than 27 months.

Since the demonstration of increased risk of admission to hospital and serious illnesses with iron supplementation,[70] there has been concern about administration of iron supplements in malaria endemic areas. WHO currently recommends administration of iron supplements in malaria endemic areas on the stipulation that malaria prevention and treatment is made available.[71]

Multiple micronutrient supplementation in children

Although the theoretical benefits of strategies to improve diet quality and micronutrient density of foods consumed by small children are well recognised, few resource-poor countries have clear policies in support of integrated strategies to control micronutrient deficiencies in young children.[72] Available options include the provision of multiple micronutrients via supplements, micronutrient powders, or fortified ready-to-use foods including lipid-based nutrient supplements. A comprehensive review of the effects of multiple micronutrients compared with two or fewer micronutrients showed small benefits on linear growth (mean difference [MD] 0·13, 95% CI 0·06–0·21) and weight gain (0·14, 0·03–0·25) but with little evidence of effect on morbidity outcomes as suggested by individual studies (table 3).[58] Another review[73] of the effect of multiple micronutrient supplementation on improvement of cognitive performance in children concluded that multiple micronutrient supplementation might be associated with a marginal increase in reasoning abilities but not with acquired skills and knowledge.

Micronutrient powders are increasingly in use at scale in programmes to address iron and multiple micronutrient deficiencies in children. We reviewed 16 randomised controlled trials to assess the effectiveness of micronutrient powders and estimated that they significantly improved haemoglobin concentration and reduced IDA by 57% and retinol deficiency by 21%.[59] We noted no evidence of benefit on linear growth. However, in-line with findings from an earlier review of liquid iron supplementation trials,[74] use of micronutrient powders was shown to be associated with a significant increase in the incidence of diarrhoea (RR 1·04, 95% CI 1·01–1·06), largely because of results from a recent large cluster-randomised controlled trial of micronutrient powders in Pakistan in malnourished children.[75] These findings underscore the need for further assessment of micronutrient powder programmes in varying contexts for safety and benefits.

Preventive zinc supplementation in children

Preventive zinc supplementation in populations at risk of zinc deficiency reduces the risk of morbidity from childhood diarrhoea and acute lower respiratory infections and might increase linear growth and weight gain in infants and young children.[60,76] A review by Yakoob and colleagues[61] assessed 18 studies from developing countries and showed that preventive zinc supplementation reduced the incidence of diarrhoea by 13% and pneumonia by 19%, with a non-significant 9% reduction in all-cause mortality (table 3). However, subgroup analysis showed that there was a significant 18% reduction in all-cause mortality in children aged 12–59 months. A daily dose of 10 mg zinc per day over 24 weeks in children younger than 5 years could lead to an estimated net gain of 0·37 cm (SD 0·25) in height in zinc-supplemented children compared with placebo.[60] There is no convincing evidence that zinc supplementation in infants or children results in improved motor or mental development.[62]

Disease prevention and management

Several interventions have the potential to affect health and nutrition outcomes through reduction in the burden of infectious diseases. Table 4[77–88] summarises the evidence for interventions for disease prevention and management.

Prevention and treatment of severe acute malnutrition

A substantial global burden of wasting exists, especially severe acute malnutrition (SAM; weight-for-height *Z* score [WHZ] <–3), which coexists with moderate acute malnutrition (MAM; WHZ <–2). In stable non-emergency situations with endemic malnutrition, MAM can often present in combination with stunting. Most of the interventions previously discussed should be implemented to prevent the development of SAM in food insecure populations. Several approaches for prevention and treatment are in use. Although the provision of complementary and supplementary foods could be considered in targeted food distribution programmes, other ways to stimulate access and purchasing power can be conceived. Where markets are fragmented or food access is constrained, appropriate food supplements might be considered as in-kind transfers. WHO recommends inpatient treatment for children with complicated SAM, with stabilisation and appropriate treatment of infections, fluid management, and dietary therapy and also supports community-based care for uncomplicated SAM.[89] Although facility-based treatment of SAM remains important, community management of SAM continues to grow rapidly globally. This shift in treatment norms from centralised, inpatient care towards community-based models allows more affected children to be reached and is cost effective. Up to an estimated 15% of cases of SAM will need initial facility-based care, whereas the rest can receive only community-based treatment.[90]

Facility-based management of SAM according to the WHO protocol

A scientific literature review by Schofield and Ashworth[91] showed that between the 1950s and 1990s, case fatality rates were typically 20–30% in children with SAM treated in hospitals or rehabilitation units, and rates were higher (50–60%) for oedematous malnutrition. A previous review[4] of existing studies had estimated that following the WHO protocol, as opposed to standard care, would lead to a 55% reduction in deaths (RR 0·45, 95% CI 0·32–0·62; random effects).

In view of the limitations of analysis and variable quality of studies in the previous review, we updated the review to assess the effect of the WHO protocol or adaptations thereof on recovery and case fatality of children with SAM.

Case fatality rates ranged from 3·4% to 35%. The highest case fatality rate stemmed from a cohort of children with HIV infection.[92,93] Only two studies provided information on recovery rates, which were 79·7% and 83·3%.[94,95] In summary, the WHO protocol is substantiated through much evidence, based both on research and expert opinion. However, a clear need exists for continued work to improve staff training and quality[96] to achieve high rates of survival across various resource-constrained settings.

Community-based management of SAM

The products used to deliver nutrients for management of SAM and MAM, and the approaches used to target and deliver these products, evolved rapidly during the past decade. Innovations include new formulations and packaging and a shift from institutional to community-based management.

We reviewed interventions to treat SAM in community settings, and were largely able to pool studies comparing

	Settings	Estimates
WASH interventions		
Overview of three systematic reviews[77]	Developing countries	Significant effects: reduced risk of diarrhoea with hand washing with soap (RR 0·52, 95% CI 0·34–0·65), with improved water quality, and with excreta disposal
DHS data from 65 countries[78]	Developing countries	Significant effects: a recent World Bank report[78] based on analysis of trends in DHS data suggests that open defecation explained 54% of international variation in child height by contrast with GDP, which only explained 29%. A 20 percentage point reduction in open defecation was associated with a 0·1 SD increase in child height A Cochrane review of the effect of WASH interventions on nutrition outcomes is underway[87]
Maternal deworming		
Systematic review of five RCTs[79]	Developing countries	Non-significant effects: one dose of anthelminthic in second trimester of pregnancy had a non-significant effect on maternal anaemia, low birthweight, preterm births, and perinatal mortality
Deworming in children (for soil-transmitted intestinal worms)		
Systematic review of 34 RCTs[80]	Developing countries	Non-significant effects: one-dose deworming had a non-significant effect on haemoglobin and weight gain. For multiple doses at 1 year follow up, there was a non-significant effect on weight, haemoglobin, cognition, and school attendance Treatment after confirmed infection Significant effects: one-dose of deworming drugs increased weight (0·58 kg, 95% CI 0·40–0·76) and haemoglobin (0·37 g/dL, 95% CI 0·1–0·64). Evidence on cognition was inconclusive These analyses are corroborated by the large-scale DEVTA trial[88] of regular deworming and VAS over 5 years, which also did not show any benefits on weight gain or mortality
Feeding practices in diarrhoea		
Review of 29 RCTs[81]	Developing countries	Significant effects: in acute diarrhoea, lactose-free diets, when compared with lactose-containing diets, significantly reduced incidence of diarrhoea (SMD –0·36, 95% CI –0·62 to –0·10) and treatment failure (RR 0·53, 95% CI 0·40–0·70) Non-significant effects: weight gain
Zinc therapy for diarrhoea		
Systematic review of 13 studies[82]	Mostly Asia	Significant effects: reduced all-cause mortality reduced by 46% (95% CI 12–68), diarrhoea-related admissions to hospital by 23% (95% CI 15–31) Non-significant effects: diarrhoea-specific mortality, diarrhoea-prevalence Zinc reduced duration of acute diarrhoea by 0·50 days and persistent diarrhoea by 0·68 days
IPTp/ITN for malaria in pregnancy		
Systematic review of 16 RCTs[83]	Mostly Africa	Significant effects: Anti-malarials to prevent malaria in all pregnant women reduced antenatal parasitemia (RR 0·53, 95% CI 0·33–0·86), increased birthweight (MD 126·7 g, 95% CI 88·64–164·75), reduced low birthweight by 43% (RR 0·57, 95% CI 0·46–0·72) and severe antenatal anaemia 38% (RR 0·62, 95% CI 0·50–0·78) Non-significant effects: perinatal deaths
Systematic review of six RCTs[84]	Developing countries	Significant effects: ITNs in pregnancy reduced low birthweight (RR 0·77, 95% CI 0·61–0·98) and reduced fetal loss (first to fourth pregnancy; RR 0·67, 95% CI 0·47–0·97) Non-significant effects: anaemia and clinical malaria
Malaria prophylaxis in children		
Systematic review of seven RCTs[85]	Developing countries of West Africa	Significant effects: Reduced clinical malaria episodes (RR 0·26; 95% CI 0·17–0·38), reduced severe malaria episodes (RR 0·27, 95% CI 0·10–0·76). IPTc also reduced risk of moderately severe anaemia (RR 0·71, 95% CI 0·52–0·98) Non-significant effects: all-cause mortality
Systematic review of 22 RCTs[86]	Developing countries in Africa	Significant effects: ITNs improved packed cell volume of children by 1·7 absolute packed cell volume percent. When the control group used untreated nets, the difference was 0·4 absolute packed cell volume percent. ITNs and IRS reduced malaria-attributable mortality in children (1–59 months) by 55% (95% CI 49–61) in *Plasmodium falciparum* settings

