Nutrition interventions and programs for reducing mortality and morbidity in pregnant and lactating women and women of reproductive age: a systematic review

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List of abbreviations

BCC: behaviour change and communication
CCT: conditional cash transfer
I/IF: iron and/folic acid
ICU: intensive care unit
IEC: information education and communication
LMIC: low and middle income country(ies)
MCH: maternal and child health
MMN: multiple micronutrient supplementation
PLW: pregnant and lactating women
RCT: randomised controlled trial
WRA: women of reproductive age (who are not pregnant)
Executive Summary

Background
The main causes of maternal death are haemorrhage, infection, obstructed labour and complications of unsafe abortion. Nutrition interventions or other interventions aimed at improving women’s nutritional status may work directly to improve maternal survival by preventing or treating disease, infections or nutritional deficiencies; by improving immune status; or by improving health-care seeking behaviour including the use of quality antenatal, intrapartum and postnatal care (where addressing nutrition should be a fundamental component).

Objectives
To assess the effects of nutrition interventions or programs, or those directed at influencing maternal nutritional status (nutrition-sensitive interventions/programs), on maternal mortality and serious maternal morbidities.

Methods
Search methods
We searched a range of databases and other sources (last searched June 2012) using formal search strategies, pearling and cited references features.

Selection criteria
Studies of various designs addressing the effects of the nutrition interventions on maternal, fetal and neonatal outcomes of interest (as well as studies evaluating implementation of these interventions) were considered for inclusion. We also included qualitative studies that addressed reasons for adherence or lack of uptake of these interventions. We did not include studies published prior to 1990. Participants were girls and women of reproductive age (including pregnant and lactating women) from low and middle income (LMICs) countries and marginalised and/or disadvantaged girls and women of reproductive age from high income countries; and health care providers or policy makers from the studies reporting information on implementation, up-scaling or sustainability of programs.

Data collection and analysis
We included both quantitative and qualitative data, and performed a mixed-methods systematic review. We used the principles and methods of the Campbell and Cochrane Collaborations integrated with evaluation of program impact, context (setting, population characteristics, feasibility, sustainability, scalability) and analysis of barriers and enablers, and we assessed the risk of bias in individual studies.

Results
We included 250 studies of various designs, the majority of which were randomised controlled trials (187; 75%). We included 13 qualitative studies. The studies were grouped into four main topics:
1. Micronutrient supplementation
2. Food (macronutrient) supplementation, production and security
3. Behaviour change interventions
4. Poverty reduction interventions
MICRONUTRIENT SUPPLEMENTATION

Maternal mortality: There was no apparent impact on maternal mortality from:
• vitamin A supplementation compared with no vitamin A (9 RCTs; 177,425 women);
• antioxidants (vitamin C and E) compared with placebo (3 RCTs; 1,119 women);
• calcium compared with no calcium (2 RCTs; 8,467 women);
• magnesium supplementation versus no magnesium (2 RCTs; 10,595 women);
• zinc supplementation versus no zinc (1 RCT; 400 women);
• selenium supplementation versus no selenium (1 RCT; 905 women); or
• multiple micronutrient supplementation (MMN) versus iron/folic acid alone (IF) (5 RCTs; 11,113 women).

Maternal death/serious morbidity: Women given calcium were significantly less likely (by 20%) to either die or suffer serious morbidity compared with women who did not receive calcium (4 RCTs, 9,732 women).

Serious maternal morbidities:
• a composite of serious maternal morbidity showed no significant difference between magnesium and no magnesium groups;
• there were significantly fewer cases of eclampsia for magnesium supplementation compared with no magnesium (4 RCTs, 11,087 women). There were significantly fewer cases of pre-eclampsia (severe or any) when calcium supplementation was compared with no calcium (10 RCTs; 11,362 women) although no significant differences were seen for eclampsia. No significant differences in eclampsia, pre-eclampsia or hypertensive disorders were seen for IF, or F, versus vitamin A; IF versus F; antioxidants versus placebo; zinc versus no zinc; selenium versus no selenium; MMN versus vitamin A or IF;
• significantly fewer women were unconscious in the first 24 hours after childbirth if supplemented with IF or MMN rather than vitamin A (1 RCT each); with no significant differences seen between MMN and IF;
• significantly fewer women receiving antioxidants (compared with placebo) had antenatal hospital or ICU admissions (2 RCTs).

Anaemia: Various combinations of IF or MMN versus no IF were effective in preventing or reducing anaemia in pregnant and/or breastfeeding women, although MMN was no more effective than IF alone. Daily IF supplementation was more effective than weekly in preventing anaemia. There were no significant differences in rates of anaemia between vitamin A and placebo; vitamin A as a supplement or as food; vitamin A versus F; calcium versus no calcium; I versus iron+zinc; selenium versus placebo; MMN supplementation versus placebo, or MMN versus IF.

In WRA who were not pregnant, I/IF supplementation had a significant impact (often about a 50% reduction) on controlling anaemia compared with placebo. MMN did not appear to be any more effective than IF. Iron used as fortification (NaFeEDTA) also showed a halving of the risk for anaemia in WRA.

Fetal, neonatal and infant and later child/adult outcomes: No significant impact of I/IF supplementation was seen on fetal and neonatal mortality although low birthweight (LBW) was reduced. MMN showed benefit over IF supplementation for stillbirth, perinatal mortality, LBW and small-for-gestational age (SGA).

Inadequate supply is a major barrier to microsupplementation (especially IF). In WRA, free supply has been shown to be an effective and practical way to implement weekly iron and folic acid supplementation.
A small number of studies have used anthelminths or malaria treatment in conjunction with supplements to optimise anaemia control in mothers, and in women of reproductive age.

**FOOD (MACRONUTRIENT) SUPPLEMENTATION, DIVERSITY AND SECURITY**

Food supplements on their own did not generally show improvement in important maternal outcomes in RCTs included in this review although a lipid/MMN and maize supplement did result in less postpartum weight loss in women with HIV.

Only two studies on food production reported maternal outcomes – one of these studies found that training women to growing orange sweet potato increased their retinol concentrations.

The addition of information, education and communication components (IEC) to food supplementation shows promise, for example, in reducing maternal anaemia.

Women's food insecurity can be associated with anxiety about being able to breastfeed and/or provide for their infants. Food insecurity can be associated with stunting in children.

Maternal child double burden where a stunted child and overweight mother co-exist in the same household is becoming more common, particularly as countries make economic transitions. Some studies have reported associations between women's short stature and obesity, even when women's energy intake has not increased, perhaps indicating a programming effect from early poor nutrition.

**BEHAVIOUR CHANGE**

Pooling of six behaviour change and communication (BCC) RCTs showed no significant differences for maternal mortality. One of these trials had an excess of maternal deaths in the intervention group but most of these women were not exposed to the intervention. When this trial is omitted in a sensitivity analysis, there is a significant effect on reducing maternal deaths, indicating that nutrition-sensitive interventions such as BCC may be able to influence maternal mortality and morbidity.

Though it is difficult to pinpoint which components of these often complex interventions might be responsible for changes, it does seem that targeted and intensive IEC may be of benefit in a number of areas, particularly in increasing women's uptake of supplements and ultimately on outcomes such as anaemia.

**POVERTY REDUCTION**

**Conditional cash transfer**

We found only two studies of conditional cash transfer that specifically addressed maternal nutrition. In one RCT maternal depression and hypertension showed some improvements and use of modern forms of contraception increased. Maternal anaemia was not reported in this trial. In a conditional cash transfer (CCT) study from Mexico, however, women's obesity increased.

**Microcredit**

One study of microcredit found that women's participation increased their haemoglobin concentrations and decreased their food insecurity. Another study found that longer term microcredit program participation was associated with low rates of malnutrition in adult females.

Qualitative studies revealed findings that help to explain women's dietary behaviours including dietary restrictions during pregnancy and fear of obstructed labour from a large
baby. Other factors were being too poor to purchase the right foods, influence of family members, lack of decision-making power and household food allocation which disadvantages women. Quality of antenatal care was also a factor, with one study reporting that antenatal visits were too short to cover nutritional issues. In the absence of ‘frank’ illness, the need for interventions such as vitamin and mineral supplementation may not be fully appreciated.

Discussion and conclusions
Strengths and limitations of the evidence
The comprehensive nature of this review, combining rigorous quantitative methods with implementation impact and qualitative findings is a real strength of this synthesis. However, some of the included studies concentrated on infant outcomes and reported very few maternal outcomes. If studies did not report any maternal outcomes, they were excluded as prespecified in our protocol. As many of these studies would have been able to report relevant maternal outcomes, this indicates that some study investigators have concentrated on infant outcomes and contributed to the relative neglect of maternal issues in this literature. Our results may differ from other systematic reviews on similar topics as we only included studies from low and middle income countries, and studies reporting at least one of our prespecified maternal outcomes.

This review has shown that there are both nutrition and nutrition-sensitive interventions with the potential to substantially reduce maternal mortality and morbidity. Many of these interventions have been directed towards reducing maternal and female anaemia. IF supplementation during pregnancy, and IF supplementation for WRA, particularly adolescents, have received most attention but as noted above, anaemia can be reduced in a number of other ways such as information education and communication strategies.

Although the effectiveness of iron-folic acid supplementation is clear, coverage and sustainability are still unacceptably poor (Victora 2012). The tradeoff between clinical effectiveness and women’s adherence also needs to be considered. A 50% reduction of anaemia risk (seen for iron-folic acid supplementation) can be dramatically diluted by poor uptake of effective prevention or treatment strategies.

Many barriers to implementation and scaling up remain - access and distribution seem to be more important barriers than knowledge and attitudes (e.g. Souganidis 2012) indicating the need to address change at system levels – through health and more widely – and to test and evaluate implementation strategies as rigorously as possible.

Efforts to continue and expand the coverage of iron-folic acid supplements to pregnant women and women of reproductive age must remain the highest of priorities. The supplements need to be free as even low charges seem to be a barrier. Iron-folic fortification, in the form of fish sauce for example, may be very effective in the right contexts. MMN supplements are an alternative to I/IF, particularly for pregnant women and their babies (in the form of reduced neonatal mortality and low birthweight). They may, however, increase birth difficulties for undernourished women. Calcium supplementation, even for lower risk groups, has been too readily dismissed and needs to be considered much more seriously.

