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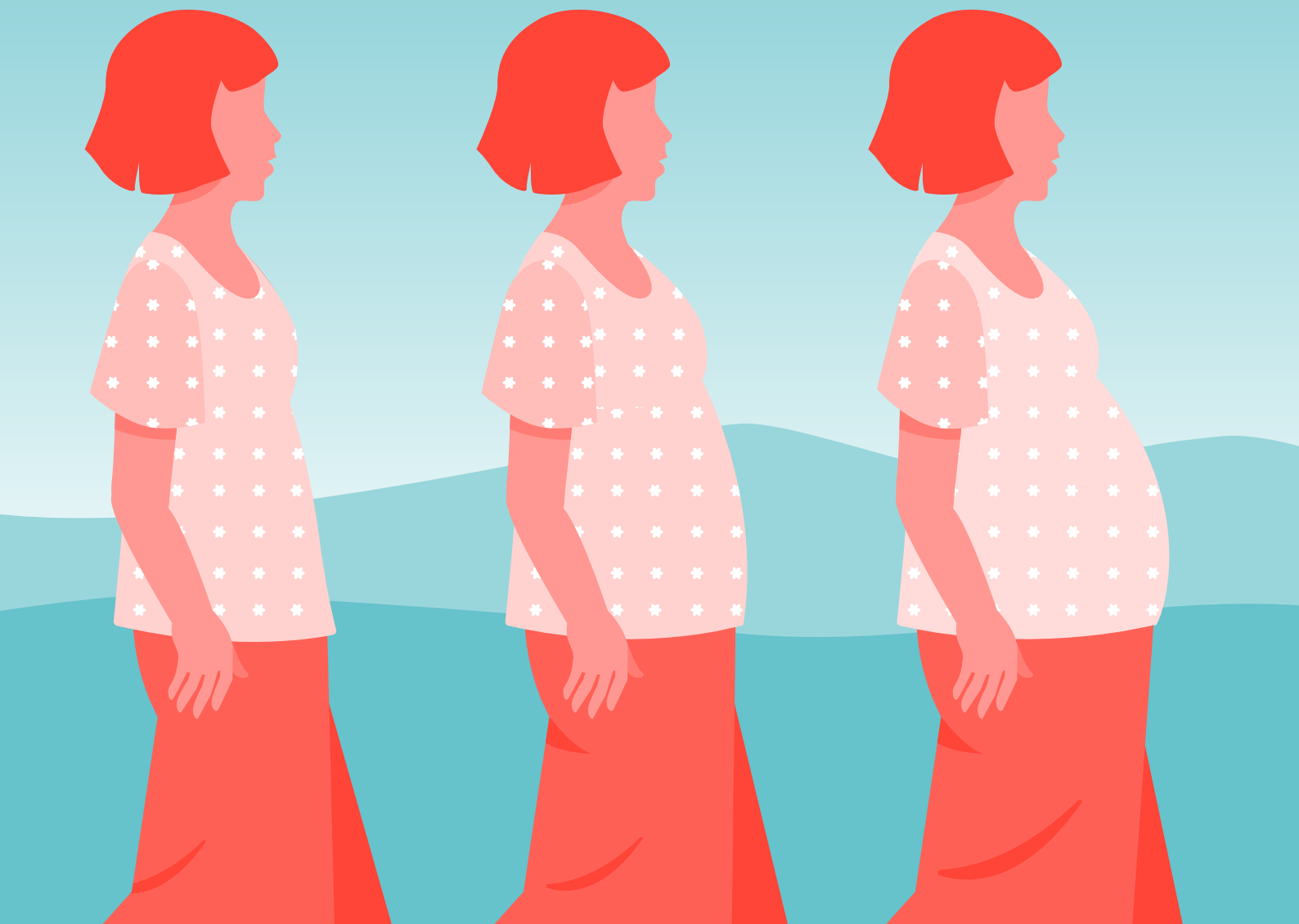
WHO antenatal care recommendations for a positive pregnancy experience

Nutritional interventions update: Multiple micronutrient supplements during pregnancy



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Acronyms and abbreviations

ANC	antenatal care
CI	confidence interval
CREP	Centro Rosarino de Estudios Perinatales (Argentina)
DALY	disability-adjusted life year
DECIDE	Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence
DOI	declaration of interest
eLENA	WHO e-Library of Evidence for Nutrition Actions
EPOC	Cochrane Effective Practice and Organization of Care
ERG	External Review Group
EtD	evidence-to-decision
FIGO	International Federation of Gynecology and Obstetrics
GDG	Guideline Development Group
GDP	gross domestic product
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRADE-CERQual	Confidence in the Evidence from Reviews of Qualitative Research
GSG	Guideline Steering Group
ICM	International Confederation of Midwives
IFA	iron and folic acid
LMIC	low- and middle-income country
MCA	Maternal, Newborn, Child and Adolescent Health and Ageing
NFS	Nutrition and Food Safety
PICO	population, intervention, comparator, outcome
QES	qualitative evidence syntheses
RCT	randomized controlled trial
RHL	WHO Reproductive Health Library
RR	Risk ratio
SGA	small for gestational age
SRH	Sexual and Reproductive Health and Research
UN	United Nations
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
UNIMMAP	United Nations International Multiple Micronutrient Antenatal Preparation
USAID	United States Agency for International Development
WHO	World Health Organization

Executive summary

Introduction

The World Health Organization's comprehensive antenatal care (ANC) guideline *WHO recommendations on antenatal care for a positive pregnancy experience* was published in 2016 with the objective of improving the quality of routine health care that all women and adolescent girls receive during pregnancy. The overarching principle – to provide pregnant service users with a positive pregnancy experience – aims to encourage countries to expand their health-care agendas beyond survival, with a view to maximizing health, human rights and the potential of their populations.

Recognizing that ANC provides a strategic platform for important health-care functions, including health promotion and disease prevention, 14 out of the 49 recommendations in the WHO 2016 ANC guideline relate to nutrition in pregnancy. In April 2019, the Executive Guideline Steering Group (GSG) prioritized two of these antenatal nutrition recommendations for updating in response to new evidence on these interventions, namely:

1. Multiple micronutrient supplements during pregnancy
2. Vitamin D supplements during pregnancy.

Evidence on these interventions was evaluated by a Guideline Development Group (GDG) composed of an international group of experts convened during an online GDG meeting held on 4–5 December 2019. The respective recommendations were updated in accordance with WHO's living guidelines approach. For consistency and continuity, the GDG, including the chair, comprised the same members as the ANC guideline GDG.

This guideline presents that evidence and updated recommendation on antenatal multiple micronutrient supplements (MMS), which supersedes the corresponding recommendation issued in the WHO 2016 ANC guideline.

Target audience

The target audience of this updated recommendation includes national and local public health policy-makers, implementers and managers of national and local maternal and child health programmes, concerned nongovernmental and other organizations, professional societies involved in the planning and management of maternal and child health services, health professionals (including obstetricians, midwives, nurses and general medical practitioners) and academic staff involved in training health professionals.

Guideline development methods

The updating of this recommendation was guided by the standardized operating procedures described in the *WHO handbook for guideline development.* This involves: (i) identification of priority questions and outcomes (done as part of the ANC guideline development process); (ii) evidence retrieval and synthesis; (iii) assessment of the evidence; (iv) formulation of the recommendations; and (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendations. The scientific evidence supporting the recommendations was synthesized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and Confidence in the Evidence from Reviews of Qualitative Research (GRADE-CERQual) approaches, for quantitative and qualitative evidence, respectively. Up-to-date systematic reviews were used to prepare evidence profiles for the recommendation prioritized for updating. The DECIDE (Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence) framework – an evidence-to-decision tool that includes intervention effects, values, resources, equity, acceptability and feasibility criteria – was used to guide the formulation and approval of the recommendation by the GDG.

Recommendation

The WHO technical consultation led to the formulation of one recommendation related to the use of antenatal MMS. The GDG had the option to recommend the intervention, not to recommend the intervention, or to recommend the intervention under certain conditions (in specific contexts, targeted monitoring and evaluation, in the context of rigorous research). The GDG experts also provided additional remarks where they considered them necessary. Users of the guideline should refer to these remarks, as well as to the evidence summary, for further information about the basis of this WHO recommendation.

The updated WHO recommendation on antenatal MMS for a positive pregnancy experience

This recommendation applies to pregnant women and adolescent girls within the context of routine ANC.

WHO recommendation on antenatal multiple micronutrient supplements (MMS)

Antenatal multiple micronutrient supplements that include iron and folic acid are recommended in the context of rigorous research[1]. *(Context-specific recommendation – research)*

Remarks

- This recommendation updates and supersedes the WHO recommendation found in the WHO ANC guideline issued in 2016 *(1)*.
- The evidence is derived from trials using MMS containing 13 to 15 micronutrients (including iron and folic acid) and the widely available United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP), which contains 15 micronutrients, including 30 mg of iron and 0.4 mg of folic acid (see Box 2).
- As the evidence was mainly derived from low- and middle-income countries, its applicability to high-income countries or to populations not at risk of micronutrient deficiencies – for example, due to an adequate diet and food fortification programmes – is unclear.
- Research in this context therefore includes:
  - controlled clinical trials in which early pregnancy ultrasound is used to establish gestational age with certainty,[2] with assessment of critical maternal and perinatal outcomes, and follow-up of infants sustained into childhood; and
  - where programmes of MMS are being considered, implementation research to establish the impact of switching from iron and folic acid supplements to MMS, including evaluation of acceptability, feasibility, sustainability, equity and cost-effectiveness.
- Many MMS contain 30 mg or less of elemental iron and WHO recommends antenatal iron and folic acid supplements containing 60 mg of elemental iron in populations where anaemia is a severe public health problem (a prevalence of 40% or higher) *(2)*. Therefore, countries should consider their population magnitude and distribution of anaemia, its nutritional determinants (i.e. iron deficiency), as well as the magnitude and distribution of the complex low birthweight and its component parts (i.e. preterm, small for gestational age [SGA] or a combination of these) *(3)*, when undertaking any research in the context of this recommendation.
- Pregnant women should be supported and encouraged to receive adequate nutrition, which is best achieved through consumption of a healthy, balanced diet consistent with guidelines on healthy eating *(4)*.

This recommendation on multiple micronutrients in pregnancy has changed from "not recommended" to "recommended in the context of rigorous research". The reason for the change in the nature of the recommendation is because, whilst the evidence suggests that there may be a limited benefit and little harm in replacing iron and folic acid supplements with MMS, the evidence on low birthweight and its component parts (preterm birth and SGA) is difficult to interpret. Gestational age accurately assessed by ultrasound emerged as an important feature of future trials. In addition, the sustainability of switching to the higher-cost MMS is not known and more evidence is needed on the effects of switching to a 30 mg dose of iron from a higher dose of iron (e.g. 60 mg), particularly in settings where higher doses of iron are routinely used due to a high anaemia prevalence or other reasons.

1 The GDG clarified that rigorous research includes implementation research using high-quality methods appropriate to the specific research questions.

2 Gestational age accurately assessed by ultrasound emerged as an important feature of future trials because of the conflicting and confusing differences in intervention effects found on low birthweight and its component parts (preterm birth, and SGA).

Introduction

Background

The comprehensive antenatal care (ANC) guideline, *WHO recommendations on antenatal care for a positive pregnancy experience,* was published by the World Health Organization (WHO) in 2016 with the objective of improving the quality of routine health care that all women and adolescent girls receive during pregnancy *(1)*. The overarching principle – to provide pregnant service users with a positive pregnancy experience – aims to encourage countries to expand their health-care agendas beyond survival, with a view to maximizing health, human rights and the potential of their populations. Recognizing that ANC provides a useful platform for important health-care functions, including health promotion and disease prevention, 14 out of the 49 recommendations in the WHO ANC guideline relate to nutrition in pregnancy *(1)*.