WASH=water, sanitation, and hygiene. RCT=randomised controlled trial. DHS=Demographic and Health Survey. GDP=gross domestic product. RR=relative risk. MD=mean difference. SMD=standard mean difference. WAZ=weight-for-age Z score. HAZ=height-for-age Z score. DEVTA=de-worming and enhanced vitamin A. IPTp=intermittent preventive treatment of malaria in pregnancy. IPTc=IPT in children. ITN=insecticide-treated bednets. IRS=indoor residual spraying.

Table 4: **Review of evidence for disease prevention and management**

ready-to-use therapeutic foods (RUTF) with standard care, as opposed to rigorous evaluation of effectiveness of the approach in programme settings.[97] We identified no significant differences in mortality; however, children who received RUTF had faster rates of weight gain and had 51% greater likelihood to recover (defined as attaining WHZ ≥ –2) than did those receiving standard care.

Notably, a new randomised controlled trial[98] compared standard RUTF with RUTF and additional 7 day course of antibiotics, either amoxicillin or cefdinir, in children with uncomplicated SAM. This trial showed that the children receiving an antibiotic had a lower mortality rate, faster recovery rate, and higher weight gain compared with children receiving placebo. Although further research on this topic is needed, especially in children with HIV infection, this study shows that effective community management of SAM might require an approach that goes beyond merely the choice of specially formulated foods to the entire package of care.

Substantial programmatic evidence supports use of RUTF for community-based treatment,[99] which has substantially changed the approach to treatment of SAM. Yet because of the nature of the evidence, establishing effect estimates for the overall approach to community management has proved challenging. Available evidence shows some positive effects with the use of RUTF compared with standard care for the treatment of SAM in community settings, yet the differences were for the most part small and several outcomes had substantial heterogeneity. An emphasis not only on the choice of commodities, but also on the quality of programme design and implementation is crucial to improvement of outcomes for children with SAM, as is research to fill information gaps, such as optimum treatment methods and approaches for treatment of breastfed infants younger than 6 months.

Interventions for prevention and management of obesity

Obesity is increasing in many populations and is one of the most important challenges of the 21st century. Obese women are at an increased risk of adverse pregnancy outcomes. A Cochrane review[100] assessed the effectiveness of interventions (eating, exercise, behaviour modification, or counselling) that reduce weight in obese pregnant women and identified no evaluable trials. Some studies assessed the effect of diet, exercise, or both for weight reduction in women after childbirth, and showed that women who exercised did not lose significantly more weight, but women who took part in a diet (MD –1·70 kg, 95% CI –2·08 to –1·32), or diet plus exercise programme (–2·89 kg; –4·83 to –0·95), did so. These interventions did not seem to adversely effect breastfeeding performance in any setting.[101]

We identified six reviews that examined breastfeeding in infancy and its association with obesity prevalence or average body-mass index (BMI) in childhood or adulthood.[102–107] All studies suggested a small protective effect of breastfeeding on obesity later in life, although the magnitude of the effect varied between reviews and the strength of the affect of confounding was unclear. The largest prospective follow up study in healthy term infants in Belarus showed that improving the duration and exclusivity of breastfeeding did not prevent overweight or obesity in children, nor did it affect insulin-like growth factor I concentrations at age 11·5 years.[108] These findings suggest that despite the myriad advantages of breastfeeding, population strategies to increase the duration and exclusivity of breastfeeding are unlikely to curb the obesity epidemic.

A Cochrane review[107] examined the effects of obesity prevention interventions delivered for more than 12 weeks on changes in BMI and BMI *Z* scores in children and suggested a significant beneficial effect across age groups with a SMD of –0·15 kg/m (95% CI –0·21 to –0·09). The subgroup analysis showed significant effects for children aged 6–12 years with non-significant effects in younger children and adolescents. Interventions that combined physical activity and diet were more effective than either delivered alone. Findings suggested that short-term interventions (<12 months duration) were more effective than were those delivered over a longer duration (SMD –0·17, 95% CI –0·25 to –0·09 and SMD –0·12, 95% CI –0·21 to –0·03, respectively); however, there was substantial heterogeneity in all pooled estimates. Another review[109] of interventions to treat obesity in children showed that combined behavioural and lifestyle interventions or self-help could benefit overweight children and adolescents. Overall the evidence of effectiveness of all obesity prevention and therapeutic interventions is weak, underscoring the need for high-quality research in this discipline.

Delivery platforms and strategies for implementation of nutrition-specific interventions

Delivery strategies are crucial to achieve coverage with nutrition-specific interventions and to reach populations in need. A range of channels can provide opportunities for scaling up and reaching large segments of the population.

Fortification of staple foods and specific foods

A detailed discussion of fortification strategies is beyond the scope of this review. As supported by the Copenhagen consensus,[110] fortification is one the most cost-effective strategies to reach populations at large. Further discussion of fortification as a means for delivery of key micronutrients is provided in panel 3[111–118] and the accompanying report by Stuart Gillespie and colleagues.[119]

Cash transfer programmes

Financial incentives are widely used as policy strategies to ameliorate poverty, reduce financial barriers, and improve

Panel 3: **Effect of fortification strategies**

Food fortification is safe and cost effective in the prevention of micronutrient deficiencies and has been widely practised in developed countries for more than a century.[111] Foods can be fortified at three levels: mass or universal, targeted, and household. Mass or universal fortification—ideally legislated to be mandatory for industries—has the potential to produce foods and food products that are widely consumed by the general population (eg, salt iodisation and flour fortification with iron and folate). Mass fortification is by far the most cost-effective nutrition intervention, particularly when produced by medium-to-large scale industries.[111] Targeted fortification (eg, nutrient-fortified complementary foods for children aged 6–24 months) is important for subgroups of nutritionally vulnerable populations and populations in emergency situations whose nutrient intake is insufficient through available diets. Targeted fortification is also effective in resource poor settings where family foods do not include animal-source foods that are typically necessary to meet nutrient requirements of young children. Home fortification involves addition of nutrients directly to food consumed by women or children, or both, in the form of micronutrient powders or small quantities of food-based fortified lipid spreads (eg, lipid-based nutrient supplement). Such direct addition of micronutrients to foods is different from foods fortified in the preparatory processes, has the advantage that it does not require changing dietary practices, and has little effect on the taste of food. However, addition of micronutrient powders to prepared foods has characteristics akin to supplementation as opposed to foods fortified at source. Biofortification of food crops (fortification of food at source) is an alternative to more common fortification interventions and is rapidly advancing in technology with much success, particularly with regard to increasing iron, provitamin A, zinc, and folate contents in staple foods.[112]