Food supplements have not generally shown dramatic effects but few high quality studies were located. Supplementation may need to happen as early as possible in pregnancy, and
some effects may not be evident until the next generation (e.g. reduced stunting in offspring). Interventions that help women to enter pregnancy in a well-nourished state need a higher priority - time of pregnancy recognition may be too late to achieve optimal effects.

Multi-component interventions such as supplementation combined with information, education and communication show promise. It is not clear whether this is due to increased uptake of supplements such as iron and folic acid or whether the effects are operating though nutrition-sensitive mechanisms such as increased health care seeking and increased empowerment. Other nutrition-sensitive interventions such as conditional cash transfers and microcredit should be explored as ways of reducing maternal mortality and morbidity through alleviation of poverty.

**Implications for research**

Trials of nutrition and nutrition sensitive interventions in LMICs are often difficult to conduct and expensive - but not as expensive as introducing unproven programs on a large scale.

Some questions needing further rigorously designed studies include conditional cash transfer, microcredit and incentives. Further replications of behaviour change interventions are required. They need to report nutritional inputs and outcomes, in order to try to distinguish the effects of different components of these complex interventions.

Further trials of food fortification are needed, as are trials comparing multiple micronutrients with iron and folic acid in women of reproductive age who are not pregnant. Optimum MMN compositions (and regimens) need to be determined. Any antenatal intervention studies need to address maternal outcomes as well as perinatal and infant outcomes. This could be achieved by developing sets of core outcomes that could be used by investigators when designing studies. Long term follow-up is needed - this may need to be over several generations. Evidence about the role of programming is now emerging from some of the large food and nutrient supplementation studies and this needs to be further investigated to understand the intergenerational impacts (such as prevention of maternal short stature).
Description of the condition

Although many maternal deaths are preventable, health of mothers has been a much neglected issue especially in low income countries (Cook 2004; DFID 2011a). In 2010, 287,000 mothers died from preventable complications related to pregnancy and childbirth (WHO 2012). Almost all (99%) maternal deaths continue to occur in poorly resourced countries (Lozano 2011), and Sub-Saharan (56%) Africa and Southern Asia (29%) accounts for 85% (245,000) of all maternal deaths (WHO 2012).

Achieving Millennium Development Goal 5 (MDG5) - to reduce maternal mortality by 75% between 1990 and 2015 - will require an annual decline in mortality of 5.5% (Wilmoth 2010). Although methods for estimating maternal deaths are acknowledged to be weak (Wilmoth 2010), recent estimates show maternal deaths to be declining. There has been a one-third drop from 409,100 maternal deaths in 1990 to 273,500 deaths in 2011 (Lozano 2011). This current rate of decline clearly will not be sufficient to meet the overall MDG5 target by 2015 – a mere two years away.

A maternal death is defined as the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration, the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes (WHO 2012). A maternal near-miss case is where a woman nearly died but survived a complication that occurred during pregnancy, childbirth or within 42 days of the termination of the pregnancy (Say 2009). Common life-threatening complications include severe postpartum haemorrhage, severe pre-eclampsia, eclampsia, sepsis/severe systemic infection, and ruptured uterus (WHO 2011a).

Links between maternal mortality and morbidity and nutrition

The main causes of maternal death are haemorrhage, infection, obstructed labour and complications of unsafe abortion (Khan 2006). Many of these causes have a link with nutrition, and may even reach back to before the woman’s own birth (Rush 2000). For example, severe anaemia is linked to deaths from complications such as postpartum haemorrhage; and short stature of mothers (due to their own early undernutrition and undernourishment in their own mothers) may lead to obstructed labour.

In many low income countries, diets are often based on cereals or legumes, with little variety, few animal products and a restricted range of fruits and vegetables (Lapido 2000). Over 40% of the world’s pregnant women have anaemia, with 90% living in Africa or Asia (Sanghvi 2010). Women with anaemia typically have deficiencies of many other nutrients such as iodine, vitamin A, and zinc that can lead to greater morbidity and mortality for both mother and child (Black 2008, Shankar 2009, van den Broek 2003).

Description of the intervention

Many life-threatening or serious events/morbidities in pregnant women may be amenable to nutrition interventions (Christian 2002). Ideally many of these interventions would have a preventive focus e.g. iron supplementation, food fortification or dietary diversification to decrease the incidence of anaemia in women before they become pregnant.
Nutrition is the business of both the health and agriculture sectors, and consequently has not always been high on the list of development priorities (DFID 2011b). Relevant interventions range from large national programs to local programs or interventions targeted at particular groups of women. These interventions can be classified as:

- **Nutrition specific interventions** and programs which include fortification, supplementation (food or nutrients) and behaviour change communications interventions aimed at improving nutrition practices and use of nutrition services. Examples include multiple micronutrient, iron/folate or vitamin A supplementation, iron fortification, dietary diversification, protein or energy supplements and nutrition education interventions.

- **Nutrition sensitive interventions and programs** which include programs that address some of the underlying determinants of nutrition (e.g. poverty, food insecurity, poor health, gender inequity, etc). Such programs include agriculture programs, social safety net programs, health programs, and education programs.

Some potentially effective solutions such as supplementation may seem straightforward to implement, but the reality of achieving health gains is very complex. There are many access, contextual, behavioural and system barriers to implementation of nutritional programs for women of reproductive age. One fundamental cause of pregnant women and other women of reproductive age being undernourished is poverty which leads to a limited ability to purchase and consume sufficient and/or suitable food. Discrimination against women and girls which restricts their access to food (Gittelsohn 1997) and health care, lack of quality antenatal care, and cultural and social beliefs and practices such as ‘eating down’ to avoid giving birth to a large baby, may also contribute to undernourishment (Nag 1994).

**How the intervention might work**

Nutrition interventions or other interventions aimed at improving women’s nutritional status may work directly to improve maternal survival by preventing or treating disease, infections or nutritional deficiencies; by improving immune status; or by improving health-care seeking behaviour including the use of quality antenatal, intrapartum and postnatal care. Early nutritional interventions may influence growth of young women and girls and thus reduce the incidence of obstructed labour, specifically when due to cephalopelvic disproportion. Improved nutrition may lessen fatigue, improve cognition and also improve women’s emotional well being.

Fetal, neonatal and infant survival and health is closely related to maternal nutrition: deficiencies in key micronutrients such as folate can lead to serious congenital birth defects, and intra-uterine growth retardation, which can result from poor maternal nutrition, can lead to low birth weight in newborns (Kramer 1987). Therefore, the prevention and reduction of maternal undernutrition is vital for ensuring fetal, neonatal and infant health and survival.

A long-term aim would be for all women to enter pregnancy in an adequately nourished state. Almost one third of adolescent girls in low-middle income countries are married and conceive within a year of marriage (WHO 2011b); in sub-Saharan Africa, nearly two-thirds of women have their first child before the age of 20 years (Bongaarts 1998). Clearly intergenerational perspectives and activities are required to break the cycles of poverty and malnutrition and ensure that women are well nourished at all stages of life.
It is likely that single nutritional interventions will need to be supported by other strategies in order to be effective on a broad scale. However nutrition programs have not always been well integrated with maternal and child health (MCH) programs and "there is an emerging international consensus that the convergence of nutrition and MCH is essential" (Streatfield 2008, p.238). There are many impediments to the implementation of effective interventions, particularly in poor countries. Some important considerations are access to food (physical, social, economic and cultural access); workforce availability and retention and program transferability and sustainability; weak health systems; and policy barriers (Zehner 2009).

The effectiveness of nutritional interventions at improving nutritional and health status among females of reproductive age and pregnant and lactating women in low and middle income countries (LMICs) depends on several overlapping factors ranging from cost of food and availability of a diversity of foods, to broader factors associated with social and political structures. Underlying chronic conditions can also affect a woman’s ability to adequately absorb nutrients and diseases such as HIV/AIDS and malaria can also lead to serious nutritional deficiencies and severely compromised immune systems. Many interventions (household, community or facility based) have been used to address the poor nutritional status of women, including provision of food directly or improved access to the means to produce food or purchase food such as through voucher systems or cash transfers; macronutrient and micronutrient supplementation; nutritional advice and counselling; and preventing and treating diseases which adversely affect nutritional status. Successful interventions can not only improve a woman’s nutritional status but can also decrease maternal morbidity and mortality. Ideally each woman would enter pregnancy in a well-nourished state but this may be largely dependent on the nutritional status of one’s own mother and whether or not a woman has been adequately nourished throughout her whole life, including during the prenatal months. Evidence suggests that poor nutrition in the womb can lead to long-term, chronic health problems (Barker 1997). An intergenerational perspective is therefore crucial.

There are many pathways to improving women’s nutrition – and many barriers which hinder the ability of nutritional interventions to prevent maternal morbidity and mortality. These are outlined in the logic model/conceptual framework shown below (Anderson 2011) (Figure 1).

The factors that reduce program effectiveness are complex and relate to issues as diverse as distribution failures and lack of adherence (women are unwilling or unable to adhere in the short or longer term). For example, non-nutritional factors such as inflammation, infection, thalassaemia, worm infestation and malaria may lessen the effectiveness of nutritional programs to reduce anaemia (Rah 2012). This illustrates the importance of understanding the processes of implementation and the reasons for sustainability of improved outcomes, which may well differ between contexts.
Figure 1: logic model/conceptual framework
Why it is important to do this review

Every two minutes around the world there is a maternal death – and one woman dies every seven minutes from postpartum haemorrhage, the single most common cause of maternal mortality (Potts 2010). It is therefore important to synthesise the evidence about the effects of interventions to prevent maternal deaths and reduce maternal morbidities. In this review we present the evidence about the potential of nutritional interventions or interventions to change nutritional status in women of reproductive age in making an impact on maternal mortality and morbidity.

Maternal mortality and morbidity are the main focus of the review. Maternal mortality and morbidity are also inextricably linked with stillbirth and neonatal deaths and there have been recent calls for health systems to perform more effectively for both mothers and babies (Pattinson 2011). Pregnancy outcomes are important in their own right, and also as an indicator of maternal health due to problems in accurately measuring maternal mortality prevalence (maternal mortality is usually measured in terms of prevalence rates per 100,000 live births, requiring very large sample data sets for precise estimates) or self-reported morbidity. Pregnancy outcomes are therefore also included in this review.

There are systematic reviews that examine maternal and child health impacts of some nutrition interventions such as iron supplementation (Fernandez-Gaxiola 2011 CR) and magnesium sulphate supplementation (Duley 2003), and agricultural interventions such as home gardens (Masset 2012). Our proposed review is the only one that we are aware of that encompasses such a wide scope in terms of target population and breadth of the various interventions.