In April 2019, following pre-established prioritization criteria, the Executive Guideline Steering Group (GSG) prioritized updating of the recommendation on multiple micronutrient supplements (MMS). This resulting recommendation updates and supersedes the previous recommendation on antenatal MMS issued in the 2016 WHO ANC guideline.

Pregnancy and micronutrients

Pregnancy requires a healthy diet that includes an adequate intake of energy, protein, vitamins and minerals to meet increased maternal and fetal needs. However, for many pregnant women, dietary intake of fruit, vegetables, meat and dairy products is often insufficient to meet these needs, and may lead to micronutrient deficiencies. In resource-poor countries in sub-Saharan Africa, south-central Asia and south-east Asia, maternal undernutrition is highly prevalent and is recognized as a key determinant of poor perinatal outcomes *(5)*. However, understanding of the individual requirements and contributions of all essential vitamins and minerals to optimize maternal and fetal health during the antenatal period is limited *(6)*.

Maternal iron deficiency is the most common known micronutrient deficiency that causes anaemia. Anaemia is estimated to affect 40% of pregnant women globally, with the highest prevalence in the WHO regions of South-East Asia (49%), Africa (46%) and the Eastern Mediterranean (41%). A lower prevalence is estimated in the WHO regions of the Western Pacific (33%), the Americas (26%) and Europe (27%) *(7)*. Supplementation with iron during pregnancy is therefore considered essential *(1,6)*. Daily folic acid is also recommended as a routine antenatal supplement to prevent fetal neural tube defects *(1)*. Iron and folic acid (IFA) are often combined in a single tablet, such as the daily IFA supplement of the United Nations Children's Fund (UNICEF), which may include 30 mg or 60 mg elemental iron and 0.4 mg folic acid *(8,9)*. They are also included in the United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP), an established multiple micronutrient formulation that is widely available and contains 15 micronutrients, including IFA in doses of 30 mg and 0.4 mg, respectively *(10)*.

For populations with low dietary intake of calcium, antenatal calcium supplementation is also recommended by WHO to prevent pre-eclampsia *(1,11)*. In addition, in certain populations at risk of night blindness, vitamin A supplementation during pregnancy is recommended *(1)*.

The updated recommendation in the context of the WHO ANC guideline

Several trials have addressed the question of whether an antenatal MMS with various vitamins and minerals, including IFA, would be more appropriate than the currently recommended IFA supplements, especially in low- and middle-income countries (LMICs). A Cochrane review *(12)* that synthesized this evidence was evaluated by the Guideline Development Group (GDG) during the 2016 ANC guideline development process. As the review included many different multiple micronutrient formulations in its analyses, the GDG at that time requested revised analyses to answer the following questions:

- What are the effects of MMS containing at least 13 to 15 micronutrients (including IFA) compared with IFA supplements?
- What are the effects of UNIMMAP compared with IFA supplements?

The GDG also requested additional subgroup analyses according to the dose of iron in the control group because most trials in the review evaluated MMS containing 30 mg of elemental iron, and this was compared with IFA controls that employed either 30 mg or 60 mg of iron. Similarly, as the existing WHO recommendation on IFA supplements recommends a folic acid dose of 0.4 mg, the GDG requested additional analyses restricting trials to those comparing MMS to these IFA doses. The rationale for these additional analyses was that, if countries are to consider transitioning to MMS, they would most likely be switching from one of these two IFA formulations (i.e. 30 mg iron/0.4 mg folic acid or 60 mg iron/0.4 mg folic acid).

In 2016, the resulting evidence suggested that MMS (containing 13 to 15 micronutrients, including IFA) were associated with an average 11% reduction in low birthweight compared with IFA supplements. However, lack of other beneficial effects, the added cost of MMS, equivocal evidence on neonatal mortality related to the dose of iron in IFA supplements, possibility of unknown harms, lack of evidence on cost-effectiveness, and concerns about feasibility led the GDG to decide not to recommend a change from existing IFA supplements strategies at the time *(1)*.

Since the publication of the WHO ANC guideline, the Cochrane review has been updated to include four additional trials *(13)*. This framework presents the updated research evidence on antenatal MMS compared with IFA supplements, which supports the updated recommendation on MMS.

Rationale and objectives

As part of the WHO's normative work on supporting evidence-informed policies and practices and its living guidelines approach *(14)*, the Department of Sexual and Reproductive Health and Research (SHR), the Department of Maternal, Newborn, Child, Adolescent Health and Ageing (MCA) and the Department of Nutrition and Food Safety (NFS) prioritized the updating of this recommendation on MMS following the advice of the Executive GSG 2017–2019, particularly the identification of new evidence on this intervention.

Target audience

The recommendation in this global guideline is intended to inform the development of relevant national- and local-level health policies and clinical protocols. Therefore, the target audience of this guideline includes national and local public health policy-makers, implementers and managers of national and local maternal and child health programmes, concerned nongovernmental and other organizations, professional societies involved in the planning and management of maternal and child health services, health professionals (including obstetricians, midwives, nurses and general medical practitioners) and academic staff involved in training health professionals.

Scope of the recommendations

This updated recommendation is relevant to all pregnant women and adolescent girls receiving ANC in any health-care facility or community-based setting, and to their unborn fetuses and newborns. The question was prioritized during the ANC guideline development process. In 2019, it was prioritized for updating in the context of WHO's living guideline commitment *(14)*. The authors of the Cochrane review on which the 2016 ANC guideline panel's recommendation was based updated their review to include new studies. The outcomes of interest are therefore the same as those prioritized for the ANC guideline relevant to nutritional interventions (see Box 1).

Box 1. ANC nutritional interventions outcomes of interest

Maternal outcomes	Fetal/neonatal outcomes
Infections	Neonatal infections
Anaemia	Small for gestational age
Pre-eclampsia/eclampsia	Low birthweight
Gestational diabetes mellitus	Preterm birth
Mode of delivery	Congenital anomalies
Excessive weight gain	Macrosomia/large for gestational age
Side effects	Fetal/neonatal mortality
Maternal mortality	
Maternal satisfaction	

Methods

This recommendation is an update of one of 49 recommendations that were published in the *WHO recommendations on antenatal care for a positive pregnancy experience* (2016) guideline *(1)*. The recommendation was developed initially using the standardized operating procedures described in the *WHO handbook for guideline development (15)*. In summary, the process included: (i) identification of priority questions and outcomes, (ii) retrieval of evidence, (iii) assessment and synthesis of the evidence, (iv) formulation of recommendations, and (v) planning for the implementation, dissemination, impact evaluation and updating of the recommendation. This recommendation was identified by the Executive GSG as a high priority for updating in response to new evidence on MMS.

Contributors to the guideline

Executive Guideline Steering Group (Executive GSG)

The Executive GSG is an independent panel of external experts and relevant stakeholders from the six WHO regions. This group advises WHO on the prioritization of new and existing questions in maternal and perinatal health for recommendation development or updating.

WHO Steering Group

The WHO Steering Group that managed the updating process comprised the same staff members from the Departments of SRH, MCA and NFS who were part of the Steering Group for the WHO ANC guideline of 2016 (see Annex 1 for the list of members). The Steering Group drafted the key recommendation question in PICO (population, intervention, comparator, outcome) format and identified individuals to be invited to participate as guideline methodologists, as well as the guideline development and external review groups. In addition, the WHO Steering Group supervised the evidence retrieval and synthesis, organized the technical consultation, and drafted and finalized the guideline document. The Steering Group in collaboration with WHO regional offices will oversee the dissemination of the updated recommendation.

Guideline Development Group (GDG)

The Steering Group identified and invited 15 external experts and stakeholders from the six WHO regions to constitute the GDG, ensuring geographic representation, gender balance, and no important conflicts of interest. These were the experts who had also served in the GDG for the WHO ANC guideline's nutrition recommendations of 2016. This is a diverse group of individuals with expertise in research, guideline development methods, and clinical policy and programmes relating to ANC interventions, and includes a patient/consumer representative. The GDG appraised the evidence used to inform the recommendation, advised on the interpretation of this evidence, and formulated the final recommendation during an online GDG meeting on 4–5 December 2019. In addition, GDG members reviewed and approved the final guideline document before its submission to the WHO Guidelines Review Committee for approval. A list of the GDG members can be found in Annex 1.

External Review Group (ERG)

The External Review Group was a geographically and gender-balanced group with no important conflicts of interest (see Annex 1 for ERG members). There were four members, including technical experts and other stakeholders with interests in the provision of evidence-informed ANC. This group peer-reviewed a preliminary version of the guideline document to identify any factual errors and to comment on the clarity of the language, contextual issues and implications for implementation. The group ensured that the guideline decision-making processes had considered and incorporated the contextual values and preferences of persons affected by the recommendation, including pregnant women and adolescent girls, health-care professionals and policy-makers. It was not within the ERG's remit to change recommendations previously formulated by the GDG.

Systematic review team and guideline methodologists

The managing editors of the Cochrane Pregnancy and Childbirth Group coordinated the updating of the quantitative systematic review and facilitated collaboration between systematic review authors and guideline

methodologists. Methodologists from the Evidence-based Medicine Consultancy Ltd in the United Kingdom worked closely with the WHO Steering Group to conduct the additional pre-specified analysis required by the GDG for this recommendation, and with methodologists from the Centro Rosarino de Estudios Perinatales (CREP) in Argentina, who appraised the quantitative evidence using standard operating procedures using GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology *(16).* Two qualitative evidence experts from the University of Central Lancashire in the United Kingdom systematically reviewed qualitative studies related to women's and health professionals' views on ANC, and synthesized this evidence.

External partners and observers

Representatives of the International Federation of Gynaecology and Obstetrics (FIGO), the International Confederation of Midwives (ICM), the United Nations Population Fund (UNFPA), the United States Agency for International Development (USAID), the United Nations Children's Fund (UNICEF) and the Bill & Melinda Gates Foundation were invited to the final GDG meeting to serve as observers. All these organizations are potential implementers of the proposed guideline with a history of collaboration with WHO in guideline dissemination and implementation. Observers do not participate in the formulation of recommendations.

Declaration of interests by external contributors

WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to actual or ostensible conflicts of interest. In accordance with the *WHO guidelines for declarations of interests (WHO Experts) (17)*, all GDG members, as well as ERG members and other external collaborators, were asked to declare in writing any competing interests (whether academic, financial or other) at the time of the invitation to participate in the ANC guideline development process. The standard WHO form for declarations of interest (DOI) was completed and signed by each expert and sent electronically to the responsible technical officer. The WHO Steering Group reviewed all the DOI forms before finalizing experts' invitations to participate. Where any conflicts of interest were declared, the Steering Group determined whether they were serious enough to affect the individual's ability to make objective judgements about the evidence or recommendation. To ensure consistency, the Steering Group applied the criteria for assessing the severity of a conflict of interest in the *WHO handbook for guideline development (15).*

All findings from DOI statements were managed in accordance with the WHO DOI guidelines on a case-by-case basis and communicated to the experts. Where a conflict of interest was not considered significant enough to pose any risk to the guideline development process or reduce its credibility, the expert was only required to declare such conflict at the GDG meeting and no further action was taken. A summary of the DOI statements and information on how conflicts of interest were managed are included in Annex 2. In order to strengthen public trust and transparency in connection with WHO meetings involving the provision of expert advice in developing technical norms and standards, the names and brief biographies of individuals considered for participation on this guideline – together with a description of the objectives of relevant meetings – were made public ahead of the first meeting planned to allow time for public notice and comment.