Despite many limitations to establishing causality during assessment of food fortification programmes, several studies have reported outcomes. Fortification for children shows significant benefits on serum micronutrient concentrations, which could indirectly be used to work out the population-level effect. A meta-analysis of multiple micronutrient fortification in children shows an increase in haemoglobin concentrations by 0·87 g/dL (95% CI 0·57–1·16) and reduced risk of anaemia by 57% (relative risk [RR] 0·43; 95% CI 0·26–0·71). The mean ferritin increase with fortification was 11·3 μg/L (95% CI 3·3–19·2) compared with control groups. Fortification also increased vitamin A serum concentrations compared with control groups (four studies, mean retinol increase 3·7 μg/dL, 95% CI 1·3–6·1).[113] A meta-analysis of 60 trials showed that iron fortification of foods resulted in 41% reduction in the risks of anaemia (RR 0·59, 95% CI 0·48–0·71, p< 0·001) and a 52% reduction in iron deficiency (0·48, 0·38–0·62, p<0·001).[114] Other studies have also shown that use of vitamin D fortified bread increased serum 25-hydroxyvitamin D concentration as effectively as the cholecalciferol supplement in women.[115] Zinc fortification has also shown significantly higher zinc concentrations in serum and erythrocytes and lower serum copper concentrations compared with a placebo group in preterm infants.[116]

Fortification has the greatest potential to improve the nutritional status of a population when implemented within a comprehensive nutrition strategy. Key issues to ensure a sustainable programme include: identification of the right food (accounting for bioavailability, interaction with food, availability, acceptability, and cost) and target population, ensuring quality of product, and consumption of sufficient quantity of the fortified foods.[117] To accomplish these aims, there needs to be demand that is sustained through behaviour change communication at the consumer level and ready access to a sufficient supply of products that maintain standards set through legislative process from production to point-of-consumption. Government monitoring of compliance to standards and public-private partnerships are essential to ensure a competitive market for fortified products.[118] Fortification seems to be a potentially effective strategy but evidence of benefits on morbidity and functional outcomes from large-scale programmes in developing countries is scarce.

population health. We reviewed relevant studies reporting the effect of financial incentives on coverage of health and nutrition interventions and behaviours targeting children younger than 5 years.[120] The affect of financial incentive programmes on five categories of interventions (breastfeeding practices, immunisation coverage, diarrhoea management, healthcare use, and other preventive strategies) was assessed. The review concluded that financial incentives have the potential to promote increased coverage of several important child health interventions, but the quality of evidence available was low. The more pronounced effects seemed to be achieved by programmes that directly removed user fees for access to health services.[120] Some indication of effect was also noted for programmes that conditioned financial incentives on participation in health education and attendance to health-care visits. Further information on the benefit of such programmes for health and nutrition outcomes is provided in the accompanying report by Stuart Gillespie and colleagues.[119]

Community-based platforms for nutrition education and promotion

Community-based interventions to improve maternal, newborn, and child health are now widely recognised as important strategies to deliver key maternal and child survival interventions[121] and have been shown to reduce inequities in childhood pneumonia and diarrhoea deaths.[122] These interventions are delivered by health-care personnel or lay individuals, and implemented locally in homes, villages, or any defined community group. A full spectrum of promotive, preventive, and curative interventions can be delivered via community platforms,

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including provision of basic antenatal, natal, and postnatal care; preventive essential newborn care; breastfeeding counselling; management and referral of sick neonates; development of skills in behaviour change communication; and community mobilisation strategies to promote birth and newborn care preparedness. For example, a review[123] of community-based packages of care suggested that these interventions can improve rates of facility births by 28% (RR 1·28, 95% CI 1·04–1·59) and result in a doubling of the rate of initiation of breastfeeding within 1 h (RR 2·25, 95% CI 1·70–2·97). Lewin and colleagues[124] reviewed 82 studies with lay health workers and showed moderate quality evidence of effect on initiation of breastfeeding (RR 1·36, 95% CI 1·14–1·61), any breastfeeding (1·24, 1·10–1·39), and exclusive breastfeeding (2·78, 1·74–4·44) when compared with usual care. Although much of the evidence from large-scale programmes using community health workers is of poor quality, process indicators and assessments do suggest that community health workers are able to implement many of these projects at scale, and have substantial potential to improve the uptake of child health and nutrition outcomes among difficult to reach populations.[125] It is important to underscore the crucial importance of community engagement and buy-in to ensure effective community outreach programmes, behaviour change, and access.

Integrated management of childhood illnesses

WHO, in collaboration with UNICEF and other agencies, developed the Integrated Management of Childhood Illness (IMCI) strategy in the 1990s.[126] IMCI includes both curative and preventive interventions targeted at improvement of health practices at health facilities and at home. The strategy includes three components: improvements in case management; improvements in health systems; and improvements in family and community practices. Assessments of IMCI in Uganda, Tanzania, Bangladesh, Brazil, Peru, South Africa, China, Armenia, Nigeria, and Morocco have shown various benefits in health service quality, mortality reduction, and health-care cost savings.[127] In Tanzania, implementation of IMCI was associated with significant improvements in equity differentials for six child health indicators, with the largest improvements noted for stunting in children between 24 and 59 months of age.[128] Much the same findings were reported from Bangladesh, where implementation of IMCI was associated with a significant

Panel 4: Nutrition in emergencies

Irrespective of the underlying cause, humanitarian emergencies are often characterised by high and rising rates of severe acute malnutrition (SAM), moderate acute malnutrition (MAM), and micronutrient deficiencies in children (and sometimes adults). The foremost intent of nutrition-specific interventions in such situations is to prevent mortality, and involves management of wasting and resolution of specific nutrient deficiencies, and ensuring adequate food consumption. The humanitarian community largely agrees that emergency nutrition interventions have improved in the past 10–15 years in terms of coverage, scale of operations, reporting standards, and effectiveness (assessed by Sphere[133] and other standards of practice). Until the early 2000s, nutrition programming in emergencies was dominated by facility-based therapeutic care, targeted or blanket supplementary feeding, and provision of micronutrient supplements.[134–136] More recently, the focus has widened, with attention being given to both short-term and longer-term concerns, and to a choice of actions from a more comprehensive range of interventions.[137] The options for effective management for both SAM and MAM in emergencies have improved in the past 10–15 years as products used have been improved and coverage has increased through community-based treatment. Potential alternatives to the use of food to address seasonal or emergency-driven peaks in wasting are being explored, including combinations of food plus cash, cash alone, or vouchers; however, cost-effectiveness studies of various strategies are scarce. There is evidence that in contexts in which markets have not been seriously disrupted, appropriate foods are readily accessible, and rates of undernutrition are not dangerously high, alternatives or complements to food-based rations might be viable and potentially cost-effective.[138,139]

Concern has also grown about the potential trade-offs between long-term versus short-term objectives of emergency nutrition interventions. Although life-saving actions are justifiably prioritised over the prevention of chronic diseases, food assistance programmes suitable for acute emergencies might be less appropriate for protracted situations.[140] This has important implications when thinking through seasonal blanket distribution of ready-to-use foods to prevent a worsening of levels of acute malnutrition. As a result of the difficulty of generating experimental data specific to programming in emergencies,[141] the discipline has evolved relying less on randomised controlled trials and more on the sharing of lessons learned, which are used to inform technical or operational guidelines disseminated by WHO and UN bodies.[142–144] Although practice must still be improved in many areas, and outcomes better documented, it remains crucially important to secure appropriate resources to support nutrition actions in this most challenging of disciplines and to assess outcomes for future learning. The nutritional status of individuals assessed and treated in emergency contexts overlaps substantially with non-emergency settings. Although high-quality programmatic research can and must help improve the design and outcome of effective emergency nutrition interventions, these interventions should be seen as entry points that support, rather than supplant, longer-term actions seeking to address underlying causes of poor nutrition.

increase in exclusive breastfeeding and comparatively faster reduction in the prevalence of stunting in children aged 24–59 months.[129]

School-based delivery platforms

Many countries have school feeding programmes targeting children who are older than 5 years. The main purpose of such programmes is to provide incentives for school enrolment and evidence of nutrition benefits is scarce. A Cochrane review[130] of 18 relevant studies of the effectiveness of school feeding programmes in improving physical and psychosocial health for disadvantaged school pupils reported an increase in school attendance by 4–6 days annually and weight gains averaging 0·39 kg (95% CI 0·11–0·67) over 11 months and 0·71 kg (0·48–0·95) over 19 months. The results were inconclusive for height gain, so there must be caution that these programmes do not lead to obesity. A detailed discussion of school feeding programmes is provided in the accompanying report by Stuart Gillespie and colleagues.[119] Notwithstanding the scarce evidence, schools offer an enormous opportunity for promotion of health and nutrition for older children and adolescents and could have an important role in future.