This review will synthesise the evidence about which programs are likely to successfully influence maternal nutrition and therefore lead to improvements in maternal mortality and morbidity. It also aims to outline what is necessary to implement effective programs and interventions and will therefore aim to be highly relevant for both policy and practice.
METHODS

Objective:
To assess the effects of nutrition interventions or programs or those directed at influencing maternal nutritional status (nutrition-sensitive interventions/programs) on maternal mortality and serious maternal morbidities.

Criteria for considering studies for this review
Types of studies
Studies of various designs addressing the effects of the nutrition interventions on maternal, fetal and neonatal outcomes of interest as well as studies evaluating implementation of these interventions were considered for inclusion, along with qualitative studies that addressed reasons for adherence or lack of uptake of these interventions.

Quantitative studies
Randomised controlled trials (RCTs) (including cluster trials), other controlled trials, or observational cohort studies without controls, interrupted time series, case-control and cross-sectional studies were included in synthesis of effects.

Qualitative studies
Qualitative studies (reporting surveys or interviews) were included where they reported on primary evidence and address behaviours such as adherence, or report information on barriers and enablers, and/or factors affecting scaling up or sustainability of programs. Relevant qualitative information was also collected from studies providing quantitative data.

Types of participants
- Girls and women in their reproductive age years (including pregnant and lactating women (PLW)) from LMICs (World Bank 2011) and marginalized and/or disadvantaged girls and women of reproductive age (WRA) from high income countries. Clusters of women from regions or villages were eligible.
- Health care providers or policy makers from the studies reporting information on implementation, up-scaling or sustainability of programs.

Types of interventions
To reflect the reality that “solutions to undernutrition must go beyond the provision of specific nutrients” (DFID 2011b), we adapted the typology outlined in this report which makes a distinction between specific nutrition interventions and those which are nutrition-sensitive:
- Nutrition specific interventions and programs which include fortification, supplementation (food or nutrients) and behaviour change communications (BCC) interventions aimed at improving nutrition practices and use of nutrition services;
- Nutrition sensitive interventions and programs (which include programs that address some of the underlying determinants of nutrition (e.g. poverty, food insecurity, poor health, gender inequity, etc). Such programs include agriculture programs, social safety net programs, health programs, and education programs.
Comparators were standard care or no program/intervention or delayed intervention, or different types of nutrition program or package.
Interventions included were those that were delivered during pregnancy and/or lactation, pre-pregnancy or inter-pregnancy.

Types of outcome measures

Primary outcomes

- Maternal death (ideally reported as standardised definition (WHO 2009), but as reported by study investigators if not)
- Causes of maternal death (as reported by study investigators)
- Near-miss maternal cases (ideally reported as standardised definition (WHO 2011a), but as reported by study investigators if not)
- Severe maternal complications (adapted from WHO 2011a; or as reported by study investigators): severe postpartum haemorrhage; severe pre-eclampsia; eclampsia; sepsis or severe systemic infection; ruptured uterus; severe complications of abortion; obstructed labour
- Critical interventions (WHO 2011a) – any of: admission to intensive care unit; interventional radiology; laparotomy (includes hysterectomy, excludes caesarean section); use of blood products.

Secondary outcomes include:

- Anaemia
- Perinatal death (stillbirth and early neonatal death)
- Stillbirth
- Neonatal death
- Infant death
- Complications of pregnancy
- Mode of birth
- Neonatal morbidity
- Intrauterine growth restriction (as defined by study investigators)
- Small for gestational age (as defined by study investigators)
- Preterm birth (< 37 weeks)
- Low birthweight (< 2500g)
- Admission to neonatal intensive care
- Maternal emotional health (distress, anxiety, depression)

Intermediate outcomes include:

- Adherence and uptake of interventions and programs
- Women’s knowledge, attitudes and behaviour, such as breastfeeding
- Women’s nutritional status

Long-term outcomes include:

- Postpartum maternal health
- Infant and child growth (e.g. height-for-age, weight-for-age, weight-for-height)
- Child development and cognition

For qualitative synthesis

- Reasons for adherence and uptake of interventions and programs
- Barriers and enablers related to implementation, up-scaling, transferability and sustainability of the interventions.
- Strategies used in implementation, up-scaling, transferability and sustainability of the interventions.
• Suggestions to optimise implementation, up-scaling, transferability and sustainability of the intervention

Search methods for identification of studies
We searched a range of databases and other sources (last searched June 2012) including: MEDLINE, EMBASE, The Campbell Library, The Cochrane Library, The Reproductive Health Library, Maternal and Infant Care, Web of Science, CAB Abstracts, Scopus, Popline, SCIRUS, Electronic Theses and Dissertations (ETD), Google, WHO Global Health Library World Bank, DFID, Partnership for Maternal, Newborn and Child Health, Healthy Newborn Network, International Food Policy Research Institute (US), Micronutrient Institute and Global Alliance for Improved Nutrition. We used formal search strategies, pearling and the cited references feature in Web of Science and Scopus, as well as following links in Google.

Data extraction and management
Data from the included studies were independently coded and extracted by at least two review authors using predefined data extraction forms. If there were two or more papers describing the same study, they were combined and coded as a single study. A third review author was consulted in the event of any disagreements, and consensus was sought. We attempted to contact authors of the original reports to obtain further details where required.

For intervention studies, we conducted random-effects meta-analyses with an inverse variance weight when it was sensible to combine studies (clinical or statistical heterogeneity was not of high concern). Results were presented as the average treatment effect - risk ratios and mean difference with 95% confidence intervals were computed for dichotomous and continuous outcomes, respectively.

The adjusted effect sizes were also collected for observational studies if possible. For qualitative findings, we extracted all themes or qualitative information identified in the primary studies and relevant to the research questions. Extraction of qualitative data was driven by a theoretical framework of behaviour change and motivation (Michie 2011).

Assessment of risk of bias in included studies
Two review authors independently assessed the quality of studies and risk of bias for each study. The quality of the quantitative studies and qualitative studies were separately assessed using different approaches.

Quantitative controlled studies
We used the criteria recommended by the Cochrane Effective Practice and Organization of Care Group (EPOC 2009) to assess risk of bias for controlled studies, including randomised controlled trials and non-randomised studies that have a well-defined control group; and the methods outlined by NICE (NICE 2009) for other study designs (case control and cohort studies). The risk of potential bias was assessed as low, high or unclear for each component.

Qualitative studies (or qualitative data reported within quantitative studies)
Two review authors independently used core criteria adapted from the Critical Appraisal Skills Programme (CASP) checklist for appraising qualitative studies or qualitative content.
within quantitative studies (www.casp-uk.net). Any disagreements were resolved by discussion or by involving a third assessor. These criteria are as follows:

1. Is the aim of the research clearly stated?
2. Is there a clear link to relevant literature/theoretical framework?
3. Does the paper include a clear description of:
   • the context?
   • the sample selection?
   • methods for data collection and recording?
   • methods of analysis?
RESULTS

We included 250 studies of various designs, the majority of which were randomised controlled trials (187; 75%). We included 13 qualitative studies. The studies were grouped into four main topics:

- Micronutrient supplementation (190 studies)
- Food (macronutrient) supplementation, production and security (27 studies)
- Behaviour change interventions (22 studies)
- Poverty reduction interventions (11 studies)

The uneven representation of studies by topic was also reflected in the numbers of women taking part in these studies – see Figure 2. For example, although only 22 studies in the behavior change category were eligible for inclusion, these studies included a total of nearly 150,000 women, largely due to a number of large cluster RCTs addressing behavior change interventions.

Over 50 studies reaching full assessment stage were subsequently excluded from this review, most commonly due to no maternal outcomes being reported.

Risk of bias (study quality) and reporting bias

Risk of bias in individual studies ranged from very low (e.g. very large community trials often with factorial or cluster designs) to studies with high risks of bias. The main concerns at an individual study level were failure to report how randomisation sequences were generated and how allocations were concealed in RCTs or how study samples were selected in other comparative studies. Many study interventions were not feasible to blind. Other common sources of bias were high attrition rates and failure to report, or fully report, key outcomes (selective reporting bias). Qualitative studies in this review appeared to be of high to reasonable quality, with the most common deficit being a failure to provide a clear link to a theoretical framework.

Reporting bias at a between study level could only be assessed for three comparisons. Contour funnel plots for these comparisons indicate that between study reporting bias (such as important levels of missing unpublished studies) is not evident.
Figure 2: Number of women taking part in the included studies by topic
Green circles denote interventions/strategies shown to work
Figure 3: Maternal mortality and morbidity

1: MICRONUTRIENT SUPPLEMENTATION

1.1 Vitamin A

1.1a Pregnant and lactating women

We found 13 RCTs (Canfield 2001 RCT; Coutsoudis 1999 RCT; Cox 2005 RCT; ObaapaVitA 2010 RCT(c); Radhika 2003 RCT; Suharno 1993 RCT; Stoltzfus 1993 RCT; Tanumihardjo 2002 RCT; West 1999 RCT (NNIPS-2); West 2011 RCT (Ji VitA); WHO/CHD IVASSG RCT; Zibuvita RCT 2001; ZVITAMBO RCT) (including 185,314 pregnant and lactating women) comparing vitamin A supplementation with placebo.