Identifying priority questions and outcomes

The priority question and outcomes were aligned with those of the ANC guideline *(1).* This question and its outcomes were originally informed through an extensive scoping exercise of existing clinical practice guidelines relevant to routine ANC, supplemented by searching the Cochrane Database of Systematic Reviews for existing key systematic reviews relevant to ANC. Critical and important outcomes were informed by these reviews, as well as by a WHO-commissioned scoping qualitative review of what women want during pregnancy *(18).* The findings of the latter revealed that pregnant women want a positive pregnancy experience, defined as maintaining physical and sociocultural normality; maintaining a healthy pregnancy and baby; having an effective transition to positive labour and birth; and achieving a positive motherhood. This composite outcome of a "positive pregnancy experience" became the overarching principle of ANC guideline recommendations.

Evidence identification and retrieval

Evidence to support this recommendation was derived from a number of sources by the methodologists working closely with the WHO Steering Group. An updated Cochrane systematic review was the primary

source of evidence on effectiveness of oral antenatal MMS. Earlier versions of this review, in which evidence on effectiveness was derived from randomized controlled trial (RCT) data assessed and synthesized using standardized Cochrane methodology, supported the ANC guideline recommendation of 2016. The up-to-date RevMan file was retrieved from the Cochrane Pregnancy and Childbirth Group and customized to reflect the key comparisons, GDG-specified subgroup analyses, and outcomes relevant to the ANC guideline. Evidence was evaluated according to standard operating procedures approved by the WHO Steering Group, and evidence profiles (in the form of GRADE tables) were prepared, including assessment of the certainty of the evidence, for comparisons of interest.

The latest versions of two qualitative systematic reviews commissioned by the WHO Steering Group for the 2016 guideline development process informed the values, acceptability and feasibility criteria of these evidence-to-decision (EtD) frameworks *(18,19)*. Additionally, systematic reviews of cost-effectiveness were identified through PubMed searches of the literature.

Quality assessment and grading of the evidence

The GRADE approach *(16)* to appraising the certainty of quantitative evidence was used, meaning that the certainty of evidence for each outcome was rated as "high", "moderate", "low", or "very low" based on a set of established criteria. As a baseline, the evidence from the Cochrane reviews was rated "high certainty" because it was derived from RCTs; this rating was then downgraded according to considerations of risk of bias, inconsistency, imprecision, indirectness, and publication bias or other considerations.

Qualitative evidence was derived from qualitative evidence syntheses (QES) performed for the WHO 2016 ANC guideline *(18,19)*. Previously subjected to quality appraisal using the Confidence in the Evidence from Reviews of Qualitative Research (GRADE-CERQual) tool, the evidence was not re-graded for this updated recommendation. The GRADE-CERQual tool, which uses a similar approach conceptually to other GRADE tools, rates the level of confidence that can be placed in QES evidence according to four components: methodological limitations of the individual studies; adequacy of data; coherence; and relevance to the review question of the individual studies contributing to a QES finding *(20)*.

Preparation of the evidence summary

The WHO Steering Group supervised and finalized the preparation of the evidence summary and profile, in collaboration with the guideline methodologists, using the DECIDE (Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence) framework. DECIDE is an EtD tool that includes explicit and systematic consideration of research evidence on interventions according to six criteria, namely, effects, values, resources, equity, acceptability and feasibility *(21)*. These six EtD criteria were populated with the research evidence, where available; in addition, information from other sources was described in the "additional considerations" subsections of each criterion. Certainty of the graded evidence on intervention effectiveness was systematically interpreted in EtD frameworks according to Cochrane Effective Practice and Organization of Care (EPOC) Group guidance *(22)*.

Formulation of the recommendation

GDG members and other participants were provided with the evidence summary in advance of the online GDG meeting held on 4–5 December 2019, organized by the Steering Group from Geneva, Switzerland. During the technical consultation, under the leadership of the GDG chair, the GDG members reviewed, discussed and made judgements on the impact of the interventions for each of the EtD criteria. GDG judgements were summarized in a table before finalization of the recommendation and remarks. The intervention could either be recommended, not recommended, or recommended in specific contexts, namely, rigorous research, targeted monitoring and evaluation, or another GDG-specified context.

Decision-making process

The online GDG meeting was guided by a clear protocol, designed to allow the recommendation to be formulated through a process of group discussion, until consensus was reached. The final adoption of the recommendation and its context, if applicable, was confirmed by unanimous consensus (i.e. full agreement among all GDG members).

Guideline preparation and peer review

Following the online GDG meeting, members of the WHO Steering Group, assisted by a methodologist, drafted a full guideline document to accurately reflect the deliberations and decisions of participants. A preliminary version of the document was sent electronically to participants and the ERG for final review and technical comments. The Steering Group carefully evaluated the input of the peer reviewers for inclusion in the guideline document and made revisions to the guideline draft as needed. After the GDG meetings and peer-review process, further modifications to the guideline by the Steering Group were limited to corrections of factual errors and improvements in language to address any lack of clarity. The document was then submitted for executive clearance according to established WHO publication procedures.

Evidence and recommendation on antenatal multiple micronutrient supplements

This section provides the WHO recommendation adopted by the GDG on antenatal MMS, with its corresponding evidence summary. Evidence on the effectiveness of MMS is further detailed in GRADE tables in Annex 3 along with selected forest plots. To ensure that the recommendation is correctly understood, additional remarks reflecting the summary of the discussion by the GDG are included below the recommendation.

WHO recommendation on antenatal MMS

Antenatal multiple micronutrient supplements that include iron and folic acid are recommended in the context of rigorous research.[3] *(Context-specific recommendation – research)*

Remarks

- This recommendation updates and supersedes the WHO recommendation found in the WHO ANC guideline *(1)*.
- The recommendation is based on evidence derived from trials using MMS containing 13 to 15 micronutrients (including IFA) and the widely available UNIMMAP, which contains 15 micronutrients, including 30 mg of iron and 0.4 mg of folic acid) (see Box 2).
- As the evidence was mainly derived from LMICs, its applicability to high-income countries or to populations not at risk of micronutrient deficiencies – for example, due to an adequate diet and food fortification programmes – is unclear.
- Research in this context includes:
  - controlled clinical trials in which early pregnancy ultrasound is used to establish gestational age with certainty,[4] with assessment of critical maternal and perinatal outcomes, and follow-up of infants sustained into childhood; and
  - where programmes of MMS are being considered, implementation research to establish the impact of switching from IFA supplements to MMS, including evaluation of acceptability, feasibility, sustainability, equity and cost-effectiveness.
- Most MMS, including UNIMMAP, contain 30 mg of elemental iron. WHO recommends antenatal supplements containing 60 mg of elemental iron in populations where anaemia is a severe public health problem (a prevalence of 40% or higher) *(2)*. Therefore, countries should consider their population magnitude and distribution of anaemia, as well as its nutritional determinants (i.e. iron deficiency), as well as the magnitude and distribution of the complex low birthweight and its component parts (i.e. preterm, small for gestational age [SGA] or a combination of these) *(3)*, when undertaking any research in the context of this recommendation.
- Pregnant women should be supported and encouraged to receive adequate nutrition, which is best achieved through consumption of a healthy, balanced diet consistent with guidelines on healthy eating *(4)*.

A. The priority question

The following priority question was formulated using the PICO format: For pregnant women (P), does antenatal MMS (I) that includes IFA compared with routine IFA supplementation (C) improve maternal and perinatal health outcomes (O)?

B. Assessment

1) Effects of the intervention

What are the anticipated effects of antenatal MMS compared with routine IFA supplements?

3 The GDG clarified that rigorous research includes implementation research using high-quality methods appropriate to the specific research questions.

4 Gestational age accurately assessed by ultrasound emerged as an important feature of future trials because of the conflicting and confusing differences in intervention effects found on low birthweight and its component parts (preterm birth, and SGA).

Research evidence

This evidence was derived from RCT data in a Cochrane systematic review *(13)*. The Cochrane review included 20 trials involving 141–849 women; however, only 16 trials contributed data to the updated WHO analysis, as two trials compared MMS with placebo, one trial evaluated a supplement with eight micronutrients plus IFA, and one trial did not provide folic acid to the control group. Of these 16 trials, six evaluated supplements with 13 or 14 micronutrients *(23–28)*, including IFA; and 10 evaluated supplements with 15 micronutrients *(29–38)* including vitamins A, D, E; niacin; folic acid; vitamins B1, B2, B6, B12, C; zinc, iron, iodine, selenium and copper, as per the UNIMMAP formulation (see Box 2). All the trials were conducted in LMICs.

The GDG-specified WHO analyses were updated with these revised data to include:

- Comparison 1: MMS with 13 to 15 micronutrients compared with IFA supplements.
- Comparison 2: UNIMMAP supplements compared with IFA supplements.

The random effects model was used in all meta-analyses, which also included subgroup and sensitivity analyses as per the 2016 evaluation; therefore, estimates represent the average effect across trials. Data from individual RCTs (9) and cluster RCTs (7) were combined using cluster-adjusted effect estimates and generic inverse variance methods; therefore, participant numbers and events for most outcomes have been estimated based on trial sample sizes for informational purposes only. GRADE tables for the main comparisons can be found at the end of this document and forest plots can be found in the accompanying Annex. Evidence from sensitivity analyses was not graded.

Comparison 1: MMS with 13 to 15 micronutrients compared with IFA supplements

Sixteen trials contributed data to this comparison. Trials were conducted in the following countries: Bangladesh *(28,36)*, Burkina Faso *(33)*, China *(31,38)*, Gambia *(27)*, Ghana *(25)*, Guinea-Bissau *(30)*, Indonesia *(34,35)*, Malawi *(23)*, Nepal *(24,32)*, the Niger *(37)*, Pakistan *(29)* and Zimbabwe *(26)*. Enrolment occurred at less than 20 weeks of pregnancy in nine out of the 16 trials.

Box 2. UNIMMAP formulation supplementation *(10)*

Vitamin A	800 µg
Vitamin D	200 IU
Vitamin E	10 mg
Niacin	18 mg
Folic acid	400 µg
Vitamin B1	1.4 mg
Vitamin B2	1.4 mg
Vitamin B6	1.9 mg
Vitamin B12	2.6 µg
Vitamin C	70 mg
Zinc	15 mg
Iron	30 mg
Selenium	65 µg
Copper	2 mg
Iodine	150 µg

The dose of iron in the control arm was 60 mg in most trials, except for three trials using a dose of 30 mg *(31,34,36),* one using 27 mg *(28),* and one that did not specify the dose used *(26).* In analyses, trials were subgrouped accordingly, with data from the trial by West et al. *(28)* grouped together with the trials using a 30 mg IFA supplement.

Thirteen trials used MMS that included 30 mg of elemental iron or less, and three trials used MMS that included 60 mg of elemental iron *(24,27,30).* The latter three trials compared MMS with IFA supplements with the same iron content. However, in eight trials, MMS containing a lower iron dose (30 mg or less) were compared with IFA supplements containing a higher iron dose (60 mg). Most trials used a dose of 0.4 mg of folic acid in the control arm; however, one used 0.6 mg *(28),* one used 0.25 mg *(35),* and one did not state the dose *(26).* In sensitivity analyses, these three trials were excluded.

Maternal outcomes

Maternal anaemia (third trimester Hb < 110 g/L): The evidence suggests that MMS probably make little or no difference to maternal anaemia compared with IFA supplements (eight trials; risk ratio [RR]: 1.03, 95% confidence interval [CI]: 0.92 to 1.15; *high-certainty evidence*).

Caesarean section: The evidence suggests that MMS may make little or no difference to caesarean section rates compared with IFA supplements (four trials; RR: 1.04, 95% CI: 0.76 to 1.43; *low-certainty evidence, downgraded due to study design limitations and imprecision).*

Maternal mortality: The evidence suggests that MMS may make little or no difference to maternal mortality compared with IFA supplements (six trials; RR: 1.06, 95% CI: 0.72 to 1.54; *low-certainty evidence, downgraded due to design limitations and imprecision).*

Subgroup findings and sensitivity analyses were consistent with the overall findings for these outcomes. There were no relevant data in the review on pre-eclampsia/eclampsia, gestational diabetes mellitus, infection, side effects or positive pregnancy experience outcomes.