Child health days

Child health days have been introduced in weak health systems to rapidly enhance coverage of essential child survival interventions. There are few robust assessments or reported experiences with child health days, which commonly include delivery of vitamin A supplements, immunisations, insecticide-treated nets, and deworming drugs. Available evidence suggests that these days can achieve greater coverage than stand-alone campaigns in previously low-coverage countries.[131] A descriptive review[132] of scale-up of child health days from 1999 to 2009 suggests that these days were more effective than stand-alone campaigns, provided that the number of interventions did not exceed four. The overall equity effect of these approaches are uncertain and further studies are needed to establish how best to integrate this approach within routine health-care services.

Delivery of nutrition interventions in humanitarian emergency settings

Delivery strategies for nutrition interventions in humanitarian emergencies necessitate a different approach to what might be deemed optimum in stable circumstances. In view of variability in the characteristics of emergencies and protracted population displacement, humanitarian emergencies might closely mirror situations of endemic malnutrition in food insecure settings. Hence prevention and health promotion strategies, such as breastfeeding and complementary feeding education and support, should also become essential parts of the packages of interventions in emergency contexts (panel 4[133–144]).

***Panel 5:* Evidence for emerging interventions**

Household air pollution

Household air pollution (HAP) from solid fuels used in simple stoves for cooking and heating, is recognised as a risk factor for several health outcomes with important consequences for child survival, including pneumonia,[146] low birthweight, and stillbirths.[147] A review of observational studies[148] shows significant risk reduction estimates for HAP for low birthweight (29%), stillbirth (34%), stunting (21%), and all-cause mortality (27%). Reduction of exposure to HAP could substantially reduce risk of several important outcomes for child survival. One randomised controlled trial in rural Guatemala,[149] with an improved stove intervention, reduced average exposure to indoor air pollution by 50% and resulted in a reduction in physician-diagnosed pneumonia (relative risk [RR] 0·84, 95% CI 0·63–1·13) although this difference was not statistically significant. However, this finding was supported by the results of an exposure-response analysis which showed a statistically significant reduction in the same outcome (0·82, 0·70–0·98). This intervention also resulted in a reduction in low birthweight (0·74, 95% CI 0·33–1·66), with babies weighing 89 g more (95% CI –27 to 204) than those in the control group.[150] A range of interventions, including both clean fuels and improved solid fuel stoves are available, but substantial challenges remain in achieving sustained use of low-cost low-emission technologies at scale in low-income households.

Maternal vitamin D supplementation

Vitamin D is an essential requirement of the body at any age. Vitamin D can be acquired through three main channels: through the skin via exposure to sunlight, from the diet, and from supplements or fortified foods. However, natural low-cost sources of dietary sources of vitamin D are very scarce. A systematic review[151] assessing the association of vitamin D status in pregnancy, suggests that women with circulating 25-hydroxyvitamin D (25[OH]D) concentrations of less than 50 nmol/L in pregnancy have an increased risk of preeclampsia (odds ratio [OR] 2·09, 95% CI 1·50–2·90), gestational diabetes mellitus (1·38, 1·12–1·70), preterm birth (1·58, 1·08–2·31) and small-for-gestation age ([SGA] 1·52, 1·08–2·15). A long-term cohort study[152] did not find any association of low maternal vitamin D concentrations with bone mineral content in late childhood. Similarly, a Cochrane review[153] assessed the effectiveness of vitamin D supplementation in pregnancy and revealed little evidence of benefits on functional pregnancy outcomes, although significant increase in serum vitamin D concentrations at term were noted and borderline reduction in low birthweight was reported in three trials (RR 0·48, 95% CI 0·23–1·01). The number of high-quality trials with maternal vitamin D supplementation is too small to draw conclusions on its usefulness and safety.

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Maternal zinc supplementation

A Cochrane review[154] suggests that zinc supplementation in pregnancy results in a 14% reduction in preterm birth (RR 0·86, 95% CI 0·76–0·97). This decrease was not accompanied by a similar reduction in stillbirths, neonatal death, SGA, or low birthweight. No subgroup differences were identified in women with low versus normal zinc nutrition levels or in women who complied with their treatment versus those who did not. We conclude that there is presently insufficient evidence for a beneficial role of isolated zinc supplementation in pregnancy.

Omega-3 fatty acid supplementation

Several reviews[155–162] have been done to assess the effectiveness of maternal supplementation with omega-3 fatty acids during pregnancy and its effects on various outcomes including nutritional, morbidity, mortality, cognitive, and neurodevelopmental measures. Findings from these reviews, consisting of studies done in developed countries and of variable quality, suggest that marine omega-3 fatty acids administered in pregnancy reduce the rate of preterm birth and increase birthweight. However, a Cochrane review[155] suggests that there is not enough evidence to support the routine use of marine oil supplements or other prostaglandin precursors during pregnancy to reduce the risk of pre-eclampsia, preterm birth, low birthweight, or SGA. A review[163] of the intake of omega-3 and omega-6 fatty acids in low-income countries showed that the total omega-3 fatty acid supply was below the recommended intake range for infants and young children, and below the minimum recommended level for pregnant and lactating women, in the nine countries with the lowest gross domestic product. The review noted that supply of omega-3 fatty acids could be increased by using vegetable oils with higher alpha-linolenic acid and by increasing fish production through fish farming. Another review[164] on the effect of fatty acid status on immune function of children in low-income countries suggested that fatty acid interventions could yield immune benefits in children in poor settings, especially in non-breastfed children and in relation to inflammatory disorders, such as persistent enteropathy, although more trials are needed for a conclusive association.

Antenatal psychosocial assessment and mental health support

Stable maternal mental health during pregnancy is crucial for the development of the early mother–child relationship and for health. Although there is ample evidence of the link between maternal mental health and child health and growth,[165] there is insufficient evidence to support routine psycho-social screening for all pregnant women.[166] There is promising evidence that cognitive-behaviour therapy-based interventions provided by community health workers to pregnant women, can effectively reduce depression at 3 months post-partum (adjusted OR 0·22, 95% CI 0·14–0·36) and at 1-year follow-up (0·23, 0·15–0·36).[167] However, there was no effect on weight gain or linear growth in infancy. There is a need for further robust trials of maternal mental health interventions with longer term follow up.

Role of massage for promoting growth in preterm Infants

Preterm infants have been noted to benefit from massage therapy and the suggested mechanisms include increased vagal activity and gastric motility, which leads to increased concentrations of insulin and Insulin-like growth factor 1.[168] A Cochrane review[169] of the effect of massage in preterm infants showed that massage increased daily weight gain by 5 g, reduced the length of hospital stay by 4·5 days, and had a slight effect on development and weight gain at 4–6 months, although the evidence was of weak quality. A more recent review[170] of the effects of massage therapy for preterm infants showed that 5–10 days of moderate pressure massage, typically 15 min three-times daily, resulted in improved weight gain (mean for studies 28–48%) and bone density, and reduced length of hospital stay. Related evidence from studies of emollient therapy in preterm infants from the developing world suggest potential synergistic benefits of skin barrier protection, thermoregulation, and light massage.

Vitamin D supplementation in children

In view of the widespread deficiency of vitamin D and associated health consequences and rickets, preventive vitamin D supplementation to high-risk populations, including infants and toddlers, might be a useful strategy. A Cochrane review of vitamin D supplementation in children in at-risk populations is underway, and an existing review[171] of postnatal supplementation shows relatively few studies assessing effects on bone density, growth, and other functional outcomes.