Maternal mortality

Vitamin A supplementation compared with placebo or no treatment had no significant impact on reducing maternal mortality (risk ratio (RR) 0.94 95% confidence interval (CI) 0.80 to 1.10 (6 trials, n = 175,425)) – see Analysis 1. This was also the case when vitamin A+IF was compared with IF alone (RR 0.98 95% CI 0.73 to 1.31 (3 trials, n = 1803) – see Analysis 2. We did not detect any subgroup differences between general populations of pregnant women and those with HIV, nor between pregnant women and those women who had given birth.
Analysis 1: Maternal mortality – vitamin A versus placebo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>vitamin A</th>
<th>no vitamin A</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>IV, Fixed</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coubesaries 1999 RCT</td>
<td>-0.71513</td>
<td>1.2225</td>
<td>368</td>
<td>368</td>
<td>49</td>
<td>0.4%</td>
<td>0.49 [0.04, 5.37]</td>
<td></td>
</tr>
<tr>
<td>Cox 2005 RCT</td>
<td>1.1368</td>
<td>1.6307</td>
<td>40</td>
<td>50</td>
<td>312</td>
<td>0.2%</td>
<td>3.12 [0.13, 74.62]</td>
<td></td>
</tr>
<tr>
<td>Gabapamit 2010 RCT(s)</td>
<td>-0.0883</td>
<td>0.1239</td>
<td>39801</td>
<td>39234</td>
<td>3621</td>
<td>7.8%</td>
<td>0.92 [0.72, 1.17]</td>
<td></td>
</tr>
<tr>
<td>West 1999 RCT (NNIPS-2)</td>
<td>-0.5094</td>
<td>0.2901</td>
<td>7747</td>
<td>3621</td>
<td>3621</td>
<td>7.8%</td>
<td>0.69 [0.34, 1.40]</td>
<td></td>
</tr>
<tr>
<td>West 1999 RCT (INRRT-2)</td>
<td>-0.6676</td>
<td>0.3078</td>
<td>7201</td>
<td>3621</td>
<td>3621</td>
<td>7.8%</td>
<td>0.62 [0.36, 0.92]</td>
<td></td>
</tr>
<tr>
<td>West 2011 RCT (Ji VitA)</td>
<td>0.1004</td>
<td>0.2692</td>
<td>19998</td>
<td>9931</td>
<td>9931</td>
<td>7.7%</td>
<td>1.30 [0.58, 2.91]</td>
<td></td>
</tr>
<tr>
<td>West 2011 RCT (Ji VitA)</td>
<td>0.1401</td>
<td>0.2603</td>
<td>19806</td>
<td>9631</td>
<td>9631</td>
<td>7.7%</td>
<td>1.15 [0.85, 1.53]</td>
<td></td>
</tr>
<tr>
<td>ZITAMBO RCT</td>
<td>0.1263</td>
<td>0.4092</td>
<td>4002</td>
<td>4780</td>
<td>4780</td>
<td>7.0%</td>
<td>0.94 [0.80, 1.10]</td>
<td></td>
</tr>
<tr>
<td>ZITAMBO RCT</td>
<td>0.1161</td>
<td>0.1612</td>
<td>2149</td>
<td>2137</td>
<td>2137</td>
<td>10.0%</td>
<td>1.02 [0.82, 1.24]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 101720 73705 100.0% 0.94 [0.80, 1.10]

Heterogeneity: Chi² = 10.08, df = 3 (P = 0.28); P = 21%
Test for overall effect Z = 0.79 (P = 0.44)

Analysis 2: Maternal mortality – vitamin A+IF versus IF

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>vitamin A+IF</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Risk Ratio</th>
<th>IV, Fixed</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayen 2007 RCT</td>
<td>2</td>
<td>282</td>
<td>4</td>
<td>282</td>
<td>5.7%</td>
<td>0.50 [0.20, 2.71]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fawzi 1995 RCT</td>
<td>66</td>
<td>267</td>
<td>65</td>
<td>272</td>
<td>91.5%</td>
<td>1.03 [0.77, 1.39]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>van den Broek 2006 RCT</td>
<td>2</td>
<td>468</td>
<td>1</td>
<td>232</td>
<td>2.8%</td>
<td>0.17 [0.01, 4.09]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 66 70

Heterogeneity: Chi² = 1.93, df = 2 (P = 0.38); P = 0%
Test for overall effect Z = 0.14 (P = 0.89)

Maternal morbidities

Vitamin A supplementation:
- reduced maternal night blindness by an average 23% in the two West trials (West 1999 RCT (NNIPS-2); West 2011 RCT (Ji VitA)): RR 0.77 95% CI 0.64 to 0.92, random effects, n = 69,519);
- reduced bacterial vaginosis by 38% in one trial (West 2011 RCT (Ji VitA)): RR 0.62 95% CI 0.52 to 0.73, n = 1,018);
- reduced puerperal fever by 79% in one small trial (Zibuvita RCT 2001) (RR 0.21; 95% CI 0.06 to 0.70, n = 270);
- increased BMI after birth (one trial of 191 women with HIV).

Nutritional status outcomes

Compared with placebo, various forms of vitamin A showed overall significant increases in women’s haemoglobin concentrations and improvements in breastmilk composition in some trials. No significant differences were seen for other measures of vitamin A deficiency/status.

Infant outcomes

No significant differences between vitamin A and placebo were seen for low birthweight, stillbirth, or neonatal, perinatal or infant death.

Other vitamin A comparisons
- Three trials of high versus low dose vitamin A (Darboe 2007 RCT; Haskell 2005 RCT; Idindili 2007 RCT - including 1,108 pregnant women) showed very few differences in outcomes.
• Comparisons of vitamin A supplementation versus consumption of vitamin A rich/fortified food showed few differences (Haskell 2005 RCT; Ncube 2001 RCT; de Pee 1995).
• Vitamin A+IF was more effective than IF alone for outcomes such as anaemia (in the Suharno 1993 RCT) but not for most other outcomes (Muslimatun 2001 RCT; Roy 1997 RCT).

1.1b Women of reproductive age
One trial of vitamin A versus placebo reported a reduced risk of anaemia in 138 WRA (Ahmed 2001 RCT) and another trial reported no impact of vitamin A on vaginal HIV-1 DNA in 400 women who were not pregnant (Baeten 2002 RCT).

1.2 Iron or iron/folic acid (I/IF) supplementation/fortification

1.2a Pregnant and lactating women
I/IF versus placebo
Eleven trials (Cogswell 2003 RCT; Haidar 2003 RCT; Han 2011 RCT; Menendez 1994 RCT; Preziosi 1997 RCT; Siega-Riz 2006 RCT; Suharno 1993 RCT; Tanumihardjo 2002 RCT; Torlesse 2001 RCT; Ziaei 2007 RCT; Ziaei 2008 RCT) (including 2,534 pregnant women and 207 lactating women) compared iron or iron-folic acid with placebo.

Maternal morbidities
Compared with placebo, I/IF supplementation reduced anaemia by 36% in pregnant and lactating women (RR 0.64 95% CI 0.44 to 0.93; 5 trials, n = 657). There was no apparent impact on other morbidities and associated outcomes such as postpartum haemorrhage, caesarean section and malarial infection.

Nutritional status outcomes
Most markers (e.g. haemoglobin and low ferritin) showed improvements in nutritional status with I/IF supplements.

Infant outcomes
Compared with placebo, I/IF supplements showed reductions in low birthweight, but this was not the case for most of the other baby outcomes.

Other I/IF comparisons
• In three trials with 259 pregnant women (Bhatla 2009 RCT; Han 2011 RCT; Saha 2007 RCT), few differences were seen between different formulations of iron. Although more adverse effects were reported for standard iron formulations, this did not appear to impact on women's adherence.
• Daily I/IF was significantly more effective than weekly or intermittent supplementation in reducing rates of anaemia (RR 0.66 95% CI 0.44 to 0.99, random effects, n = 810, 6 trials – Casanueva 2006 RCT; Chew 1996a RCT; Chew 1996b RCT; Liu 1996 RCT; Mukhopadhyay 2004 RCT; Ridwan 1996 RCT(c). Although there were no significant differences seen in four trials for adverse effects, adherence was significantly higher in the weekly group compared with the daily group.
• I/IF+vitamin A (with or without zinc) was superior to vitamin A alone in regard to anaemia control in two trials (Christian 2003 RCT(c); Suharno 1993 RCT) and for fewer women with puerperal infection and endometritis (Christian 2003 RCT(c)).
• In one trial of 221 pregnant women (Seck 2009 RCT(c)), rates of anaemia did not differ significantly between free distribution or purchase of IF, although haemoglobin concentrations and adherence both showed significant improvement.

IF implementation/impact evaluation (PLW)
In a large scale 10-year micronutrient and nutrition program (MICAH) in Ethiopia, Ghana, Malawi and Tanzania, daily iron supplementation coverage for pregnant women increased, and anaemia decreased, in most countries over most periods (Berti 2010). Universal coverage for pregnant women has led to anaemia to be decreased to 15% in this population in Thailand (WHO SEA 2011).

1.2b Women of reproductive age
In WRA who were not pregnant, daily I/IF versus placebo resulted in a halving of anaemia - a significant 47% reduction (RR 0.53 95% CI 0.37 to 0.75, random effects, n = 2,356, 5 trials (Agarwal 2003 RCT(c); Angeles-Agdeppa 1997 RCT; Jayatissa 1999 RCT(c); Kianfar 2000 RCT; Shah 2002 RCT)).

I/IF fortification (e.g. NAFeEDTA) versus placebo significantly reduced anaemia in WRA (RR 0.61 95% CI 0.45 to 0.81, n = 1846, 5 trials - (Chen 2005 RCT(c); Haas 2005 RCT; Hotz 2008 RCT; Thuy 2003 RCT; Thuy 2005 RCT(c)).

IF implementation/impact evaluation (WRA)
In a large scale 10-year micronutrient and nutrition program (MICAH) in Ethiopia, Ghana, Malawi and Tanzania, iron supplementation was associated with a decrease in anaemia for adolescent women in most of the countries (Berti 2010). In a study of the South-East Asian countries of Bangladesh, Bhutan, DPR Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste, WHO could only identify I/IF supplementation programs in India and Myanmar (WHO SEA 2011).

A recent WHO analysis of 10 large-scale programs covering over 6 million women and girls across six countries suggests that free supply of weekly iron and folic acid supplements (WIFS) for socio-economically disadvantaged WRA (and social marketing for WRA who have the resources to purchase low-cost iron and folic acid supplements) in LMICs are effective and practical implementation strategies (WHO 2011).

1.3 Antioxidants
1.3a Pregnant and lactating women
Antioxidants versus placebo
We found six trials (Banerjee 2009 RCT; Gulmezoglu 1997 RCT; Kalpdev 2011 RCT; Sharma 2003 RCT; Spinnato 2007 RCT; Villar 2009 RCT) (including 2,620 pregnant women) that compared antioxidants with placebo.
Maternal mortality: Three trials reported maternal mortality, finding no significant differences between antioxidants and placebo (RR 0.33 95% CI 0.01 to 8.08, n=2,021 (Gulmezoglu 1997 RCT; Spinnato 2007 RCT; Villar 2009 RCT)).

Maternal morbidities: No significant differences between antioxidants and placebo were seen for eclampsia, pre-eclampsia or other serious morbidities. However in two trials (Kalpdev 2011 RCT; Villar 2009 RCT), need to be admitted to hospital was significantly less likely for antioxidant groups than for placebo (RR 0.31 95% CI: 0.11 to 0.87, n = 1399).

Infant outcomes: This group of outcomes showed mixed results.