Fetal/neonatal outcomes

SGA: The evidence suggests that MMS probably makes little or no difference to the risk of having an SGA neonate compared with IFA supplements (15 trials; RR: 0.98, 95% CI: 0.96 to 1.00; *moderate-certainty evidence, downgraded due to suspected publication bias).* Subgroup findings and sensitivity analysis restricted to the 10 studies using a 0.4 mg folic acid dose were consistent with the overall findings.

Low birthweight: The evidence suggests that MMS reduce the risk of having a low-birthweight neonate compared with IFA supplements (16 trials; RR: 0.88, 95% CI: 0.86 to 0.91; *high-certainty evidence*). Subgroup findings and sensitivity analysis restricted to the 13 studies using a 0.4 mg folic acid dose were consistent with the overall findings.

Preterm birth: The evidence suggests that MMS probably make little or no difference to preterm birth compared with IFA supplements (16 trials; RR: 0.94, 95% CI: 0.88 to 1.00; *moderate-certainty evidence, downgraded for study design limitations*). Subgroup findings and sensitivity analysis restricted to the 13 studies using a 0.4 mg folic acid dose were consistent with the overall findings.

Perinatal mortality: For this outcome, subgroup findings differed according to the dose of iron (30 mg or 60 mg) in the IFA supplements (test for subgroup differences: $P = 0.05$, $I^2 = 73.4\%$) and so subgroup data were not pooled. Evidence for the 60 mg iron subgroup suggests there is probably little or no difference between MMS and IFA supplements (nine trials; RR: 1.15, 95% CI: 0.93 to 1.42; *moderate-certainty evidence, downgraded for imprecision*), whereas evidence for the 30 mg iron subgroup suggests that MMS are probably associated with lower perinatal mortality than IFA supplements (four trials; RR: 0.92, 95% CI: 0.86 to 0.98; *moderate-certainty evidence*). On sensitivity analysis restricted to the three studies that used a 0.4 mg folic acid dose, the effect estimate for the latter subgroup included the possibility of no difference.

Neonatal mortality: As for perinatal mortality, subgroup findings for neonatal mortality differed according to the dose of iron in the IFA supplements (test for subgroup differences: $P = 0.08$, $I^2 = 68.4\%$) and so subgroup data were not pooled. Evidence from the 60 mg IFA supplements subgroup initially suggesting that there is probably little or no difference (nine trials; RR: 1.22, 95% CI: 0.94 to 1.56; *moderate-certainty evidence, downgraded for imprecision*) became a clear difference in favour of IFA supplements once sensitivity analyses were restricted to the eight trials using a 0.4 mg folic acid dose (RR: 1.32, 95% CI: 1.05 to 1.65). For the 30 mg iron subgroup, however, the evidence suggests there is probably little or no difference in neonatal mortality between MMS and IFA supplements (four trials; RR: 0.95, 95% CI: 0.87 to 1.04; *moderate-certainty evidence, downgraded for clinical inconsistency in dose of iron*).

Stillbirth: The evidence suggests there is little or no difference between MMS and IFA supplements on stillbirths (15 trials; RR: 0.98, 95% CI: 0.87 to 1.10; *high-certainty evidence*).

Congenital anomalies: MMS may make little or no difference to the risk of congenital anomalies compared with IFA supplements (two trials; RR: 1.34, 95% CI: 0.25 to 7.12; *low-certainty evidence, downgraded due to design limitations and imprecision*).

No other differences on subgroup or sensitivity analysis were evident. There were no relevant data on infection outcomes.

Summary of effects

All the evidence was derived from LMICs. Overall, there were no clear differences in maternal, fetal or neonatal outcomes, except for a 12% (9–14%) reduction in low birthweight with MMS. Some subgroup evidence suggested that IFA supplements with 60 mg iron may be associated with lower neonatal mortality than MMS. Other subgroup evidence suggested that, when MMS were compared with IFA supplements containing the same dose of iron (30 mg), MMS may be associated with lower perinatal mortality than IFA supplements.

Desirable effects

How substantial are the desirable anticipated effects of MMS compared with IFA supplements?

Judgement					
☐ Don't know	☐ Varies	☐ Trivial	☒ Small	☐ Moderate	☐ Large

Rationale for judgement: A 12% reduction in low birthweight was the main desirable effect demonstrated. The panel had difficulty interpreting the clinical significance of this finding because it reflects the number of babies born preterm plus the number of babies born at term that are defined as SGA, for which the evidence suggested no difference in effect between MMS and IFA supplements.

Undesirable effects

How substantial are the undesirable anticipated effects of MMS compared with IFA supplements?

Judgement					
☐ Don't know	☒ Varies	☐ Large	☐ Moderate	☐ Small	☐ Trivial

Rationale for judgement: Some subgroup evidence suggested that the relative effect of MMS compared with IFA supplements on neonatal mortality may vary according to the dose of iron (30 mg or 60 mg) and folic acid in the IFA supplements control group. These findings were uncertain and the panel also considered that the option of "Don't know" could apply here.

Certainty of the evidence

What is the overall certainty of the evidence of effects of MMS compared with IFA supplements?

Judgement				
☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Rationale for judgement: Moderate was the most common rating. The certainty of evidence on three outcomes (maternal anaemia, low birthweight and stillbirth) was high; certainty of evidence on four outcomes (SGA, preterm birth, perinatal mortality and neonatal mortality) was moderate; and the certainty of evidence on three outcomes (caesarean section, maternal mortality and congenital anomalies) was low.

Comparison 2: UNIMMAP formulation compared with IFA supplements

UNIMMAP contains 30 mg iron and 0.4 mg folic acid. Ten trials, conducted in Bangladesh *(36)*, Burkina Faso *(33)*, China *(31,38)*, Guinea-Bissau *(30)*, Indonesia *(34,35)*, Nepal *(32)*, the Niger *(37)* and Pakistan *(29)* contributed data to this comparison. Control arms in these trials comprised IFA in the following doses: 60 mg iron and 0.4 mg folic acid *(29,30,32,33,37,38)*, 30 mg iron and 0.4 mg folic acid *(31,34,36)*, and 60 mg iron and 0.25 mg folic acid *(35)*. In this comparison, the last trial was excluded in sensitivity analyses, which were restricted to trials using a 0.4 mg dose of folic acid.

Maternal outcomes

The evidence on maternal outcomes was consistent with Comparison 1, and suggests little or no difference in the relative effects of UNIMMAP compared with IFA supplements (30 mg or 60 mg) on maternal anaemia, caesarean section and maternal mortality, as follows:

- **Maternal anaemia:** Three trials; RR: 0.93, 95% CI: 0.83 to 1.03 (*moderate-certainty evidence, downgraded due to design limitations*).
- **Caesarean section:** Three trials; RR: 1.06, 95% CI: 0.75 to 1.49 (*low-certainty evidence, downgraded due to design limitations and imprecision*).
- **Maternal mortality:** Three trials; RR: 0.97, 95% CI: 0.63 to 1.48 *(low-certainty evidence, downgraded due to design limitations and imprecision*).

Subgroup findings according to the dose of iron used in the control group were similar to the overall findings for these outcomes. There were no relevant data in the review on pre-eclampsia, gestational diabetes mellitus, infection and positive pregnancy experience outcomes.

Fetal/neonatal outcomes

SGA: The evidence suggests that the UNIMMAP supplement probably reduces the risk of having an SGA neonate compared with IFA supplements (nine trials; RR: 0.91, 95% CI: 0.85 to 0.98; *moderate-certainty evidence, downgraded for design limitations*).

Low birthweight: Consistent with Comparison 1, the evidence suggests that the UNIMMAP supplement probably reduces the risk of having a low-birthweight neonate compared with IFA supplements (10 trials; RR: 0.87, 95% CI: 0.81 to 0.94; *moderate-certainty evidence, downgraded due to design limitations*).

Preterm birth: Consistent with Comparison 1, the evidence suggests that the UNIMMAP effect is probably similar to IFA supplements (10 trials; RR: 1.00, 95% CI: 0.96 to 1.03; *moderate-certainty evidence, downgraded due to design limitations*).

Congenital anomalies: Consistent with Comparison 1, the evidence suggests that the effect of UNIMMAP on congenital anomalies may be similar to IFA supplements (one trial with 1200 women; RR: 0.99, 95% CI: 0.14 to 7.04; *low-certainty evidence, downgraded due to imprecision and design limitations*).

Perinatal mortality: Consistent with Comparison 1, subgroup findings differed according to the dose of iron in the IFA supplements (tests for subgroup differences: $P = 0.03$, $I^2 = 77.9\%$); therefore, these subgroup data were not pooled. In the 60 mg iron subgroup, IFA supplements were favoured (six trials; RR: 1.20, 95% CI: 0.95 to 1.51;

moderate-certainty evidence, downgraded for imprecision) and in the 30 mg iron subgroup, UNIMMAP was favoured (three trials; RR: 0.90, 95% CI: 0.80 to 1.01; *moderate-certainty evidence, downgraded for imprecision*); however, neither of these effect estimates was statistically significant.

Neonatal mortality: Consistent with Comparison 1, subgroup findings differed according to the dose of iron in the IFA supplements (P = 0.05, I^2 = 74.4%) with the point estimate favouring IFA supplements in the 60 mg iron subgroup (six trials; RR: 1.25, 95% CI: 0.94 to 1.67; *moderate-certainty evidence, downgraded for imprecision*) and UNIMMAP in the 30 mg iron subgroup (three trials; RR: 0.90, 95% CI: 0.78 to 1.05; *moderate-certainty evidence, downgraded for imprecision*). Both subgroup estimates included the possibility of no difference. However, in the sensitivity analysis restricted to studies using 0.4 mg of folic acid, the trend in favour of 60 mg IFA supplements became statistically significant (five trials; RR: 1.38, 95% CI: 1.05 to 1.82).

Stillbirth: Consistent with Comparison 1, the evidence suggests that the UNIMMAP supplement may have a similar effect on stillbirth rates as IFA supplements (10 trials; RR: 1.00, 95% CI: 0.86 to 1.17; *low-certainty evidence, downgraded due to design limitations and suspected publication bias*).

There were no relevant data on fetal and neonatal infection and side effect outcomes.

Summary of effects

The evidence on effects of UNIMMAP versus IFA supplements is largely consistent with Comparison 1, showing a reduction in low birthweight of 13% (6–19%). The evidence additionally suggests a 9% (2–15%) reduction in SGA with UNIMMAP supplements versus IFA supplements. Also consistent with Comparison 1 is uncertain subgroup evidence suggesting that, when compared with IFA supplements containing a higher dose of iron (60 mg), MMS may be less effective in reducing neonatal mortality.

Desirable effects

How substantial are the desirable anticipated effects of UNIMMAP compared with IFA supplements?

Judgement					
☐ Don't know	☐ Varies	☐ Trivial	☒ Small	☐ Moderate	☐ Large

Rationale for judgement: As with Comparison 1, evidence for this comparison also suggests a small reduction (9%) in SGA in favour of MMS.

Undesirable effects

How substantial are the undesirable anticipated effects of UNIMMAP compared with IFA supplements?

Judgement					
☐ Don't know	☒ Varies	☐ Large	☐ Moderate	☐ Small	☐ Trivial

Rationale for judgement: Same as Comparison 1 – some subgroup evidence suggested that the relative effect of MMS compared with IFA supplements on neonatal mortality may vary according to the dose of iron (30 mg or 60 mg) and folic acid in the IFA supplements control group. These findings were uncertain and the panel also considered that the option of "Don't know" could apply here.