Zinc supplementation for treatment of newborn infections and childhood pneumonia

A Cochrane review[172] suggests that zinc supplementation in addition to antibiotics in children with severe and non-severe pneumonia did not have a significant effect on clinical recovery or duration of hospital stay. Other recent studies show mixed effects across a range of severity of disease,[173–176] showing the need for larger well-powered studies for the treatment of severe pneumonia with zinc in populations at-risk of deficiency. Two trials[177,178] of adjunctive zinc supplementation in presumed serious infections in neonates and young infants show disparate findings, underscoring the need for further well-designed and adequately powered studies of zinc as an adjunct to the treatment of serious infections in infancy.

Lipid-based nutrient supplementation

Lipid-based nutrient supplements (LNS, in the form of vegetable oil, peanut butter, milk powder, sugar, vitamins, and minerals) are used in small quantities (20 g) to meet micronutrient requirements in children, in combination with a normal diet. Randomised controlled trials in Malawi[179,180] and Ghana[181,182] have shown significant benefits on iron status and linear growth. Further evidence of benefits and absence of adverse effects are needed to assess the feasibility of use of LNS in programme settings and randomised controlled trials are underway—three in Africa and one in Asia—which should provide more information.

Panel 6: Overview of the Lives Saved Tool (LiST)

To model the effect of scaling up the ten proven nutrition-specific interventions on the health of children we used the Lives Saved Tool (LiST). This model has been developed under the auspices of the Child Health Epidemiology Reference Group (CHERG) to allow users to estimate the effect of scaling up interventions on maternal and child health. The present version of the model is based on previous modelling exercises, including *The Lancet*'s 2008 Maternal and Child Undernutrition series.[4,122,145,184] A more detailed description of the LiST model is provided in appendix pp 3–7 and at the LiST website.

The LiST has been characterised as a linear, mathematical model that is deterministic.[185] It describes fixed associations between inputs and outputs that will produce the same outputs each time the model is run. In LiST the primary inputs are coverage of interventions and the outputs are changes in population level of risk factors (such as wasting or stunting rates, or birth outcomes such as prematurity or size at birth) and cause-specific mortality (neonatal, mortality in children aged 1–59 months, maternal mortality, and stillbirths). The association between an input (change in intervention coverage) with one or more outputs is specified in terms of the effectiveness of the intervention for reduction of the probability of that outcome. The outcome can be cause-specific mortality or a risk factor. The overarching assumption in LiST is that mortality rates and cause of death structure will not change except in response to changes in coverage of interventions. The model assumes that changes in distal variables, such as increase in income per person or mothers' education, will affect mortality by increasing coverage of interventions or reducing risk factors.

Figure 2 shows the linkages in LiST between risk factors, interventions, and mortality. For example, the input of multiple micronutrients consumed by pregnant women has an effect on birth outcomes. It directly affects the probability of a child being born small-for-gestational-age (SGA). A child born SGA will in turn have an increased risk of dying during the neonatal period and those who survive through the first month of life then have an increased risk of being stunted. Stunted children have higher risks of mortality from 1 to 59 months of age.

A second example is promotion of breastfeeding. Scaling up breastfeeding promotion will affect breastfeeding practice, shifting the distribution of mothers who exclusively, predominately, or partly breastfeed their child or do not breastfeed. Within the model, this intervention is examined separately for the first month of life and for the period of 1–5 months. Within each of the two time periods there is a different relative risk of dying of pneumonia and diarrhoea associated with each breastfeeding practice and an effect on diarrhoea incidence. So within the model, breastfeeding promotion has an effect on breastfeeding practices, which in turn has a direct effect on mortality in the neonatal and 1–23 month period. Additionally, there is an effect on diarrhoea incidence, which then has an effect on stunting rates and mortality.

The assumptions of the effects of the ten nutrition interventions we used in the modelling are shown in appendix pp 13–16. For each of the interventions we have also shown the 95% CIs around the estimates, which were used in the sensitivity analyses. The source and methods used to develop these assumptions and others used in the model are described in a series of reports.[186–188]

Emerging interventions that need further evidence

We also reviewed interventions that are not currently recommended but that have potential and future prospects for inclusion in regular programmes. These interventions, which have possible effects on nutritional outcomes in women and children, include strategies to reduce household air pollution, maternal vitamin D supplementation, maternal zinc supplementation, omega 3 fatty acids supplementation in pregnancy, antenatal psychosocial assessment and cognitive behaviour therapy for depression, emollient and massage therapy for preterm infants, vitamin D supplementation in children, zinc therapy for pneumonia, and lipid-based nutrient supplements. Some of the existing evidence around these interventions is summarised in panel 5.[146–182]

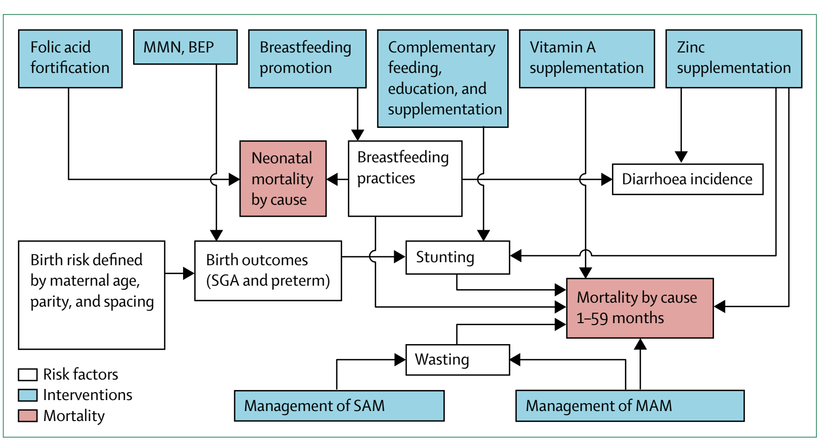

Figure 2: **Linkages between risk factors, interventions, and mortality in LiST**
LiST=Lives Saved Tool. MMN=multiple micronutrients. BEP=balanced energy protein. SGA=small-for-gestational-age. SAM=severe acute malnutrition. MAM=moderate AM.

Modelling the effect of scaling up coverage of nutrition interventions in countries with the highest burden

We used the Lives Saved Tool (LiST) to model the potential effect on child health and mortality in 2012 of scaling up a set of ten nutrition-specific interventions that could affect stunting and severe wasting[183] (panel 6,[4,122,145,184–188] figure 2). For modelling, we selected 34 countries with more than 90% of the burden of stunting (figure 3; appendix pp 8–12) and took 2011 as

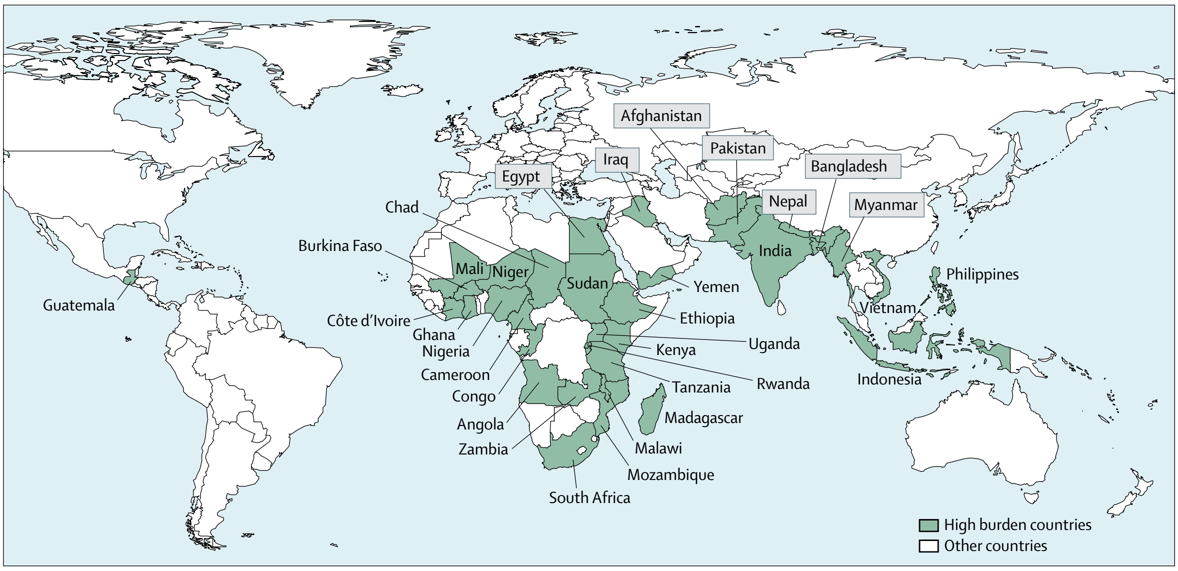

***Figure 3:* Countries with the highest burden of malnutrition**
These 34 countries account for 90% of the global burden of malnutrition.