1.4 VITAMIN C
We found one trial including 384 pregnant women that compared vitamin C with no vitamin C supplementation (Hans 2010 RCT). In this trial, vitamin C compared with no vitamin C significantly reduced the rate of hospitalisation of pregnant women (RR 0.80 95% CI 0.69 to 0.93).

1.5 VITAMIN D
In a non-randomised follow-up study of 884 pregnant women with HIV enrolled in the Fawzi 1998 RCT, Mehta 2010 reported that women with low vitamin D status were more likely to develop severe anaemia, though no significant differences were seen for anaemia overall. Combined death and disease progression (RR 1.23 95% CI 1.04 to 1.45) were also more likely in women with low vitamin D.

1.6 CALCIUM
1.6a Pregnant and lactating women
Calcium versus no calcium
We found 11 trials (Belizan 1991 RCT; Jarjou 2006 RCT; Kumar 2009 RCT; Lopez-Jaramillo 1990 RCT; Lopez-Jaramillo 1997 RCT; Niromanesh 2001 RCT; Purwar 1996 RCT; Sanchez-Ramos 1994 RCT; Taherian 2002 RCT; Villar 2006 RCT; Wanchu 2001 RCT) (including 11,556 pregnant women) that compared calcium with no calcium supplementation.

Maternal mortality and mortality/serious morbidity: There was no significant impact of calcium supplementation versus placebo/no intervention on maternal mortality (RR 0.20 95% CI 0.03 to 1.16, n = 8,467) (Jarjou 2006 RCT; Villar 2006 RCT) – see analysis 3. However combined mortality or serious morbidity was significantly lower with calcium compared with no calcium (RR 0.80; 95% CI: 0.65 to 0.97, n = 9732) (Belizan 1991 RCT; Kumar 2009 RCT; Purwar 1996 RCT; Villar 2006 RCT) – see analysis 4).

Analysis 3: Maternal mortality: Calcium versus no calcium

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Calcium supplement</th>
<th>no calcium supplement</th>
<th>Risk Ratio M-H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jarjou 2006 RCT</td>
<td>0 77</td>
<td>1</td>
<td>0.34 [0.01, 8.16]</td>
</tr>
<tr>
<td>Villar 2006 RCT</td>
<td>1 4151</td>
<td>8</td>
<td>0.17 [0.02, 1.30]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>4228</td>
<td>4239</td>
<td>0.20 [0.03, 1.16]</td>
</tr>
<tr>
<td>Total events</td>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Ch² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 1.80 (P = 0.07)
Analysis 4: Maternal mortality/serious morbidity: Calcium versus no calcium

Pre-eclampsia/eclampsia: There was significantly reduced risk of any pre-eclampsia for calcium supplementation versus no calcium (RR 0.45 95% CI: 0.27 to 0.76, n = 11,362) (Belizan 1991 RCT; Kumar 2009 RCT; Lopez-Jaramillo 1990 RCT; Lopez-Jaramillo 1997 RCT; Niromanesh 2001 RCT; Purwar 1996 RCT; Sanchez-Ramos 1994 RCT; Taherian 2002 RCT; Villar 2006 RCT; Wanchu 2001 RCT) although no significant difference was seen for eclampsia.

Infant outcomes: While perinatal mortality did not differ between groups, there were significantly fewer preterm births in the calcium versus the no calcium group (RR 0.88 95% CI 0.78 to 0.99, n = 980) (Belizan 1991 RCT; Kumar 2009 RCT; Lopez-Jaramillo 1990 RCT; Lopez-Jaramillo 1997 RCT; Purwar 1996 RCT; Sanchez-Ramos 1994 RCT; Villar 2006 RCT; Wanchu 2001 RCT).

1.7 MAGNESIUM

Four trials (Chen 1995 RCT; Coetzee 1998 RCT; MAGPIE RCT; Moodley 1994 RCT) (including 11,018 pregnant women) compared magnesium with placebo.

Maternal mortality: In two trials (Coetzee 1998 RCT; MAGPIE RCT), no significant difference in maternal mortality was seen between the magnesium and no magnesium groups (RR 0.56 95% CI 0.27 to 1.13, n = 10,595).

Eclampsia: The rate of eclampsia was significantly reduced with magnesium versus no magnesium (RR 0.40 95% CI 0.28 to 0.56, n = 11,807) (Chen 1995 RCT; Coetzee 1998 RCT; MAGPIE RCT; Moodley 1994 RCT).

1.8 ZINC

1.8a Pregnant and lactating women

Eight trials (Castillo-Duran 2001 RCT; Caulfield 1999 RCT; Danesh 2010 RCT; Dijkhuizen 2004 RCT; Fawzi 2005 RCT; Mahmoudian 2005 RCT; Osendarp 2000 RCT; Xie 2001 RCT) (including 3,196 pregnant women) compared zinc with placebo.

None of the maternal mortality or morbidity outcomes, nor any of the infant outcomes showed any significant impact of zinc supplementation.
1.9 SELENIUM

_Pregnant and lactating women_

Two trials (Kupka 2008 RCT; Tara 2010 RCT) (including 1,079 pregnant women) compared selenium with placebo, finding no significant differences for maternal mortality or morbidity or for most infant outcomes. However in Kupka 2008, the incidence of low birthweight and term birth was significantly reduced when selenium was compared with placebo (RR 0.56 95% CI 0.32 to 0.99, n = 699).

1.10 MULTIPLE MICRONUTRIENT (MMN) SUPPLEMENTATION

1.10a Pregnant and lactating women

In two trials (Brough 2010 RCT; Makola 2003 RCT - including 570 pregnant women) comparing a MMN fortified supplement or beverage with placebo, maternal anaemia was significantly reduced in the MMN group (RR 0.70 95% CI 0.58 to 0.85). Infant outcomes were not significantly different between MMN and placebo groups. In a qualitative analysis of Makola 2003 RCT, Benjamin and Ash found that the micronutrient-supplemented beverage was highly acceptable to women and their families, although they caution that in any scale up of the intervention, it will be important to ensure that those in most need gain access, e.g. by improving supply streams and by providing the fortified product free of charge.

In one trial of a double dose of MMN versus a single dose (Kaestel 2005 RCT), miscarriage rates were very significantly lower in the double MMN dose group (RR 6.52 95% CI 1.48 to 28.78, n = 1392).

In one trial (Christian 2003 RCT(c)) - including 2075 pregnant women) comparing multiple micronutrient with vitamin A supplementation alone, anaemia was significantly reduced with MMN, and women’s adherence was increased.

Eleven trials (Bhutta 2009 RCT(c); Fawzi 1998 RCT; Fawzi 2007 RCT; Friis 2004 RCT; Kaestel 2005 RCT; MISAME MMN RCT; Osrin 2005 RCT; Rumiris 2006 RCT; SUMMIT RCT(c); Sunawang 2009 RCT(c); Zeng 2008 RCT(c)) (including 52,971 pregnant women) compared multiple micronutrient supplementation with iron-folic acid supplementation.

- There were no significant differences between MMN and IF for _maternal mortality_ (RR 0.87 95% CI 0.57 to 1.33, n = 35,800, 4 trials)
- No significant differences were seen between MMN and IF for _maternal anaemia_ (RR 0.95 95% CI 0.89 to 1.02, n = 9862, 8 trials)
- Infant outcomes showed few differences between MMN and IF, although _low birthweight_ showed a 16% reduction overall for MMN compared with IF (RR 0.84 95% CI 0.77 to 0.90, n = 24,629; 8 trials)
- In a follow-up at 54 months of children born to mothers who took part in the MINIMat RCT, MMN resulted in significantly more _stunting_ than in male children of women who received iron-folic acid (60 mg iron), with no significant differences for girls. The reverse was shown in MISAME MMN RCT where, in the first year of life, infants in the MMN group were significantly less likely to be stunted than infants in the IF group (hazard ratio 0.73 95% CI 0.60 to 0.87) although no significant differences were seen for underweight, wasting and death in these infants.

1.10b Women of reproductive age
In one trial (Hyder 2007 RCT including 989 adolescent girls) anaemia was significantly reduced - by almost half - with MMN supplementation versus placebo (RR 0.59 95% CI 0.47 to 0.74, n = 989).

2. FOOD SUPPLEMENTS, PRODUCTION AND SECURITY

2a: Pregnant and lactating women

Four trials (Alam 2010 RCT(c); BAN RCT; Kindra 2011 RCT; Wijaya-Erhardt 2011 RCT) compared food supplements with no supplement. In one trial, extra tempeh, meat and fruit failed to significantly reduce rates of anaemia in pregnant women (RR 1.00 95% CI 0.52 to 1.92, n = 213). No significant differences were seen between the supplemented and unsupplemented groups in two trials for total gestational weight gain (MD 0.62 kg 95% CI -0.46 to 1.69, random effects, n = 3005).

In one trial of 107 women (Creed-Kanashiro 2000 RCT) food supplementation + IEC resulted in significantly lower rates of anaemia than no intervention (RR 0.32 95% CI 0.15 to 0.69).

In one study of 4436 women (MINIMat RCT), there was no significant difference between early and late food supplementation for maternal mortality (RR 3.00 95% CI 0.12 to 73.67). No significant differences in gestational weight gain were seen when an antenatal protein-energy supplement was compared with postnatal supplementation in a cluster RCT from Gambia (Ceesay 1997 RCT(c)) - MD 0.58 kg/week 95% CI -0.03 to 1.19, n = 1876). In one trial, stillbirth showed a significant reduction with antenatal versus postnatal supplementation (RR 0.44 95% CI 0.21 to 0.92, n = 2082, but this was not the case in the trial comparing early versus late supplementation during pregnancy (RR 0.94 95% CI 0.63 to 1.39, n = 4022).

In the MINIMat RCT, early food supplementation, compared with later invitation to access supplements, significantly reduced stunting up to 54 months for boys but not for girls.

Longer term outcomes for 1,270 adolescent offspring (11 to 17 years of age) have also been reported for Ceesay 1997 RCT(c), showing no significant differences in for body composition, blood pressure or cardiovascular risk factors. However analyses adjusted for clustering and other factors such as age and maternal height did show a small but significant height difference for girls - those born to women who had antenatal protein-energy supplementation were of shorter stature.

In one recent trial (Vadillo-Ortega 2011 RCT) that compared food supplements containing antioxidants with or without L-arginine with food supplements alone, beneficial effects such as reduced eclampsia/pre-eclampsia and preterm birth were seen. These effects are likely due to L-arginine.