Certainty of the evidence

What is the overall certainty of the evidence of effects of UNIMMAP compared with IFA supplements?

Judgement				
☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Rationale for judgement: Certainty of evidence on five outcomes (maternal anaemia, low birthweight, SGA, preterm birth and perinatal mortality) was moderate; certainty of evidence on five outcomes (caesarean section, maternal mortality, congenital anomalies, neonatal mortality and stillbirths) was low.

Additional considerations

- In general, the research evidence suggests there may be some beneficial effects with MMS and that they may cause little harm compared with IFA supplements; however, this evidence was derived mostly from trials using MMS containing 30 mg of iron and 0.4 mg of folic acid, i.e. UNIMMAP (see Box 2). Many LMICs use IFA supplements with a higher dose of iron than 30 mg. Due to some uncertainty about the effects of switching from a higher dose of iron to a lower dose, more research is needed.
- All evidence was derived from studies in LMICs; its applicability to other country settings is unclear.
- WHO advises that 60 mg iron be taken daily by pregnant women and adolescent girls in settings with a high prevalence of anaemia *(1)*.
- A non-Cochrane review of MMS in LMIC countries *(39)* found that MMS reduced the risk of low birthweight by 14% (8–19%), preterm birth by 7% (2–13%) and SGA births by 6% (2–10%) on average compared with IFA supplements; the effects on low birthweight and SGA were greater among anaemic women than non-anaemic women. The review also found that, whilst there was no difference in neonatal mortality overall (RR: 0.99, 95% CI: 0.89 to 1.09), MMS were associated with lower neonatal mortality among female neonates by about 15% (4–25%). The review used individual patient data for 112 953 pregnant women from 17 RCTs comparing MMS with IFA supplements alone. In meta-analyses, data were pooled using a fixed effects model. Two trials, SUMMIT, 2008 *(34)* and West et al., 2014 *(28)*, which used 30 mg and 27 mg of iron in the control arms, respectively, contributed more than two-thirds of the data. Trials among anaemic and/or malnourished pregnant women were also included in this review. These factors may explain differences in effect estimates between the Cochrane data used by WHO and the Smith et al. (2017) review. The latter also noted, however, that "some subgroups given multiple micronutrient supplements with low-dose iron (≤ 30 mg) had higher stillbirth and neonatal mortality than iron-folic acid alone with 60 mg iron".
- A meta-analysis of neonatal mortality data for the MMS versus 60 mg iron IFA comparison has also been the focus of a separate paper in which study methods are not reported in detail *(40)*. This meta-analysis included data from the 60 mg study group of the MINIMat trial *(36)* that were not available in the 2019 Cochrane review (the latter only included data for the 30 mg IFA study group from this trial). Sudfeld and Smith (2019) also included data from one trial *(41)* that was excluded from the WHO analyses because its multiple MMS comprised fewer than 13 micronutrients. Point estimates for RRs from these two additional trials favoured MMS and, overall, 11 trials included in their neonatal mortality analysis gave an RR of 1.05 (95% CI: 0.85 to 1.30), suggesting little or no difference in effect between MMS and IFA supplements.
- A review of the effects of antenatal MMS compared with IFA supplements on health benefits for children used data from nine of the trials included in the 2015 Cochrane review *(12)*, six of which assessed UNIMMAP *(42)*. This review found no evidence of additional health benefits in the longer term with MMS, specifically for child mortality (nine trials), weight-for-age (four trials), height-for-age (six trials), head circumference (three trials) and cognitive function (four trials).

Summary table of the evidence for Comparisons 1 and 2, with certainty ratings

Outcome	Comparison 1 – MMS with 13 to 15micronutrients	Evidence certainty	Comparison 2 – UNIMMAP	Evidence certainty	Sensitivity analysis*
Maternal anaemia	No clear difference	High	No clear difference	Moderate	Consistent with main findings.
Caesarean section	No clear difference	Low	No clear difference	Low	Consistent with main findings.
Maternal mortality	No clear difference.	Low	No clear difference.	Low	Consistent with main findings.
SGA	No clear difference.	Moderate	UNIMMAP better.	Moderate	Consistent with main findings.
Low birthweight	MMS better.	High	UNIMMAP better.	Moderate	Consistent with main findings.
Preterm birth	No clear difference.	Moderate	No clear difference.	Moderate	Consistent with main findings.
Perinatal mortality	Subgroup differences. Clear difference suggests MMS is probably better than IFA supplements containing 30 mg iron.	Moderate	Subgroup differences but no clear effect differences.	Moderate	Subgroup differences but no clear effect differences.
Neonatal mortality	Subgroup differences but no clear effect differences.	Moderate	Subgroup differences but no clear effect differences.	Moderate	Clear differences suggesting 60 mg iron IFA supplements possibly better than MMS/ UNIMMAP containing 30 mg iron.
Stillbirth	No clear difference.	High	No clear difference.	Low	Consistent with main findings.
Congenital anomalies	No clear difference.	Low	No clear difference.	Low	Consistent with main findings.

**Limited to studies with 0.4 mg folic acid in the control arm.*

Values

Is there important uncertainty about, or variability in, how much women (and their families) value the main outcomes associated with MMS?

A scoping review of what women want from ANC informed the outcomes for the ANC guideline *(18)*. Evidence showed that women from various resource settings valued having a positive pregnancy experience, which comprises three equally important components: effective clinical practices (interventions and tests), relevant and timely information, and psychosocial and emotional support – each provided by practitioners with good clinical and interpersonal skills within a well-functioning health system *(high confidence in the evidence).*

Judgement			
☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Rationale for judgement: As it is important to pregnant women to have effective clinical practices, in populations with a high prevalence of anaemia, there may be concerns about switching from an IFA supplement containing 60 mg elemental iron to an MMS containing a lower dose of iron.

Balance of effects

Does the balance between desirable and undesirable effects favour MMS or IFA supplements?

Judgement						
☐ Don't know	☐ Varies	☐ Favours IFA supplements	☐ Probably favours IFA supplements	☒ Does not favour MMS or IFA supplements	☐ Probably favours MMS	☐ Favours MMS

Rationale for judgement: MMS effects seem to be largely similar to IFA supplements.

2) Resources

How large are the resource requirements (costs)?

Research evidence

Two economic analyses published in 2019 found MMS to be cost-effective compared with IFA supplements *(43,44)*.

Kashi et al. (2019) *(43)* examined the cost-effectiveness of UNIMMAP versus antenatal IFA supplements in populations in Bangladesh, India and Pakistan. The study used effect estimates for eight outcomes derived from Smith et al. (2017) *(39)* and a 2017 version of the Cochrane review *(45)*. The analysis took account of the fact that some outcomes were not mutually exclusive (e.g. low birthweight, SGA and preterm birth). Cost calculations included the cost of supplements per woman per pregnancy (given as US$ 1.63 and US$ 3.46 for 60 mg iron IFA supplements and MMS, respectively) and patient, facility and programme costs. The total cost for IFA supplements per woman was estimated at US$ 15.04 compared with US$ 16.86 for MMS, with most of the cost in both arms being accounted for by patient and facility costs, assumed to be the same for both supplements. The effects of supplements were expressed as disability-adjusted life years (DALYs). Using more conservative Cochrane risk estimates, findings suggested that MMS would avert 8578 (Bangladesh), 5769 (India) and 6050 (Pakistan) DALYs per 100 000 pregnancies. The overall conclusion in the report was that MMS were more cost-effective than IFA supplements.

Engle-Stone et al. (2019) *(44)* also based their cost-effectiveness analysis of antenatal MMS versus IFA supplements in Bangladesh and Burkina Faso on the study by Smith et al. (2017) *(39)*. They applied effect modifiers, including anaemia, sex, and underweight, based on population prevalence in the case study countries, where these factors were associated with statistically significant subgroup differences in the review. They also conducted a sensitivity analysis using a subset of eight trials that contained the same dose of iron in the MMS and IFA supplements. Due to differences in baseline prevalence of pregnancy outcomes in the two case study countries, the composition of estimated absolute benefits was expected to vary. Increased supply costs of MMS were calculated at US$ 4878 per million tablets and other costs were assumed to be similar to IFA; the cost of transitioning was not included. Assuming 100% coverage, the additional costs with MMS amounted to US$ 2.7 million and US$ 600 000 for Bangladesh and Burkina Faso, respectively.

Additional considerations

- An intervention may be considered to be "very cost-effective" if it costs less than a country's gross domestic product (GDP) per capita to save a year of life, and "cost-effective" if it costs less than three times the GDP per capita *(46)*. However, WHO recommends using a range of considerations to inform investment decisions (Bertram et al., 2016) *(47)*.
- In addition to the published reports, a tool to estimate the cost-benefit of transitioning from IFA supplements to MMS in LMICs was recently developed by Nutrition International (https://www.nutritionintl.org/knowledge-centre/mms-cost-benefit-tool/). The tool enables users to test different scenarios relevant to their population settings. Up to eight health outcomes are included in the analysis and cost-benefits can be estimated using effect estimates from either the 2019 Cochrane review or the 2017 Smith et al. review. The primary analysis uses statistically significant impacts on health outcomes as follows: stillbirth, female neonatal mortality, preterm, low birthweight and SGA from Smith et al. (2017) *(39)*; and low birthweight and SGA from Keats et al. (2019) *(13)*. Using data from 12 LMICs (Bangladesh, Burkina Faso, Ethiopia, India, Indonesia, Kenya, Madagascar, Nigeria, Pakistan, Philippines, Senegal, United Republic of Tanzania), the tool in all scenarios modelled shows that, based on the statistically significant effects reported in these reviews, MMS may be very cost-effective compared with IFA supplements.
- To inform this EtD framework, Nutrition International modelled the data from the estimates in the WHO analysis. Key assumptions in these cost-effectiveness analyses were that 30% of pregnant women received 180 days of supplements; costs and benefits were calculated for a 10-year time span; and costs were based on the UNICEF Supply Catalogue pricing (2016). The primary analysis used the statistically significant estimates of low birthweight and SGA from the WHO meta-analysis and, in these outputs, MMS remained very cost-effective in all scenarios. Furthermore, when the dose of iron was considered, transitioning from 30 mg IFA supplements to MMS remained very cost-effective even when non-statistically significant effects were included. However, transitioning from 60 mg IFA supplements to MMS was not shown to be cost-effective when non-statistically significant outcomes were included, due to the impact of neonatal mortality estimates for this comparison.[5] These exploratory findings should be interpreted with caution.
- UNICEF Supply Catalogue pricing accessed in November 2019 is approximately US$ 3.42 for 180 × UNIMMAP supplements, US$ 2.35 for 180 × 60 mg IFA supplements, and US$ 1.75 for 180 × 30 mg IFA supplements *(48)*. Actual supply costs may be less than these estimates and are expected to come down with increased global production and distribution.[5]

Main resource requirements

Apart from the cost of the supplements, all other costs, including facility costs and programme costs, would be the same for MMS and IFA supplements. However, there would be change-over costs, which may include re-training staff, designing new teaching materials, updating guidelines and administrative costs.

Resources required

How costly are the resources required for MMS compared with IFA supplements?

Judgement						
☐ Don't know	☐ Varies	☐ Large costs	☒ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Rationale for judgement: Supply costs of MMS may be double those of IFA supplements.

Certainty of evidence on required resources

What is the certainty of the evidence on costs?

Judgement				
☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Rationale for judgement: The supply costs are taken from the UNICEF Supply Catalogue. Other costs, apart from transitioning costs, would probably be similar.

5 Information from Nutrition International, with support from Limestone Analytics. MMS cost benefit tool: integration of WHO meta-analyses draft technical report. 26 November 2019. [unpublished]

Cost-effectiveness

How cost-effective are MMS compared with IFA supplements?