the base year. The present coverage level for each intervention was taken from the latest available estimates from large-scale surveys and effectiveness of interventions (see LiST for details). We modelled the effect of scaling up the following ten nutrition interventions: periconceptional folic acid supplementation or fortification, maternal balanced energy protein supplementation, maternal calcium supplementation, multiple micronutrient supplementation in pregnancy, promotion of breastfeeding, appropriate complementary feeding, vitamin A and preventive zinc supplementation in children 6–59 months of age, management of SAM, and management of MAM, from their present level of coverage to 90% (or retention of present coverage when higher than 90%). Appendix pp 13–16 list the estimates of effect considered for each intervention. The conversion of intervention effects of preventive zinc supplementation and complementary feeding strategies from linear growth to stunting effects in LiST is detailed in appendix pp 17–22. We assessed the effect of this scale up scenario on mortality in children younger than 5 years, rates of breastfeeding, stunting, and wasting.

Our model suggested that if these ten nutrition interventions were scaled up to 90% coverage, mortality in children younger than 5 years could be reduced by 15% (range 9–19), with a 35% (19–43) reduction in diarrhoea-specific mortality, a 29% (16–37) reduction in pneumonia-specific mortality, and a 39% (23–47) reduction in measles-specific mortality (figure 4). The analysis also showed fewer deaths attributable to congenital anomalies and birth asphyxia related to periconceptual folic acid use and a reduction in SGA (figure 4; appendix pp 23–24). This scale up had a little effect on maternal mortality (data not shown). Scaling

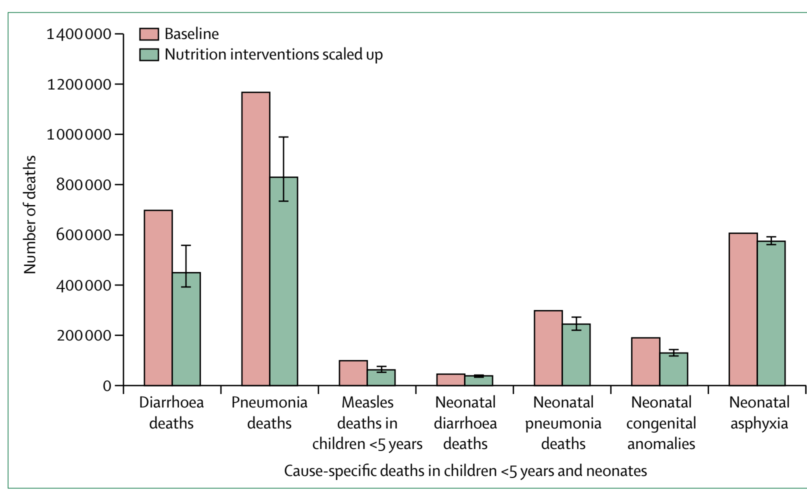

***Figure 4:* Effect of scale up of interventions on cause-specific deaths**
Error bars are ranges.

up of all ten interventions to 90% coverage was also associated with a mean 20·3% (range 11·1–28·9) reduction in stunting and a 61·4% (35·7–72) reduction in severe wasting. The maximum effect for severe wasting was noted in children in the 12–23 months age group (appendix p 25).

For more on the **Lives Saved Tool** see http://www.jhsph.edu/iip/LiST

The analysis suggested that the interventions with the largest potential affect on mortality in children younger than 5 years are management of SAM, preventive zinc supplementation, and promotion of breastfeeding (figure 5). Analysis of community support strategies for breastfeeding suggested that achieving 90% coverage of breastfeeding promotion could increase exclusive breastfeeding by 15% (7–22) in children younger than 1 month and by 20% (13–26) in children aged 1–5 months.

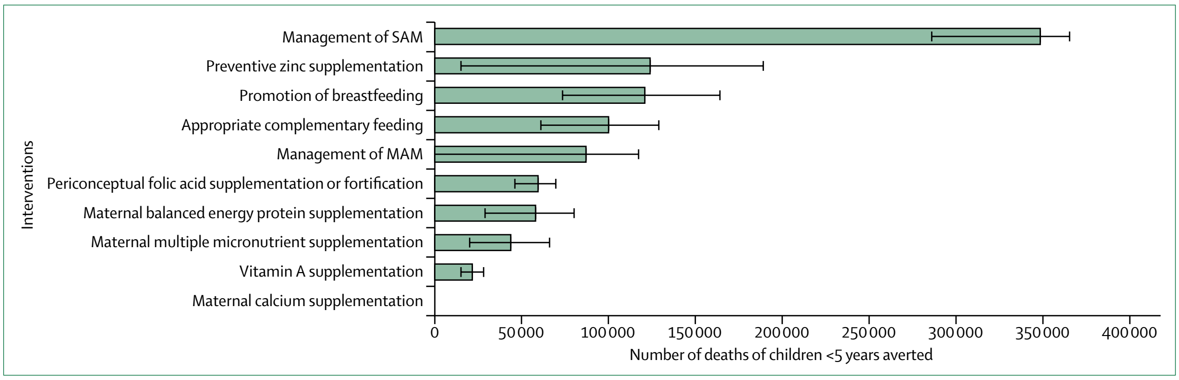

Figure 5: **Effect of scale up of interventions on deaths in children younger than 5 years**
Error bars are ranges. SAM=severe acute malnutriton. MAM=moderate AM.

	Number of lives saved*	Cost per life-year saved†
Optimum maternal nutrition during pregnancy		
Maternal multiple micronutrient supplements to all Calcium supplementation to mothers at risk of low intake‡ Maternal balanced energy protein supplements as needed Universal salt iodisation‡	102 000 (49 000–146 000)	$571 (398–1191)
Infant and young child feeding		
Promotion of early and exclusive breastfeeding for 6 months and continued breastfeeding for up to 24 months Appropriate complementary feeding education in food secure populations and additional complementary food supplements in food insecure populations	221 000 (135 000–293 000)	$175 (132–286)
Micronutrient supplementation in children at risk		
Vitamin A supplementation between 6 and 59 months age Preventive zinc supplements between 12 and 59 months of age	145 000 (30 000–216 000)	$159 (106–766)
Management of acute malnutrition		
Management of moderate acute malnutrition Management of severe acute malnutrition	435 000 (285 000–482 000)	$125 (119–152)§

Data are number (95% CI) or cost in 2010 international dollars (95% CI). *Effect of each of package when all four packages are scaled up at once. †Cost per life-year saved assumes that a life saved of a child younger than 5 years saves on average 59 life-years, based on WHO data (2011[189]) that life expectancy at birth on average in low-income countries is 60, and that most deaths of children younger than 5 years occur in the first year of life. To convert to cost per discounted life-year saved multiply these estimates by 59/32 (ie, 1·84). ‡Intervention has effect on maternal or child morbidity, but no direct effect on lives saved. §Cost per life-year saved by management of severe acute malnutrition only, costs for supplementary feeding for moderate acute malnutrition are currently unavailable.