Children exposed antenatally or as children (or both) to either atole (a high protein-energy supplement) or fresco (a supplement without protein) in the INCAP RCT were assessed when they were 11 to 27 years old. This intervention showed greater stature and fat-free mass, particularly for females, and enhanced intellectual performance. An intergeneration follow-up study was conducted in offspring of 401 Guatemalan women - 35 years after these women had been recruited as infants into the original study. These 791 offspring
(aged 0 to 12 years) had higher birth weights and were taller if their mothers had been in the atole group.

In 2000, the maternal mortality rate in Bhutanese refugee camps was 68.9 per 100,000 live births compared with an overall national figure of 475 per 100,000 live births for Nepal – a differential attributed to the quantity of food supplied and its micronutrient content along with antenatal care, water and sanitation, as well a lower rate of early teenage births (Shrimpton 2009).

In a non-randomised study assessing the impact of a sorghum production and distribution system (Schmid 2007), some components of women's diets (such as energy and carbohydrate intakes) showed improvement.

In a cross-sectional study from Ghana of 70 lactating women (Addo 2011), significant associations were seen between food insecurity and energy intake, and between food insecurity and stress; and in a cohort of 1343 children followed to 24 months from the MINIMat RCT in Bangladesh, 'relative' food security was associated with lower proportions of underweight and stunted children.

In a large scale RCT in Mozambique, a one year training program in how to grow orange sweet potato significantly increased women's consumption of this food (97 g/day mean; 393 women), leading to an average increase of 492 µg in their retinol activity equivalents (Hotz 2012 RCT(c)). In another non-randomised study of local food production (Olney 2009), no significant impacts on women's dietary intake or quality were noted. This was also the case for episodes of diarrhoea for women; women's haemoglobin concentrations; and their BMI.

A number of studies are documenting the emerging phenomenon of maternal and child double burden (MCDB) where paradoxically a stunted child and overweight mother co-exist in the same household (Jehn 2009; Oddo 2012). In a data set survey of 18 countries, MCDB prevalence ranged from 0.3% in Ethiopia to 5.3% in Guatemala (Jehn 2009). In a cross-sectional study, Saibul 2009 reported that there was a 26% MCDB prevalence in 182 indigenous households in the Selangor region of Malaysia. Recently Oddo 2012 has reported MCDB rates of 11% of households in rural Indonesia and 4% in rural Bangladesh. In this cross-sectional study, maternal short stature and older age were predictive of MCDB, whereas higher levels of maternal education were protective against MCDB in Indonesia, but not in Bangladesh. MCDB appears to be increasing, particularly in countries undergoing economic and nutrition transitions (where rising incomes in LMIC produce "changes in dietary and activity patterns that increase the risk of overweight and obesity while many of the risk factors for under-nutrition remain" (Jehn 2009)).

2b: Women of reproductive age
The impact of the Indian nutrition program, ICDS, on rural adolescent girls is reported as being less than optimal. In a cross-sectional survey of 209 girls, Malhotra and Passi 2007 (ICDS) have shown despite the program, the girls had inadequate intakes of energy and nutrients, with a high incidence of under-nutrition. They note that some ICDS adolescent interventions such as iron-folic acid supplementation and food supplementations are being implemented incompletely.
3. BEHAVIOUR CHANGE INTERVENTIONS

Ten studies (Adhikari 2009 RCT; Azad 2010 RCT(c); Belizan 1995 RCT; Bhutta 2008 RCT(c); Bhutta 2011 RCT(c); Briley 2002 RCT; Kumar 2008 RCT(c); Manandhar 2004 RCT(c); Projahnmo-2 Mirzapur RCT; Tripathy 2010 RCTc (Ekjut)) (including 137,458 pregnant women and women of reproductive age) reported the impact of behaviour change communication on maternal outcomes.

**Maternal mortality:** No significant differences in maternal mortality were seen in various behaviour change trials (e.g. community participation and mobilisation) - (RR 0.85 95% CI 0.56 to 1.30, n =~100,000, 6 trials – see analysis 5). Omitting Azad 2010 RCT(c) (where 46 of the 55 maternal deaths in the intervention clusters were to women who had no contact with the women’s groups) indicates an overall mortality advantage with community interventions (RR 0.75 95% CI 0.56 to 1.00).

### Analysis 5 – Maternal mortality – BCC

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>BCC Total</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azad 2010 RCT(c)</td>
<td>-0.642</td>
<td>0.288</td>
<td>17514</td>
<td>16599</td>
<td>0.0%</td>
<td>1.60</td>
<td>[1.08, 2.33]</td>
</tr>
<tr>
<td>Manandhar 2004 RCT(c)</td>
<td>-1.5126</td>
<td>0.7741</td>
<td>3038</td>
<td>3344</td>
<td>3.5%</td>
<td>0.22</td>
<td>[0.05, 1.10]</td>
</tr>
<tr>
<td>Tripathy 2010 RCTc (Ekjut)</td>
<td>-0.2327</td>
<td>0.1934</td>
<td>8062</td>
<td>8125</td>
<td>58.3%</td>
<td>0.78</td>
<td>[0.54, 1.11]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>11688</td>
<td>11489</td>
<td>62.0%</td>
<td>0.52</td>
<td>[0.16, 1.59]</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.50, Ch^2 = 2.57, df = 1 (P = 0.11), P = 51%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.09 (P = 0.28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Analysis 6 – Maternal mortality – Community mobilisation and home visits

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>BCC Total</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhutta 2008 RCT(c)</td>
<td>-0.5215</td>
<td>0.9117</td>
<td>28020</td>
<td>24195</td>
<td>2010</td>
<td>2.8%</td>
<td>[0.12, 0.55]</td>
</tr>
<tr>
<td>Bhutta 2011 RCT(c)</td>
<td>-0.2154</td>
<td>0.2789</td>
<td>14152</td>
<td>12345</td>
<td>25.8%</td>
<td>0.61</td>
<td>[0.47, 1.11]</td>
</tr>
<tr>
<td>Kumar 2008 RCT(c)</td>
<td>-0.3711</td>
<td>0.5389</td>
<td>2600</td>
<td>2653</td>
<td>7.5%</td>
<td>0.69</td>
<td>[0.44, 1.16]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>19618</td>
<td>16518</td>
<td>38.0%</td>
<td>0.67</td>
<td>[0.46, 1.02]</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00, Ch^2 = 0.13, df = 2 (P = 0.83), P = 88%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.12 (P = 0.26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total (95% CI)</th>
<th>31582</th>
<th>28087</th>
<th>100.0%</th>
<th>0.75 [0.56, 1.00]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterogeneity: Tau^2 = 0.00, Ch^2 = 2.74, df = 4 (P = 0.60), P = 5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.96 (P = 0.05)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Two nonrandomised studies also give some indication of a possible impact on maternal mortality. Foord 1995 assessed the impact of training mobile services staff for antenatal interventions including nutrition and Faveau 1991 compared a community midwife program with a neighbouring area without community midwives in rural Bangladesh. Nutritional components of the midwife program included vitamin A and iron supplementation and nutritional education. When these two studies were pooled, there was a large reduction in maternal mortality (RR 0.32 95% CI 0.14 to 0.72) – see analysis 6. The overall high risk of bias inherent in these study designs needs to be considered when interpreting these results.
Analysis 6 maternal mortality – BCC (nonrandomised studies)

In one trial of 284 women, the risk of maternal anaemia was significantly reduced with an education and pill count (RR 0.46 95% CI 0.26 to 0.82) or an education intervention alone (RR 0.47 95% 0.27 to 0.84) but not with pill count alone (RR 0.93 95% CI 0.60 to 1.43) when compared with control.

Infant outcomes: There were significantly fewer neonatal deaths in the BCC groups compared with control (RR 0.83 95% CI 0.72 to 0.96, 9 trials, n = 132,018) – see analysis 7). None of the other infant outcomes showed significant differences between BCC and controls. An economic assessment of the Manandhar 2004 RCT(c) estimated the incremental cost of each year of a neonatal life saved to be $179 to $251 (US dollars).

Analysis 7: BCC – neonatal deaths

POVERTY REDUCTION

a) Conditional cash transfers

- In the OPORTUNIDADES RCT(c) cluster RCT, pregnant and lactating women (and other family members) were asked to take nutritional supplements (whole milk plus vitamins and minerals in the form of a powder) as well as participate in other forms of preventive health care and educational activities. Doubling the cash transfer to
households had some negative effects such as higher rates of being overweight or obese, and higher rates of hypertension in women (n = 2639). After 18 months or more in the program, no significant differences were seen in numbers of women who were overweight or obese. Significantly fewer women were hypertensive.

- Women exposed to the intervention in the OPORTUNIDADES RCT(c) had lower depressive symptom scores; were more likely to use modern forms of contraception and were less likely to give birth to a low birthweight baby.

- When analysed by amount of cash transferred (adjusted analyses), 24-72 month old children from households with doubled cash transfers had significantly increased physical growth and health (including fewer children with stunting), significantly higher haemoglobin concentrations, significantly better motor endurance (but not motor skill), and significantly increased cognitive and language development. The children in higher cash transfer households were also significantly less likely to be overweight (Fernald 2008; OPORTUNIDADES RCT(c)).

- In Colombia's conditional transfer program, comparison over time (2001 to 2006), and with control areas, suggests that women in the program (pregnant and lactating women were excluded) had more rapidly increasing BMI and rates of overweight and obesity compared with women not in the program (Attanasio 2005).

- Adato 2011 describes attitudes and actions of women from Mexico, El Salvador, Nicaragua and Turkey who were participants in the OPORTUNIDADES RCT(c) conditional cash transfer program. Although women's (and families') diets and nutritional status improved, new foods and new ways of preparing foods sometimes presented barriers. Food is often shared, which meant that antenatal supplements might be shared with the family and foods purchased with the cash transfer may have been shared even more widely.

b) Microcredit

- In a Peruvian cohort study of microcredit (small loans for people too poor to access traditional financial services), Hamad 2012 found associations between length of participation (number of 6-month loan cycles) and several indicators of nutritional status in 1593 women. Under multivariate analysis, women's BMI did not show a significant increase with longer participation, which can be interpreted as a positive result, as three-quarters of women were overweight or obese at baseline. Haemoglobin concentrations did show a positive association with longer participation and lower food insecurity was also positively associated with longer participation.