Judgement						
☐ Don't know	☒ Varies	☐ Favours IFA	☐ Probably favours IFA	☐ Does not favour MMS or IFA	☐ Probably favours MMS	☐ Favours MMS

Rationale for judgement: Cost-effectiveness may vary depending on the population setting, including the dose of iron in the existing IFA supplements, and the prevalence of anaemia, low birthweight and other health outcomes.

3) Equity

What would be the impact of MMS compared with IFA supplements on health equity?

Research evidence

The WHO *State of inequality* report (2015) shows that women who are poor, least educated, and residing in rural areas have lower health intervention coverage and worse health outcomes than the more advantaged women in LMICs *(49).* ANC coverage of at least four visits differed according to the women's education and income levels; inequalities in ANC coverage of at least one visit were also demonstrated, though to a lesser extent. In 50% of study countries, infant mortality was at least eight deaths per 1000 live births higher in rural than in urban areas and, in about a quarter of the study countries, neonatal mortality was at least 15 deaths per 1000 live births higher among the least educated. Stunting prevalence in children under 5 was also substantially unequal between the least and most educated mothers.

Additional considerations
Nutritional deficiencies are common in disadvantaged populations, including humanitarian and emergency settings. Effective interventions to improve the general nutritional status of pregnant women and adolescent girls in LMICs could help to address maternal and neonatal health inequalities by improving general health and preventing maternal illness related to vitamin and mineral deficiencies.

Judgement						
☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Rationale for judgement: Improving general health and preventing maternal illness related to vitamin and mineral deficiencies may help to reduce health inequalities.

4) Acceptability

Would switching from IFA supplements to MMS be acceptable to key stakeholders?

Research evidence

A systematic review of qualitative research exploring women's views and experiences of ANC suggests that they tend to view ANC as a source of knowledge and information, and generally appreciate any advice (including dietary or nutritional) that may lead to a healthy baby and a positive pregnancy experience *(high confidence in the evidence) (19).*

The same review explored health professionals' views of ANC, which suggested that health professionals are keen to offer general health-care advice and specific pregnancy-related information *(low confidence in the evidence)* but sometimes feel they do not have the appropriate training and lack the resources and time to deliver the service in the informative, supportive and caring manner that women want *(high confidence in the evidence) (19).*

Additional considerations

- At a WHO technical meeting on MMS during pregnancy, it was noted that lack of appropriate training of health workers was a barrier to supplementation programmes in LMICs *(50)*.
- If women are expected to pay for supplements, the higher cost of MMS may not be acceptable to them.
- MMS may be more acceptable than IFA supplements in settings where taking IFA supplements involves taking more than one tablet.
- MMS containing 30 mg iron may be more acceptable than IFA supplements containing higher doses of iron if MMS are associated with fewer gastrointestinal side effects.

Judgement

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Rationale for judgement: If women are not expected to pay for supplements, there is probably no reason for MMS to be less acceptable than IFA supplements.

5) Feasibility

Would switching from IFA supplements to MMS be feasible to implement?

Research evidence

Evidence derived from a QES conducted to support the guideline development shows that where there are likely to be additional costs associated with supplementation *(high confidence in the evidence)* or where the recommended intervention is unavailable because of resource constraints *(low confidence in the evidence),* women may be less likely to engage with services *(19).* In addition, in a number of LMIC settings, providers felt that a lack of resources – both in terms of the availability of the supplements and the lack of suitably trained staff to deliver nutritional information – may limit the implementation of this intervention *(high confidence in the evidence).*

Additional considerations

- From the demand side, if supplements are free and available, routine MMS should be as feasible as IFA supplements. However, on the supply side there may be several considerations to take into account, such as changes in regulatory norms and policies (e.g. tariffs, labelling, imports, government oversight, etc.), how sustainable the production is (local or imported), and how to guarantee product availability *(50).*

Judgement

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Rationale for judgement: If MMS supplies are guaranteed and affordable, there is probably no reason for MMS to be less feasible than IFA supplements.

C. Summary of GDG judgements on antenatal multiple micronutrient supplements

Desirable effects	- Don't know	- Varies		- Trivial	✓ Small	- Moderate	- Large
Undesirable effects	Don't know	✓ Varies		- Large	- Moderate	- Small	- Trivial
Certainty of the evidence on effects	- No included studies			- Very low	- Low	✓ Moderate	- High
Values				- Important uncertainty or variability	✓ Possibly important uncertainty or variability	- Probably no important uncertainty or variability	- No important uncertainty or variability
Balance of effects	- Don't know	- Varies	- Favours IFA supplements	- Probably favours IFA supplements	✓ Does not favour MMS or IFA supplements	- Probably favours MMS	- Favours MMS
Resources required	- Don't know	- Varies	- Large costs	✓ Moderate costs	- Negligible costs or savings	- Moderate savings	- Large savings
Certainty of evidence on required resources	- No included studies			- Very low	Low	✓ Moderate	- High
Cost-effectiveness	- Don't know	✓ Varies	- Favours IFA supplements	- Probably favours IFA supplements	- Does not favour MMS or IFA supplements	- Probably favours MMS	- Favours MMS
Equity	- Don't know	- Varies	- Reduced	- Probably reduced	- Probably no impact	✓ Probably increased	- Increased
Acceptability	- Don't know	- Varies		- No	- Probably No	✓ Probably Yes	- Yes
Feasibility	- Don't know	- Varies		- No	- Probably No	✓ Probably Yes	- Yes

Dissemination and implementation of the recommendation

Recommendation dissemination

This updated global guideline will be available online for download and also as a printed publication. Online versions will be available via the WHO websites and other online platforms developed by the WHO Departments of SRH, NFS and MCA, and through the WHO Reproductive Health Library (RHL)[6] and e-Library of Evidence for Nutrition Actions (eLENA).[7] Print versions will be distributed to WHO regional and country offices, ministries of health, WHO collaborating centres, NGO partners, among others, using the same distribution list that was developed for the WHO ANC guideline *(1)*. The updated recommendation and updated derivative products, in particular, the WHO Antenatal Care Recommendations Adaptation Toolkit and its Instruction Manual, will be disseminated during meetings and scientific conferences attended by WHO staff. To increase awareness of the updated recommendation, a short commentary will be published in a peer-reviewed journal and social media channels will also be used. The executive summary and recommendation from this publication will be translated into the six UN languages for dissemination through the WHO regional offices and during meetings organized by, or attended by, WHO staff.

Implementation considerations and applicability issues

This updated recommendation supersedes the respective WHO ANC guideline recommendation on MMS that was issued in 2016 (recommendation A6) *(1)*. The GDG agreed that there were no new implementation considerations or applicability issues specific to this recommendation, as it is recommended in a research context. For GDG considerations relevant to each of these recommendations, stakeholders should refer to the "Remarks" sections beneath the recommendation in the "Evidence and recommendations" sections. For general implementation considerations related to *WHO recommendations on antenatal care for a positive pregnancy experience,* please refer to this guideline *(1)* and associated derivative products, which are available on the WHO website.

6 RHL is available at: http://apps.who.int/rhl/en/.
7 eLENA is available at: https://www.who.int/elena/en/.

Research implications

During the recommendation development process, the GDG identified an important knowledge gap that needs to be addressed through primary research. This is stated in Box 3.

Box 3. Priority research questions for MMS

What is the impact of switching from routine antenatal IFA supplements (either with 30 mg or 60 mg elemental iron) to MMS on important health outcomes (maternal, perinatal, child), equity, acceptability, feasibility, sustainability and health-care resources in different country settings?

Updating the guideline

WHO convenes the Executive GSG biannually to review WHO's current portfolio of maternal and perinatal health recommendations, and to advise on the prioritization of new and existing questions for recommendation development and updating. Accordingly, this recommendation will be reviewed and updated in the event that new evidence is identified that could potentially impact the current evidence base. Any concern about the validity of the recommendation will be promptly communicated via the guideline website[8] and plans will be made to update the recommendation, as necessary. WHO will prioritize its independent normative guidance informed by the strategic shifts embedded in its Constitution and the Thirteenth General Programme of Work 2019–2023.

All technical products developed during the process of developing this recommendation – including the Cochrane RevMan[9] file customized for priority outcomes – and the basis for quality rating of outcomes within the GRADE process will be archived in the departmental shared folder for future reference and use.

8 Available at: https://www.who.int/reproductivehealth/publications/maternal_perinatal_health/anc-positive-pregnancy-experience/en/.
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Annex 2. Summary of declarations of interest from the Guideline Development Group (GDG) members and how they were managed

Name (with title)	Gender	Expertise	Disclosure of interest	Conflict of interest and management
Dr Niveen Abu-Rmeileh	F	Community and public health, statistical epidemiology	None declared.	Not applicable.
Dr Luz Maria De-Regil	F	Nutrition, epidemiology, systematic reviews, programme implementation	Authored two publications on MMS for pregnant women and two on vitamin D supplementation. Former full-time staff employee of Nutrition International (2013–2018), not-for-profit organization that delivers micronutrient interventions, including IFA supplementation to women, in multiple countries in Asia and Africa. Nutrition International received grants from the Government of Canada to support research and implementation of iron and folic acid supplementation programmes.	The conflict was not considered serious enough to affect GDG membership or participation in the GDG meeting.
Dr Atf Ghérissi	F	Systematic reviews, qualitative evidence, maternal and perinatal health, community health	None declared.	Not applicable.
Ms Gill Gyte	F	Consumer representative, pregnancy and childbirth	None declared.	Not applicable.
Dr Rintaro Mori	M	Perinatology, neonatology, systematic reviews, evidence synthesis and guideline development using GRADE	None declared.	Not applicable.
Prof. Jim Neilson	M	General obstetrics, perinatology, gynaecology, systematic reviews, evidence synthesis and guideline development using GRADE	None declared.	Not applicable.
Dr Lynnette Neufeld	F	Micronutrients, programmes, epidemiology	None declared.	Not applicable.

Name (with title)	Gender	Expertise	Disclosure of interest	Conflict of interest and management
Dr Lisa Noguchi	F	Midwifery, delivery of care, implementation science	Employer anticipated research funding from Bill & Melinda Gates Foundation related to studying introduction of innovations and improving quality of care in ANC and post-natal care.	The conflict was not considered serious enough to affect GDG membership or participation in the technical consultation.
Prof. Nafissa Osman	F	Obstetrics and gynaecology, implementation research	None declared.	Not applicable.
Dr Erika Ota	F	Nutrition, evidence synthesis, guideline development	None declared.	Not applicable.
Prof. Robert Pattinson	M	Obstetrics and gynaecology, delivery of care, evidence synthesis	None declared.	Not applicable.
Prof. Harshi Sachdev	M	Paediatrics, nutrition, systematic reviews	Contributed data from India to subsequent meta-analyses and contributed to a published opinion paper on the subject of multiple micronutrients in pregnancy. Was involved in the epidemiological design and analysis of this publication; however, did not receive funding for this work.	The conflict was not considered serious enough to affect GDG membership or participation in the technical consultation.
Ms Rusidah Selamat	F	Maternal and infant nutrition, community-based programmes, implementation research	None declared.	Not applicable.
Dr Charlotte Warren	F	Maternal and perinatal health, systematic reviews, implementation research	None declared.	Not applicable.
Prof. Charles Wisonge	M	Health systems, systematic reviews, delivery of care	None declared.	Not applicable.

Annex 3. Multiple micronutrient supplements: GRADE tables and forest plots

GRADE tables for effects of multiple micronutrient supplements (MMS) vs iron and folic acid supplements (IFAS): Comparison 1

Question: Antenatal MMS with 13–15 micronutrients, including iron (27 mg to 60 mg) and folic acid compared with iron (30 mg or 60 mg) and folic acid supplements.

Setting: Low- and middle-income countries.