Table 5: **Effect of packages of nutrition interventions at 90% coverage**

Implementation of nutrition-specific packages of care

We also assessed the potential effect of nutrition-specific packages of care by scaling up these interventions to 90% coverage. Four packages were assessed for effect on child survival: optimum maternal nutrition during pregnancy (maternal multiple micronutrients, use of iodised salt, calcium, and balanced energy protein supplementation), an infant and young child nutrition package (breastfeeding promotion and appropriate complementary feeding education or provision), micronutrient supplementation (preventive zinc and vitamin A supplementation), and management of acute malnutrition (management of MAM, management of SAM). Analysis of these nutrition-specific packages showed that the most lives could be saved by the therapeutic feeding for severe acute malnutrition, followed by the infant and young child nutrition package (table 5[189]).

Can these interventions promote equitable access?

To assess the potential benefit of community-based delivery strategies on reaching and engaging poor and marginalised populations, we assessed the effect of community-based promotion and delivery of seven nutrition-specific interventions (multiple micronutrient supplementation in pregnancy, promotion of breastfeeding, appropriate complementary feeding, management of SAM, vitamin A supplementaton, preventive zinc supplementation, and treatment of diarrhoea with zinc) across various wealth quintiles in three target countries—Pakistan, Bangladesh, and Ethiopia (figure 6). Baseline data were stratified by wealth quintiles by reanalysing the most recently available Demographic Health Survey for each country. Since no recent estimates existed for cause-specific mortality across wealth quintiles for Bangladesh and Ethiopia, we used LiST to recompute the cause of death structure using the procedures described by Amouzou and colleagues.[190] For Pakistan, we used the recent national verbal autopsy study[191] for the cause of death structure and distribution of deaths by asset quintiles from a recent analysis.[192] As shown in figure 6 and appendix p 26, the effect of this scale up is greatest in the poorest quintiles, suggesting that scaling up these interventions through community-based approaches would not only reduce the overall burden of childhood mortality but also substantially reduce existing disparities in access and mortality.

Cost analysis

We used a so-called ingredients approach to work out the cost of nutrition interventions, based on the UN One Health Tool,[193] which allows for regional variation due to personnel costs. We constructed cost estimates as add-ons to existing antenatal, postnatal, and standard infant

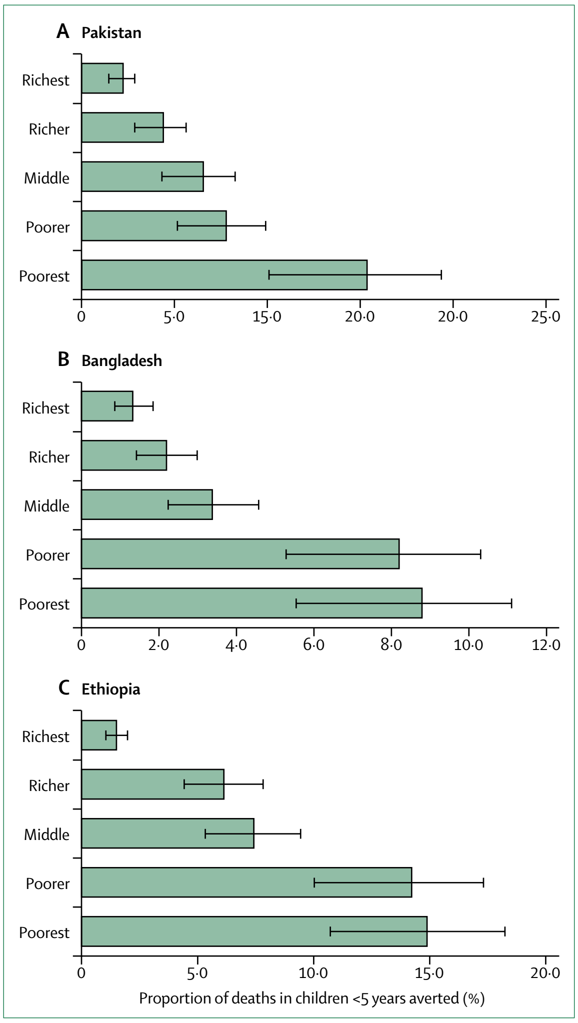

***Figure 6:* Equity analysis showing effect of scale up of nutrition interventions on proportion of deaths of children younger than 5 years averted in Pakistan, Bangladesh, and Ethiopia**
Error bars are ranges.

	Cost
Salt iodisation	$68
Multiple micronutrient supplementation in pregnancy (includes iron-folate)	$472
Calcium supplementation in pregnancy	$1914
Energy-protein supplementation in pregnancy	$972
Vitamin A supplementation in childhood	$106
Zinc supplementation in childhood	$1182
Breastfeeding promotion	$653
Complementary feeding education	$269
Complementary food supplementation	$1359
SAM management	$2563
Total	$9559

Data are 2010 international dollars, millions.

***Table 6:* Total additional annual cost of achieving 90% coverage with nutrition interventions, in 34 countries with more than 90% of the burden**

visits as part of WHO's Expanded Program on Immunisation, plus five stand-alone nutrition visits between 6 and 35 months of age. The few interventions targeted at children between 36 and 59 months of age were assumed to be delivered opportunistically (at clinic visits, or during outreach visits for younger siblings). The base delivery platform assumed was outreach programmes for sub-Saharan Africa, and primary health-care clinics elsewhere (appendix pp 27–28 provides details). We compared the unit costs from the ingredients method with actual costs as used in the Scaling up Nutrition (SUN) costing.[194] Although the ingredients method allows greater detail than an actual costs method such as SUN for planning purposes, the comparison to actual costs serves as a useful check on the appropriateness of assumptions made. Costs were estimated for ten nutrition interventions (one population-wide, three in pregnancy, and six after birth; intervention definitions and assumptions are provide in appendix pp 29–30).

We calculated unit costs separately for WHO subregions (appendix p 31).[195] Unit costs were higher in Africa compared with elsewhere, because of higher labour costs and the extra travel time required for delivery using outreach (associated with lower population density in many areas, and also the lower coverage of primary care facilities). The unit costs for interventions were much the same between the ingredients and SUN approaches, allowing for some difference in interventions based on updated recommendations.

Our analysis shows that the estimated total additional cost involved to achieve 90% coverage of the population in need in the 34 focus countries with the selected set of ten nutrition interventions is Int$9·6 billion per annum (table 6). Of this $9·6 billion, $3·7 billion (39%) is for micronutrient interventions, $0·9 billion (9%) for educational interventions, and $2·6 billion (27%) for SAM management. The amount required for provision of supplementary food for pregnant women and for children aged 6–23 months in poor households (those with <$1·25 per person per day) constitutes the remaining $2·3 billion (24%). When these costs are broken down by region, $3·4 billion is needed in the 20 countries included from sub-Saharan Africa, $4·8 billion in the four in south Asia plus Myanmar (Burma), $1·0 billion for the six in eastern Mediterranean, and $0·5 billion for the three remaining countries (Vietnam and the Philippines in western Pacific region, plus Guatemala; appendix p 32). The $9·6 billion estimate for the nutrition interventions is lower than the 2008 SUN estimate of $11·8 billion.[194] The SUN figure included $1·2 billion for capacity-building and monitoring and assessment, which we excluded from the present analysis because we do not have a mechanism to allocate this cost by region or country and category.

There are differences in the details of our results compared with the earlier SUN estimates. Unit costs are similar but not identical. The list of focus countries is likewise similar but not identical (using 2005 data, Turkey, Peru, Cambodia, and Burundi were included in the list of countries with 90% of the world's stunted children, but not with 2010 data; Rwanda and Chad entered this list with 2010 data). Some interventions are excluded from the new total (deworming, therapeutic zinc for diarrhoea), whereas some new ones are included (calcium supplements and balanced energy protein supplements in pregnancy). Complementary food supplementation is targeted only to the 6–23 month age group in this new analysis. Population in need has changed since the SUN estimates were calculated, with changes in coverage of some interventions (notably, management of SAM has begun to scale up).