- Doocy 2005 compared three groups of Ethiopian households (n = 819). Two groups had received loans, while the third group, while eligible for the microcredit program, were not currently seeking a loan and had not received a loan in the past year. In the two groups receiving loans, one had clients who had completed one loan cycle or less and had been in the program up to 10 months and the other group consisted of established clients who had completed two or more cycles. While no significant differences were seen between groups for dietary practices and dietary content, adult females in the community control group had significantly higher rates of acute malnutrition (MUAC < 22 cm) than those in the established client group (6/116 (7%) versus 4/240 (2%)). The incoming client group had acute malnutrition rates of 3/100 (3%) in adult females.
INSIGHTS FROM QUALITATIVE STUDIES

Knowledge and beliefs
Knowledge about micronutrient supplementation may be low in some areas. There may be concerns that vitamins are contraception ‘in disguise’ or that supplementation will make birth more difficult (Hill 2007; Galloway 2002; Ghanekar 2002).

Prevention and ‘illness’ priorities
Women may be reluctant to take 'medicines' for long periods when they feel healthy (Hill 2007). This is consistent with a study from eight low and middle incomes countries where half of all women interviewed did not consider symptoms of maternal anaemia to be a priority health concern (Galloway 2002) and a Vietnamese study found that preventing anaemia was not a high community priority (Aikawa 2006).

Supply
In an Indian study, reported common problems to be inadequate or unevenly distributed supplies of iron-folic acid tablets, insufficient monitoring and supervision by the health workers, irregular antenatal visits and late seeking of treatment by women. Other studies also found inadequate supply of IF to be a major barrier (Galloway 2002; Aikawa 2006).

Uptake
Uptake of micronutrients can less than optimal due to women not attending all antenatal visits, antenatal visits being too short to cover nutritional issues, as well as adverse effects and traditional beliefs about the effect of supplements (Titaley 2010, Choudhury 2011, Anya 2008). Other more generic barriers included lack of physical access to care and lack of money, although this was sometimes due to lack of awareness about conditional and unconditional cash transfer schemes (Titaley 2010).

Food choices and restrictions
Reasons for decreasing food consumption during pregnancy include aversion to specific foods, lack of money to purchase food and dietary restrictions which were often imposed by elders (Choudhury 2011, Dykes 2011, Shannon 2008). Despite women's knowledge of nutritional importance and benefits, they may still choose to restrict nutritional intake for other reasons, e.g. eating down to reduce baby size. Key structural and cultural barriers to mothers securing optimal nutrition for themselves and infants included: lack of general education, low level of awareness of nutritional issues, gender inequalities and poverty. Provision of incentives such as food and supplements for women to take home may increase participation in interventions (Dykes 2011).

Lack of food and concern about feeding children:
- In a qualitative analysis of the ongoing JiVitA-3 RCT, Sikder 2011 describes the experiences of 40 women who experienced severe obstetric complications. For two of these women who had life-threatening complications resulting from induced abortions, current lack of food and the inability to feed another child were the main reasons for taking steps to end the pregnancy.
- Most (77%) of the women interviewed in a Kenyan study were experiencing moderate to severe food insecurity. This experience increased women's perceptions that they have, or will have, insufficient milk, and that they will need greater access to food in order to successfully breastfeed. Food insecurity also increased anxiety about their children going hungry (Webb Girard 2012).
DISCUSSION AND CONCLUSIONS

This review has shown that there are both nutrition and nutrition-sensitive interventions with the potential to substantially reduce maternal mortality and morbidity. Many of these interventions have been directed towards reducing maternal and female anaemia. IF supplementation during pregnancy, and IF supplementation for WRA, particularly adolescents, have received most attention but as noted above, anaemia can be reduced in a number of other ways such as information, education and communication strategies. Although the effectiveness of IF supplementation is clear, coverage and sustainability are still unacceptably poor (Victora 2012). The tradeoff between clinical effectiveness and women’s adherence also needs to be considered. A 50% reduction of anaemia risk (seen for IF supplementation) can be dramatically diluted by poor uptake of effective prevention or treatment strategies.

Many barriers to implementation and scaling up remain - access and distribution seem to be more important barriers than knowledge and attitudes (e.g. Souganidis 2012) indicating the need to address change at system levels – through health and more widely – and to test and evaluate implementation strategies as rigorously as possible.

Efforts to continue and expand the coverage of iron-folic acid supplements to pregnant women and women of reproductive must remain the highest of priorities. The supplements need to be free as even low charges seem to be a barrier and distribution needs to be made through other places in communities other than health centres. Iron-folic fortification, in the form of fish sauce for example, may be very effective in the right contexts.

Multiple micronutrients are an alternative to iron-folic acid supplements, particularly for pregnant women and their babies (in the form of reduced neonatal mortality and low birth weight). They may, however, increase birth difficulties for undernourished women.

Calcium supplementation, even for lower risk groups of women, has been too readily dismissed and needs to be considered much more seriously. Food supplements have not generally shown dramatic effects but only a few high quality studies were located. Supplementation may need to happen as early as possible in pregnancy, and some effects may not be evident until the next generation (e.g. reduced stunting in offspring).

There is increasing recognition of the importance of the first thousand days of a child’s life – this is counted from conception through to the child’s second birthday. Interventions that help women to enter pregnancy in a well-nourished state need a higher priority - time of pregnancy recognition may be too late to achieve optimal effects.

Combined interventions such as supplementation combined with information, education and communication show promise. It is not clear whether this is due to increased uptake of supplements such as iron and folic acid or whether the effects are operating through nutrition-sensitive mechanisms such as increased health care seeking and increased empowerment.
Other nutrition-sensitive interactions such as conditional cash transfers and microcredit should be explored as ways of reducing maternal mortality and morbidity through alleviation of poverty. There is also emerging evidence that rapid nutritional transitions may also be increasing rates of obesity and overweight in young children from environments of past nutritional deprivation. Two recent studies from Australia report high rates of overweight and obesity in Aboriginal children by the time they turn four, even though many of these children would have been born small for gestational age. This underlines the need for primary prevention as these children approach reproductive age (Spurrier 2012, Schulz 2012).

**Limitations of the evidence**
We had to exclude many potentially relevant studies as they did not report any maternal outcomes at all (although they often could have done so). Furthermore, some of the studies we did include reported very few maternal outcomes. Our results may differ from other systematic reviews as we only included studies from low and middle income countries, and studies reporting at least one of our prespecified maternal outcomes.

**Quality of the evidence**
Studies ranged from well-designed and conducted very large cluster or factorial RCTs to small inadequately designed and powered RCTs and in other studies sometimes poor reporting hindered interpretation. Attrition bias was the major threat to internal validity, but the nature of the interventions and populations often meant that losses to follow-up were inevitable. However, in some studies, follow-up probably could have been improved.

**Implications for research**
Trials of nutrition and nutrition-sensitive interventions in low and middle income countries are often difficult to conduct and expensive - but not as expensive as introducing unproven programs on a large scale (Victora 2012).

Some questions needing further rigorously designed studies include conditional cash transfer, microcredit and incentives. Further replication of behaviour change interventions (such as information, education and communication) is also needed. They need to report nutritional inputs and outcomes, in order to try to distinguish the effects of different components of these complex interventions.

Further trials of food fortification are needed, as are trials comparing multiple micronutrients with iron and folic acid in women of reproductive age who are not pregnant. Optimum MMN compositions (and regimens) need to be determined.

Any antenatal intervention studies need to address maternal outcomes as well as perinatal and infant outcomes. This could be achieved by developing sets of core outcomes that could be used by investigators when designing studies.

More implementation studies with rigorous designs (e.g. concurrent comparisons) are required.
Long term follow-up is needed - this may need to cover several generations. Evidence about the role of programming is now emerging from some of the large food and nutrient supplementation studies, including differential effects in males and females. This needs to be further investigated to understand the intergenerational impacts, particularly for mothers of the future (such as prevention of maternal short stature).
REFERENCES

INCLUDED STUDIES:

Abel 2000

Addo 2011

Adhikari 2009 RCT

Agarwal 2003 RCT(c)

Aguayo 2005

Ahmed 2005 RCT

Ahmed 2005 RCT

Ahmed 2010 RCT

Ahmed 2012 RCT

Ahrari 2006(c)

Aikawa 2006

Alam 2010 RCT(c)

Aloofè 2009

Angeles-Agdeppa 1997 RCT

Angeles-Agdeppa 2005

Anya 2008

Attanasio 2005
conditional cash subsidy on child health and nutrition in Colombia. EDePo, The Institute for Fiscal Studies, 2005.


Atukorala 1994


Ayah 2007 RCT


Azad 2010 RCT(c)


Baeten 2002 RCT


Banerjee 2009 RCT


BAN RCT

- van der Horst C, Chasela C, et al. Modifications of a large HIV prevention clinical trial to fit changing

• www.thebanstudy.org.

Baqui 2008 RCT(c)

Beard 2005 RCT

Beasley 2000 RCT

Belizan 1991 RCT

Belizan 1995 RCT

Berger 2005

Berti 2010

Bezerra 2010 qRCT

Bhatla 2009 RCT

Bhutta 2008 RCT(c)

Bhutta 2009 RCT(c)

Bhutta 2011 RCT(c)

BINP 2003
BINP 2009

Bouzari 2011 RCT

Briley 2002 RCT

Brough 2010 RCT

Canfield 2001 RCT

Casanueva 2001 RCT

Casey 2010
• Casey GJ, Phuc TQ, MacGregor L, Montresor A, Mihrshahi S, Thach TD, Tien NT, Biggs BA. A free weekly iron-folic acid supplementation and regular deworming program is associated with improved haemoglobin and iron status indicators in Vietnamese women. BMC Public Health 2009;9:261.

Castillo-Duran 2001 RCT

Caulfield 1999 RCT
Ceesay 1997 RCT(c)


Chen 1995 RCT


Chen 2005 RCT(c)


Chew 1996a RCT


Chew 1996b RCT


Choudhury 2011


Christian 2003 RCT(c)


- Stewart CP, Christian P, Schulze KJ, Arguello M, LeClerq SC, Khatry SK, West KP. Low maternal vitamin B-12 status is associated with offspring insulin resistance regardless of antenatal


Christian 2009 RCT

Coetzee 1998 RCT

Cogswell 2003 RCT

Coutsoudis 1999 RCT


Cox 2005 RCT

Crape 2005

Creed-Kanashiro 2000 RCT

Danesh 2010 RCT

Darboe 2007 RCT

de Pee 1995

Deshmukh 2008(c)

Dijkhuizen 2004 RCT

Doocy 2005

Dos Santos 1999

Dykes 2011

Ekström 2002 RCT(c)

Faveau 1991

Fawzi 1998 RCT
• Fawzi WW, Msamanga GI, Hunter D, Renjifo B, Antelman G, Bang H, et al. Randomized trial of vitamin supplements in relation to transmission of HIV-1 through breastfeeding and early child


- McGrath N, Bellinger D, Robins J, Msamanga GI, Tronick E, Fawzi WW. Effect of maternal multivitamin supplementation on the mental and psychomotor development of children who are born to HIV-1-infected mothers in Tanzania. Pediatrics 2006;117(2).