Source: Guideline Development Group (GDG)-specified WHO analysis based on data found in: *Keats EC, Haider BA, Tam E, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. Cochrane Database of Systematic Reviews. 2019;3(3):CD004905 (13).*

Certainty assessment							Number of participants		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Comparison 1: 13–15 micronutrients	IFAS	Relative (95% CI)	Absolute (95% CI)		
Maternal anaemia (third trimester Hb <110 g/L)												
8	randomized trials	not serious	not serious	not serious	not serious	none	27 832	27 731	**RR 1.03** (0.92 to 1.15)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗⊗ HIGH	CRITICAL
Maternal anaemia (third trimester Hb <110 g/L) – versus 60 mg iron plus folic acid												
7	randomized trials	not serious	serious [a]	not serious	not serious	none	5332	5231	**RR 1.04** (0.90 to 1.21)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗◯ MODERATE	CRITICAL
Maternal anaemia (third trimester Hb <110 g/L) – versus 30 mg iron plus folic acid												
1	randomized trial	not serious	not serious	not serious	not serious	none	22 500	22 500	**RR 1.01** (0.89 to 1.14)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗⊗ HIGH	CRITICAL

Certainty assessment							Number of participants		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Comparison 1: 13–15 micronutrients	IFAS	Relative (95% CI)	Absolute (95% CI)		
Mode of delivery: Caesarean section												
4	randomized trials	serious [b]	not serious	not serious	serious [c]	none	3299	3374	**RR 1.04** (0.76 to 1.43)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Mode of delivery: Caesarean section – versus 60 mg iron plus folic acid												
3	randomized trials	serious [b]	not serious	not serious	serious [c]	none	2462	2542	**RR 1.06** (0.75 to 1.49)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Mode of delivery: Caesarean section – versus 30 mg iron plus folic acid												
0 [d]							0	0	not pooled	not pooled	-	CRITICAL
Mode of delivery: Caesarean section – iron dose not specified												
1	randomized trial	serious [b]	not serious	not serious	serious [c]	none	837	832	**RR 0.96** (0.41 to 2.25)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Maternal mortality												
6	randomized trials	serious [b]	not serious	not serious	serious [c]	none	42 494	41 375	**RR 1.06** (0.72 to 1.54)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Maternal mortality – versus 60 mg iron plus folic acid												
4	randomized trials	very serious [e]	not serious	not serious	serious [c]	none	4190	3389	**RR 0.88** (0.41 to 1.87)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗○○○ VERY LOW	CRITICAL

Certainty assessment							Number of participants		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Comparison 1: 13–15 micronutrients	IFAS	Relative (95% CI)	Absolute (95% CI)		
Maternal mortality – versus 30 mg iron plus folic acid												
2	randomized trials	serious [b]	not serious	not serious	serious [c]	none	38 304	37 986	**RR 1.12** (0.73 to 1.74)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Small for gestational age												
15	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [f]	50 562	49 423	**RR 0.98** (0.96 to 1.00)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Small for gestational age – versus 60 mg iron plus folic acid												
11	randomized trials	serious [b]	not serious	not serious	not serious	publication bias strongly suspected [f]	10 197	9357	**RR 0.95** (0.89 to 1.01)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Small for gestational age – versus 30 mg iron plus folic acid												
3	randomized trials	not serious	not serious	not serious	not serious	none	39 528	39 234	**RR 0.98** (0.96 to 1.00)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗⊗ HIGH	CRITICAL
Small for gestational age – iron dose not specified												
1	randomized trial	serious [b]	not serious	not serious	serious [c]	none	837	832	**RR 0.81** (0.51 to 1.28)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Low birthweight												
16	randomized trials	not serious	not serious	not serious	not serious	none	56 814	55 689	**RR 0.88** (0.86 to 0.91)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗⊗ HIGH	CRITICAL

Certainty assessment							Number of participants		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Comparison 1: 13–15 micronutrients	IFAS	Relative (95% CI)	Absolute (95% CI)		
Low birthweight – versus 60 mg iron plus folic acid												
11	randomized trials	serious [b]	not serious	not serious	not serious	publication bias strongly suspected [f]	10 197	9357	**RR 0.90** (0.82 to 0.98)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Low birthweight – versus 30 mg iron plus folic acid												
4	randomized trials	not serious	not serious	not serious	not serious	none	45 780	45 500	**RR 0.88** (0.85 to 0.91)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗⊗ HIGH	CRITICAL
Low birthweight – iron dose not specified												
1	randomized trial	serious [b]	not serious	not serious	serious [c]	none	837	832	**RR 0.74** (0.45 to 1.22)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Preterm births												
16	randomized trials	serious [b]	not serious	not serious	not serious	none	56 814	55 689	**RR 0.94** (0.88 to 1.00)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Preterm births – versus 60 mg iron plus folic acid												
11	randomized trials	serious [b]	not serious	not serious	not serious	publication bias strongly suspected [f]	10 197	9357	**RR 0.99** (0.92 to 1.07)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL

Certainty assessment							Number of participants		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Comparison 1: 13–15 micronutrients	IFAS	Relative (95% CI)	Absolute (95% CI)		
Preterm births – versus 30 mg iron plus folic acid												
4	randomized trials	not serious	serious [g]	not serious	not serious	none	45 780	45 500	**RR 0.90** (0.80 to 1.01)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Preterm births – iron dose not specified												
1	randomized trial	serious [b]	not serious	not serious	serious [c]	none	837	832	**RR 0.79** (0.55 to 1.13)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Congenital anomalies – versus 60 mg iron plus folic acid												
2	randomized trials	serious [b]	not serious	not serious	serious [c]	none	1039	1041	**RR 1.34** (0.25 to 7.12)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Perinatal mortality												
13	randomized trials	not serious	not serious	not serious	not serious	serious [i]	53 920	52 934	Subgroup data not pooled (tests for subgroup differences $P = 0.05$, $I^2 = 73.4\%$)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	-	CRITICAL
Perinatal mortality – versus 60 mg iron plus folic acid												
9	randomized trials	not serious	not serious	not serious	serious [c]	none	8140	7434	**RR 1.15** (0.93 to 1.42)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL

Certainty assessment							Number of participants		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Comparison 1: 13–15 micronutrients	IFAS	Relative (95% CI)	Absolute (95% CI)		
Perinatal mortality – versus 30 mg iron plus folic acid												
4	randomized trials	not serious	not serious	not serious	not serious	serious [h]	45 780	45 500	**RR 0.92** (0.86 to 0.98)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Neonatal mortality												
13	randomized trials	not serious	not serious	not serious	not serious	serious [i]	53 920	52 934	Subgroup data not pooled (tests for subgroup differences $P = 0.08$, $I^2 = 68.4\%$)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	-	CRITICAL
Neonatal mortality – versus 60 mg iron plus folic acid												
9	randomized trials	not serious	not serious	not serious	serious [c]	none	8140	7434	**RR 1.22** (0.94 to 1.56)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Neonatal mortality – versus 30 mg iron plus folic acid												
4	randomized trials	not serious	not serious	not serious	not serious	serious [h]	45 780	45 500	**RR 0.95** (0.87 to 1.04)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Stillbirths												
15	randomized trials	not serious	not serious	not serious	not serious	none	56 650	55 543	**RR 0.98** (0.87 to 1.10)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗⊗ HIGH	CRITICAL
Stillbirths – versus 60 mg iron plus folic acid												

Certainty assessment							Number of participants		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Comparison 1: 13–15 micronutrients	IFAS	Relative (95% CI)	Absolute (95% CI)		
10	randomized trials	not serious	not serious	not serious	serious [c]	none	10 033	9211	**RR 1.11** (0.89 to 1.37)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Stillbirths – versus 30 mg iron plus folic acid												
4	randomized trials	not serious	not serious	not serious	not serious	serious [h]	45 780	45 500	**RR 0.89** (0.82 to 0.97)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Stillbirths – iron dose not specified												
1	randomized trials	serious [b]	not serious	not serious	serious [c]	none	837	832	**RR 1.98** (0.37 to 10.76)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Serious unexplained heterogeneity (I^2 = 61%).

b. Most of the pooled effect provided by studies with some risk of bias but without a substantial proportion (i.e. < 50%) from studies with a high risk of bias ("C" studies).

c. Wide CI crossing the line of no effect.

d. No studies were found that evaluated this subgroup for this outcome.

e. Most of the pooled effect provided by "B" or "C" studies but with a substantial proportion (i.e. > 50%) from "C" studies.

f. Evident asymmetry in funnel plot.

g. Serious unexplained heterogeneity (I^2 = 86%).

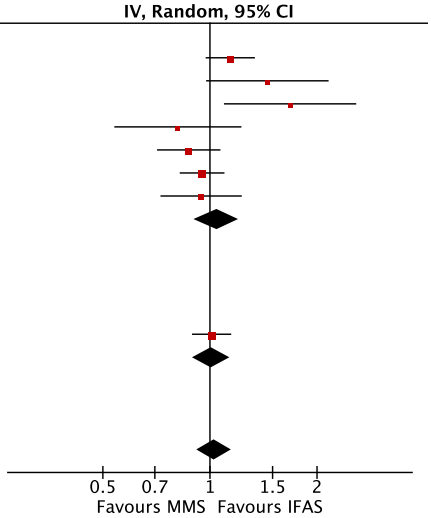
h. The study contributing the most weight (West et al., 2014) used 27 mg iron in the IFA arm, not 30 mg.

i. Substantial subgroup differences.

Forest plots for effects of MMS vs IFAS: Comparison 1

a. Anaemia

Study or Subgroup	log[Risk Ratio]	SE	MMS Total	IFAS Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 MMS vs IFAS with 60 mg iron						
Ashorn 2010	0.1317	0.0789	466	463	17.7%	1.14 [0.98, 1.33]
Christian 2003	0.3716	0.1999	1050	957	6.3%	1.45 [0.98, 2.15]
Dewey 2009	0.5188	0.2161	439	441	5.6%	1.68 [1.10, 2.57]
Moore 2009	−0.2076	0.2075	164	146	6.0%	0.81 [0.54, 1.22]
Osrin 2005	−0.1373	0.1023	600	600	14.4%	0.87 [0.71, 1.07]
Roberfroid 2008	−0.0509	0.0715	714	712	18.8%	0.95 [0.83, 1.09]
Zeng 2008	−0.0571	0.1319	1899	1912	11.1%	0.94 [0.73, 1.22]
Subtotal (95% CI)			**5332**	**5231**	**79.8%**	**1.04 [0.90, 1.21]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 15.32$, df = 6 (P = 0.02); $I^2 = 61\%$						
Test for overall effect: Z = 0.56 (P = 0.57)						
1.1.2 MMS vs IFAS with 30 mg iron						
West 2014	0.0108	0.0623	22500	22500	20.2%	1.01 [0.89, 1.14]
Subtotal (95% CI)			**22500**	**22500**	**20.2%**	**1.01 [0.89, 1.14]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.17 (P = 0.86)						
Total (95% CI)			**27832**	**27731**	**100.0%**	**1.03 [0.92, 1.15]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 15.32$, df = 7 (P = 0.03); $I^2 = 54\%$						
Test for overall effect: Z = 0.52 (P = 0.60)						
Test for subgroup differences: $Chi^2 = 0.10$, df = 1 (P = 0.75), $I^2 = 0\%$						