Discussion

This update of nutrition interventions differs from past exercises in several ways. First, we included a wider range of nutrition-specific interventions and applied more stringent assessment criteria, using the Grades of Recommendation Assessment, Development and Evaluation system and Child Health Epidemiology Reference Group criteria for most inverventions.[5] Second, in view of emerging evidence of the importance of maternal nutrition, SGA, and early stunting,[1] we specifically focused on interventions that might affect prevalence and outcomes in SGA births and early stunting. We also reviewed and modelled a range of delivery strategies and platforms and specifically explored the potential of reaching poor and disadvantaged populations through community platforms and outreach services, an approach used to assess the effect of interventions to address childhood diarrhoea and pneumonia.[122] Finally, the LiST model was substantially updated to include age-specific effects and the interrelationship of new interventions and their effect on maternal and child undernutrition, a much more complex exercise than what was undertaken previously.[4] To undertake this exercise we substantively updated LiST in a way that more accurately captures the role of undernutrition and the effect of proven interventions on maternal and child health.

Several limitations should be recognised in considering our findings. A large proportion of the evidence on interventions is still derived from efficacy trials as opposed to effectiveness studies and hence variations exist in estimates of effect size for various interventions. Few robust assessments have been done in programme settings and available data from observational studies do not permit ready assessment of intervention effectiveness. There are also very few studies that report morbidity and neurodevelopmental outcomes. We reviewed the available evidence of effects on neurodevelopmental outcomes from studies of maternal and child nutrition interventions and identified little data with evaluation methodologies for assessment. We are therefore greatly limited in the inferences that can be drawn on neurodevelopment and long-term outcomes from nutrition interventions.

Notwithstanding these limitations, our estimates of the effect of nutrition-specific interventions, though more conservative than previous findings, still suggest great benefits from a core set of interventions delivered antenatally or postnatally. Our assessments of benefits from interventions to reduce SGA are hindered by the limited range of interventions in pregnancy. Even though antenatal care services offer a unique opportunity for maternal screening and interventions, the difficulty of reaching women early enough in pregnancy is a major limitation in ensuring adequate uptake of interventions for a reasonable length of time. In parts of the world with high rates of maternal malnutrition, micronutrient deficiencies, and SGA births, these factors remain major determinants of stunting in early childhood. This finding underscores the need to address determinants of undernutrition early in the lifecycle through appropriate strategies, such as enhancing adolescent nutrition and family planning to delay the age of first pregnancy or increase spacing between births.[196] Achieving high coverage of multiple micronutrient supplementation in pregnancy offers a new avenue to reduce SGA births and their consequences for mortality and growth in early childhood. The absence of appreciation of the crucial links of maternal and fetal nutrition to fertility and repeated pregnancies has been a major barrier in targeting of interventions to address these factors appropriately.

Although the overall effect on stunting alleviation seems modest, the rate of decline suggested from the package of nutrition-specific interventions is plausible and within the broad range of observed effects across countries. A review of global stunting trends by Stevens and colleagues[197] showed average rates of reduction in stunting in the best performing countries ranging from 21–42% over the past decade, broadly consistent with what our model predicts from scaling up a core set of nutrition-specific interventions. Importantly, the countries that have made tremendous strides in improving nutrition and health outcomes (such as Brazil, China, Saudi Arabia, Kuwait, and Chile) have implemented nutrition-specific interventions, but also have been settings with exceptional economic growth, and investments in nutrition-sensitive interventions to address population health, education, and social sector development. Much the same conclusions were drawn by UNICEF in a report on undernutrition.[198]

A major advance on our previous review of interventions is the addition of delivery platforms that allow us to assess strategies to reach populations who are not being reached currently. Our findings suggest that community platforms offer a unique opportunity to engage and reach poor and difficult to access populations through communication and outreach strategies. These strategies could also lead to potential integration of nutrition with maternal, newborn, and child health interventions. Since several countries are investing in community health worker programmes to address maternal, newborn, and child health,[125] much potential exists for scaling up nutrition promotion and therapeutic interventions through such platforms and hence integrating the two at point-of -service delivery. This integration could also help achieve reductions in inequities in the short term as has been noted by universal scaling up of selected maternal and child survival interventions.[199] However, importantly, implementation of such programmes involves unique combinations and sequencing of health system policies, actions, and advocacy. Community-based nutrition programmes need meticulous planning, a rights-based framework for engagement of communities and other sectors, and piloting. Other health system pillars are crucial to success, including training and support for community health workers, strengthening of the supply chain, simplified information systems, monitoring, and regular feedback.

The model used in this review estimates feasible reductions in mortality and stunting with enhanced investments. The same investments that can achieve these results will also lead to other improvements in cognitive and socioemotional development. Although these outcomes are not included in the model, partly because the costing database differs (ie, LiST mainly addresses mortality), substantial evidence from a range of models and longitudinal studies confirms that the benefits in terms of overall development on human capacity are appreciable.

In terms of cost, an annual outlay of an additional $9·6 billion to bring to scale a range of nutrition interventions that would save nearly 1 million lives is reasonable since many interventions would be scaled up from negligible coverage rates. The cost per (discounted) life-year saved is about $370 for a set of interventions that could effectively deliver optimum nutrition to pregnant women, infants, and children, and manage SAM. These figures suggest that the nutrition interventions are well within the cost-effectiveness benchmark (less than three-times per person income) for all countries. More than half the $9·6 billion is accounted for by two large countries that could rely heavily on domestic resources (India and Indonesia). Consumables (whether drugs, or other items such as for transport or administration) account for slightly less than half the $9·6 billion, and all but the poorest countries can be expected to cover most of the expenditures on personnel; $3–4 billion from external donors could make a substantial difference to child nutrition. What proportion of development assistance for health is earmarked for nutrition is unclear. Global tracking data from the Institute for Health Metrics and Evaluation were unable to disaggregate nutrition-related funding from the annual funding of $5·17 billion for maternal, newborn, and child health programmes.[200] The Countdown collaboration estimates nutrition-specific funding for the same year (2012) at $324·5 million.[201] Much funding for nutrition-relevant programmes probably overlaps with existing programmes for maternal, newborn, and child health and health systems strengthening and there might also be potential synergies, making it possible to share costs.

The evidence from carefully conducted cohort studies[202] of benefits of higher birthweight and early linear growth on education and improved health outcomes is convincing and consistent with the overall message from our review and modelling exercise. As the world moves towards the post-2015 development agenda, it is important to draw attention to the unfinished agenda of maternal and child undernutrition and to the emerging issues of obesity. Our review reconfirms the existence of feasible and low cost evidence-based interventions and the fact that coverage rates for many of these interventions remain poor[203] and for some, non-existent. In view of the importance of fetal nutrition and poverty alleviation strategies to reach those in greatest need, priority must be given to scaling up nutrition specific and sensitive interventions in some of the highest burden countries. At the same time, in view of the increasing importance of non-communicable diseases, concerted efforts must be made to develop and implement interventions to reduce the risk of obesity.

Contributors

ZAB conceptualised the review in consultation with the coordinators (PW, AL, SH, and REB) and wrote the first draft of the paper with substantial inputs from JKD. NW, YT, and AR developed the modification of LiST for assessment of effect and equity. Costing for selected interventions was done by MFG and SH. VW contributed to the scientific literature search, screening, collection, and analysis of data for the deworming review. LL led the review of severe and moderate acute malnutrition. KW led the obesity prevention review and contributed to the severe and moderate acute malnutrition reviews. CM and SZ oversaw the obesity reviews. BAH assessed the effect of maternal multiple micronutrient supplements, neonatal vitamin A supplementation, and deworming in pregnant women. ZL contributed to reviews of complementary feeding strategies and community platforms. RAS contributed to reviews of micronutrient powders and breastfeeding. AI contributed to the reviews of calcium, balanced protein supplementation in pregnancy, and vitamin A supplementation. All authors and members of the review groups (below) saw successive drafts of the paper and provided input. ZAB finalized the paper and is the overall guarantor.

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Conflicts of interest

REB serves on the Boards of the Micronutrient Initiative, Vitamin Angels, the Child Health and Nutrition Research Initiative, and the Nestlé Creating Shared Value Advisory Committee. VM serves on the Nestlé Creating Shared Value Advisory Committee. The other authors declare that they have no conflicts of interest. As corresponding author Zulfiqar A Bhutta states that he had full access to all data and final responsibility to submit for publication.

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