Fawzi 2005 RCT

Fawzi 2007 RCT

Februhartanty 2002 RCT

Ferreira 2009

Foord 1995

Fris 2004 RCT

Galloway 2002

Garg 2006

Ghanekar 2002

Gilgen 2001 RCT

Gomber 2002 RCT

Gonzalez-Cossio 1998 RCT

Gonzalez-Rosendo 2002
• González-Rosendo G, Fernández-Ballart JD, Rodríguez-Jerez JJ, Sánchez-Muñoz J, Quintero-Gutiérrez AG. Weekly iron single dose for adolescent girls in Morelos (Mexico) [Dosis semanal de hierro en mujeres adolescentes de Morelos (Mexico)]. Ciencia y Tecnología Alimentaria 2008;6(2):37-142.

Gulmezoglu 1997 RCT

Guyon 2009
Guyon AB, Quinn VJ, Hainsworth M, Ravonimanantsoa P, Ravelojoana V, Rambeloson Z, Martin L. Implementing an integrated nutrition package at large scale in Madagascar: the Essential

Haas 2005 RCT

Haidar 2003 RCT

Hall 2002 RCT(c)

Hamad 2012

Han 2011 RCT

Hans 2010 RCT

Hartini 2005

Haskell 2005 RCT

Hill 2007

Ho 2005(c)

Hoa 2005 RCT

Horjus 2005(c)

Hotz 2008 RCT

Hotz 2012 RCT(c)

Huddle 1999
Huntington 2010

Huo 2011

Huy 2005

Huybregts 2009

Hyder 2007 RCT

ICDS

Idindili 2007 RCT

INCAP RCT
• Martorell R. Results and implications of the INCAP follow-up study. Journal of Nutrition 1995;125:1127-38S.

Jarjou 2006 RCT

Jayatissa 1999 RCT(c)

Jehn 2009
Jehn M, Brewis A. Paradoxical malnutrition in mother-child pairs: untangling the phenomenon of over- and under-nutrition in underdeveloped...

**Jennings 2010 RCT(c)**


**Jennings 2011**


**Jus'at 2000**


**Kaestel 2005 RCT**


**Kalpdev 2011 RCT**


**Kanani 2000 qRCT**


**Kardjati 1990 RCT**


**Kawai 2010 RCT**


**Khambalia 2009 RCT**


**Khan 2005**


**Khan 2007 qRCT**


**Kianfar 2000 RCT**


**Kindra 2011 RCT**


**Kinra 2008**


**Kramer 1997**

**Kumar 2008 RCT(c)**

**Kumar 2009 RCT**

**Kumwenda 2002 RCT**

**Kupka 2008 RCT**

**Larocque 2006 RCT**
- Larocque R, Casapia M, Gotuzzo E, MacLean JD, Soto JC, Rahme E, Gyorkos TW. A double-blind randomized controlled trial of antenatal mebendazole to reduce low birthweight in a hookworm-endemic area of Peru. Tropical Medicine and International Health 2006;11(10):1485-95.

**Lee 2005 RCT**

**Leenstra 2009 RCT**

**Lietz 2001 RCT(c)**

Liu 1996 RCT

Lopez de Romana 2006

Lopez-Jaramillo 1990 RCT

Lopez-Jaramillo 1997 RCT

Ma 2008 qRCT
• Ma AG, Schouten EG, Sun YY, Yang F, Han XX, Zhang FZ, Jiang DC, Kok FJ. Supplementation of iron alone and combined with vitamins improves haematological status, erythrocyte membrane fluidity and oxidative stress in anaemic pregnant women. British Journal of Nutrition 2010;104:1655-61.

MAGPIE RCT
• Duley L, Campbell L. The Magpie Trial: magnesium sulphate for pre-eclampsia, evaluating the effects on women and their babies. MIDIRS Midwifery Digest 1999;9:48-51.
• Duley L, Neilson JP. Magnesium sulphate and preeclampsia. Trial needed to see whether it’s as valuable in pre-eclampsia as in eclampsia. BMJ 1999;319:3-4.
• Duley L. The Magpie follow up study: outcome after discharge after hospital for women and children recruited to a trial comparing magnesium sulphate with placebo for pre-eclampsia. BMC Pregnancy and Childbirth 2004;4:5.
• Simon J, Gray A, Duley L, on behalf of the Magpie Trial Collaborative Group. Cost-effectiveness of prophylactic magnesium sulphate for 9996 women with pre-eclampsia from 33 countries: economic evaluation of the Magpie Trial. BJOG 2006;113(2):144-51.


Makola 2003 RCT

Makola 2007 RCT(c)


Manandhar 2004 RCT(c)


Mardones 2007 qRCT

McClelland 2004 RCT

Menendez 1994 RCT

Midhet 2010 RCT(c)

MINIMat RCT
• Eneroth H, Arifeen SE, Persson LA, Lönnerdal B, Hossain MB, Stephensen CB, Ekström EC.


**MISAME Food RCT**


**MISAME MMN RCT**


**Moodle 1994 RCT**


**Mozaffari 2010 RCT(c)**


**Mukhopadhyay 2004 RCT**


**Mumtaz 2000 RCT**

Mumtaz Z, Shahab S, Butt N, Rab MA, DeMuynck A. Daily iron supplementation is more effective than twice weekly iron supplementation in pregnant women in Pakistan in a randomized double-blind clinical trial. Journal of Nutrition 2000;130:2697-702.

**Muro 1999 RCT(c)**

Muro GS, Gross U, Gross R, Wahyuniar L. Increase in compliance with weekly iron supplementation of adolescent girls by an accompanying communication programme in secondary schools.

Muslimatun 2001 RCT


Ncube 2001 RCT


Ndiiaye 2009 RCT


Ndibazza 2010 RCT


Nduati 2001 RCT


Nguyen 2008 RCT


Niromanesh 2001 RCT

ObaapaVitA 2010 RCT(c)


Oddo 2012

Olney 2009

OPORTUNIDADES RCT(c)


• Gertler. IFPR website. 2000.


Osendarp 2000 RCT

Osrin 2005 RCT

Ouma 2006 RCT

Paulino 2005

Phuc 2009
• Phuc TQ, Mihrshahi S, Casey GJ, Phu LB, Tien NT, Caruana SR, Thach TD, Montresor A, Biggs BA. Lessons learned from implementation of a demonstration program to reduce the burden of anemia and hookworm in women in Yen Bai Province, Viet Nam. BMC Public Health 2009;9:266.

Prentice 1995 RCT

Preziosi 1997 RCT

Projahnmo-2 Mirzapur RCT

Purwar 1996 RCT

Radhika 2003 RCT

Rah 2011

Ramakrishnan 2003 RCT

RETIBETA 1999 RCT

Ridwan 1996 RCT(c)

Risonar 2008

Roschnik 2003 RCT(c)


Shrimpton 2009

Shulman 1999 RCT

Siega-Riz 2006 RCT

Sikder 2011

Soekarjo 2004 RCT(c)
Soekarjo DD, de Pee S, Kusin JA, Schreurs WHP, Schultink W, Muhilal, Bloem MW. Effectiveness of weekly vitamin A (10 000 IU) and iron (60 mg) supplementation for adolescent boys and girls through schools in rural and urban East Java, Indonesia. European Journal of Clinical Nutrition 2004;58:927-37.

Souganidis 2011

Souganidis 2012

Spinnato 2007 RCT


Stoltzfus 1993 RCT


Stuetz 2011

Suharno 1993 RCT

SUMMIT RCT(c)


• The Supplementation with Multiple Micronutrients Intervention Trial (SUMMIT) Study Group. Effect of maternal multiple micronutrient supplementation on fetal loss and

Page 57 of 63

Sunawang 2009 RCT

Suprapto 2002 qRCT

Taherian 2002 RCT

Tanumihardjo 2002 RCT
Tanumihardjo SA. Vitamin A and iron status are Improved by vitamin A and iron supplementation in pregnant Indonesian women. Journal of Nutrition 2002;132:1909-12.

Tara 2010 RCT

Vadillo-Ortega 2011 RCT
Vadillo-Ortega F, Perichart-Perera O, Espino S, Avila-Vergara MC, Ibarra I, Ahued R, Godines M,

den Broek 2006 RCT
den Broek NR, White SA, Flowers C, Cook JD, Letsky EA, Tanumihardjo SA, Mhango C, Molyneux M, Neilson JP. Randomised trial of vitamin A supplementation in pregnant women in rural Malawi found to be anaemic on screening by HemoCue. BJOG 2006;113:569-76.

Villar 2006 RCT

Villar 2009 RCT

Vinutha 2000 RCT

Vir 2008

Vyas 2009 qRCT

Wanchu 2001 RCT

Webb-Girard 2012

Welffens-Ekra 1990

West 1999 RCT (NNIPS-2)


West 2011 RCT (Ji VitA)


WHO 2011


WHO SEA 2011


Wijaya-Erhardt 2011 RCT


Xie 2001 RCT


Yakes 2011

ADDITIONAL REFERENCES

Adato 2011

Anderson 2011

Barker 1997

Black 2008

Bongaarts 1998

Casey 2011

Christian 2002

Cook 2004

DFID 2011a

DFID 2011b

Duley 2003

EPOC 2009

Fernald 2008

Fernandez-Gaxiola 2011 CR

Gittelsohn 1997

Khan 2006

Kramer 1987

Lapido 2000

Lozano 2011

Masset 2012

Michie 2011

Nag 1994
NICE 2009

Pattinson 2011

Potts 2010

Rah 2012

Rush 2000

Sanghvi 2010

Say 2009

Schulz 2012

Shankar 2009

Spurrier 2012

Streatfield 2008

van den Broek 2003

Victoria 2012

WHO 2009

WHO 2011a

WHO 2011b

WHO 2012

Wilmoth 2010

World Bank 2011

Zehner 2009