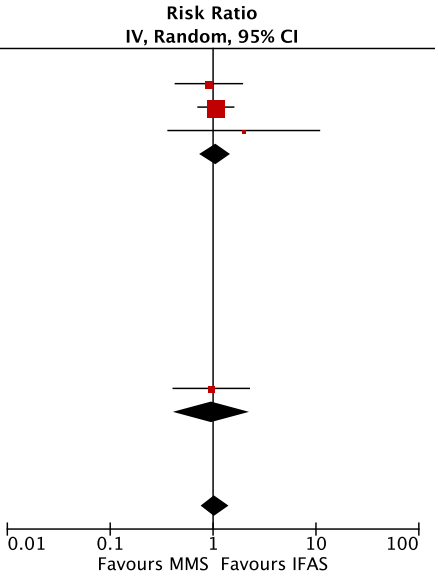


b. Caesarean section

Study or Subgroup	log[Risk Ratio]	SE	MMS Total	IFAS Total	Weight	Risk Ratio IV, Random, 95% CI
1.2.1 MMS vs IFAS with 60 mg iron						
Bhutta 2009a	−0.0943	0.3825	1148	1230	18.2%	0.91 [0.43, 1.93]
Osrin 2005	0.0621	0.2036	600	600	64.2%	1.06 [0.71, 1.59]
Roberfroid 2008	0.6868	0.8642	714	712	3.6%	1.99 [0.37, 10.81]
Subtotal (95% CI)			**2462**	**2542**	**85.9%**	**1.06 [0.75, 1.49]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.69$, df = 2 (P = 0.71); $I^2 = 0\%$						
Test for overall effect: Z = 0.31 (P = 0.76)						
1.2.2 MMS vs IFAS with 30 mg iron						
Subtotal (95% CI)			**0**	**0**		**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.2.3 Iron dose not specified						
Friis 2004 (1)	−0.0408	0.4341	837	832	14.1%	0.96 [0.41, 2.25]
Subtotal (95% CI)			**837**	**832**	**14.1%**	**0.96 [0.41, 2.25]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						
Total (95% CI)			**3299**	**3374**	**100.0%**	**1.04 [0.76, 1.43]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.73$, df = 3 (P = 0.87); $I^2 = 0\%$						
Test for overall effect: Z = 0.25 (P = 0.80)						
Test for subgroup differences: $Chi^2 = 0.04$, df = 1 (P = 0.84), $I^2 = 0\%$						

Footnotes

(1) same iron and folic acid supplements in both arms

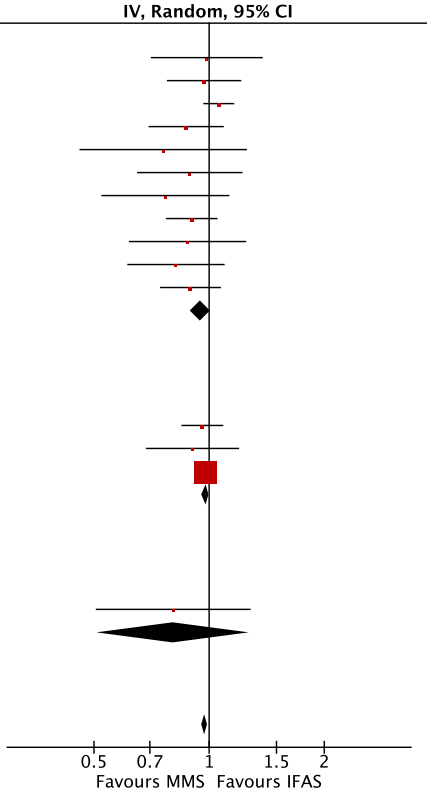


c. Maternal mortality

Study or Subgroup	log[Risk Ratio]	SE	MMS Total	IFAS Total	Weight	Risk Ratio IV, Random, 95% CI
1.3.1 MMS vs IFAS with 60 mg iron						
Ashorn 2010	−0.3268	0.7603	466	463	6.4%	0.72 [0.16, 3.20]
Dewey 2009	1.1032	1.1527	439	441	2.8%	3.01 [0.31, 28.86]
Kaestel 2005	−0.5711	0.6236	1392	708	9.5%	0.56 [0.17, 1.92]
Zagre 2007	0.1906	0.7652	1893	1777	6.3%	1.21 [0.27, 5.42]
Subtotal (95% CI)			**4190**	**3389**	**25.1%**	**0.88 [0.41, 1.87]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.89$, df = 3 (P = 0.60); $I^2 = 0\%$						
Test for overall effect: Z = 0.34 (P = 0.74)						
1.3.2 MMS vs IFAS with 30 mg iron						
SUMMIT 2008	0.02955	0.2427	15804	15486	63.0%	1.03 [0.64, 1.66]
West 2014	0.5768	0.5577	22500	22500	11.9%	1.78 [0.60, 5.31]
Subtotal (95% CI)			**38304**	**37986**	**74.9%**	**1.12 [0.73, 1.74]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.81$, df = 1 (P = 0.37); $I^2 = 0\%$						

d. Small for gestational age

Study or Subgroup	log[Risk Ratio]	SE	MMS Total	IFAS Total	Weight	Risk Ratio IV, Random, 95% CI
1.4.1 MMS vs IFAS with 60 mg iron						
Ashorn 2010	−0.0139	0.1696	466	463	0.3%	0.99 [0.71, 1.38]
Bhutta 2009a	−0.0305	0.112	1148	1230	0.8%	0.97 [0.78, 1.21]
Christian 2003	0.0583	0.0453	1050	957	4.6%	1.06 [0.97, 1.16]
Dewey 2009	−0.1381	0.1133	439	441	0.7%	0.87 [0.70, 1.09]
Kaestel 2005	−0.2763	0.2549	1392	708	0.1%	0.76 [0.46, 1.25]
Moore 2009	−0.1163	0.1597	164	146	0.4%	0.89 [0.65, 1.22]
Osrin 2005	−0.2634	0.1945	600	600	0.3%	0.77 [0.52, 1.13]
Roberfroid 2008	−0.1051	0.0772	714	712	1.6%	0.90 [0.77, 1.05]
Sunawang 2009 (1)	−0.1299	0.178	432	411	0.3%	0.88 [0.62, 1.24]
Zagre 2007	−0.1998	0.1473	1893	1777	0.4%	0.82 [0.61, 1.09]
Zeng 2008	−0.1122	0.0913	1899	1912	1.1%	0.89 [0.75, 1.07]
Subtotal (95% CI)			**10197**	**9357**	**10.7%**	**0.95 [0.89, 1.01]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 10.66$, df = 10 (P = 0.38); $I^2 = 6\%$						
Test for overall effect: Z = 1.58 (P = 0.12)						
1.4.2 MMS vs IFAS with 30 mg iron						
SUMMIT 2008	−0.0408	0.0621	15804	15486	2.5%	0.96 [0.85, 1.08]
Tofail 2008	−0.1	0.1409	1224	1248	0.5%	0.90 [0.69, 1.19]
West 2014 (2)	−0.0202	0.0105	22500	22500	86.2%	0.98 [0.96, 1.00]
Subtotal (95% CI)			**39528**	**39234**	**89.1%**	**0.98 [0.96, 1.00]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.42$, df = 2 (P = 0.81); $I^2 = 0\%$						
Test for overall effect: Z = 2.05 (P = 0.04)						
1.4.3 Iron dose not specified						
Friis 2004 (3)	−0.2163	0.2355	837	832	0.2%	0.81 [0.51, 1.28]
Subtotal (95% CI)			**837**	**832**	**0.2%**	**0.81 [0.51, 1.28]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
Total (95% CI)			**50562**	**49423**	**100.0%**	**0.98 [0.96, 1.00]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 12.13$, df = 14 (P = 0.60); $I^2 = 0\%$						
Test for overall effect: Z = 2.42 (P = 0.02)						
Test for subgroup differences: $Chi^2 = 1.44$, df = 2 (P = 0.49), $I^2 = 0\%$						



Footnotes

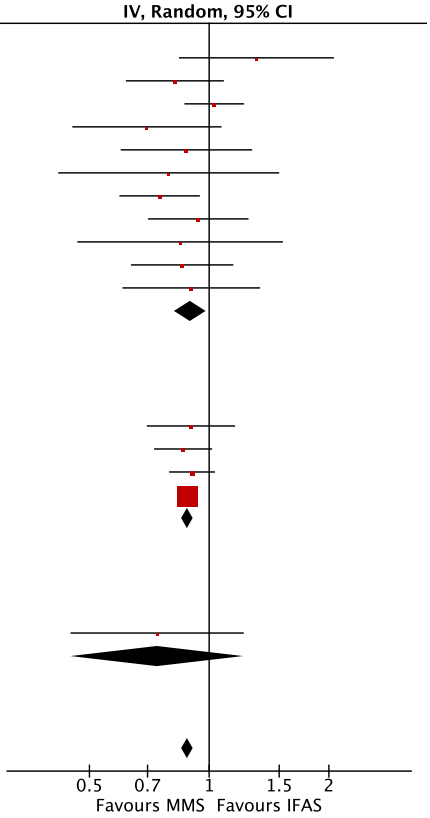
(1) Control group received 60 mg iron and 0.25 mg folic acid

(2) Control group received 27 mg of iron and 0.6 mg folic acid

(3) Iron and folic acid provided as separate supplements

e. Low birthweight

Study or Subgroup	log[Risk Ratio]	SE	MMS Total	IFAS Total	Weight	Risk Ratio IV, Random, 95% CI
1.5.1 MMS vs IFAS with 60 mg iron						
Ashorn 2010	0.2738	0.2266	466	463	0.5%	1.31 [0.84, 2.05]
Bhutta 2009a	−0.1985	0.1426	1148	1230	1.2%	0.82 [0.62, 1.08]
Christian 2003	0.0296	0.0861	1050	957	3.3%	1.03 [0.87, 1.22]
Dewey 2009	−0.3603	0.2181	439	441	0.5%	0.70 [0.45, 1.07]
Kaestel 2005	−0.1315	0.1921	1392	708	0.7%	0.88 [0.60, 1.28]
Moore 2009	−0.2341	0.3242	164	146	0.2%	0.79 [0.42, 1.49]
Osrin 2005	−0.2866	0.1167	600	600	1.8%	0.75 [0.60, 0.94]
Roberfroid 2008	−0.0629	0.1462	714	712	1.1%	0.94 [0.71, 1.25]
Sunawang 2009 (1)	−0.1682	0.3016	432	411	0.3%	0.85 [0.47, 1.53]
Zagre 2007	−0.1562	0.1491	1893	1777	1.1%	0.86 [0.64, 1.15]
Zeng 2008	−0.1034	0.2013	1899	1912	0.6%	0.90 [0.61, 1.34]
Subtotal (95% CI)			**10197**	**9357**	**11.3%**	**0.90 [0.82, 0.98]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.88$, df = 10 (P = 0.45); $I^2 = 0\%$						
Test for overall effect: Z = 2.29 (P = 0.02)						
1.5.2 MMS vs IFAS with 30 mg iron						
Lui 2013	−0.1054	0.1282	6252	6266	1.5%	0.90 [0.70, 1.16]
SUMMIT 2008	−0.1508	0.0836	15804	15486	3.5%	0.86 [0.73, 1.01]
Tofail 2008	−0.0992	0.0655	1224	1248	5.7%	0.91 [0.80, 1.03]
West 2014 (2)	−0.1278	0.0177	22500	22500	77.7%	0.88 [0.85, 0.91]
Subtotal (95% CI)			**45780**	**45500**	**88.4%**	**0.88 [0.85, 0.91]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.29$, df = 3 (P = 0.96); $I^2 = 0\%$						
Test for overall effect: Z = 7.62 (P < 0.00001)						
1.5.3 Iron dose not specified						
Friis 2004 (3)	−0.3011	0.2537	837	832	0.4%	0.74 [0.45, 1.22]
Subtotal (95% CI)			**837**	**832**	**0.4%**	**0.74 [0.45, 1.22]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.19 (P = 0.24)						
Total (95% CI)			**56814**	**55689**	**100.0%**	**0.88 [0.86, 0.91]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 10.82$, df = 15 (P = 0.77); $I^2 = 0\%$						
Test for overall effect: Z = 8.00 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 0.65$, df = 2 (P = 0.72), $I^2 = 0\%$						



Footnotes

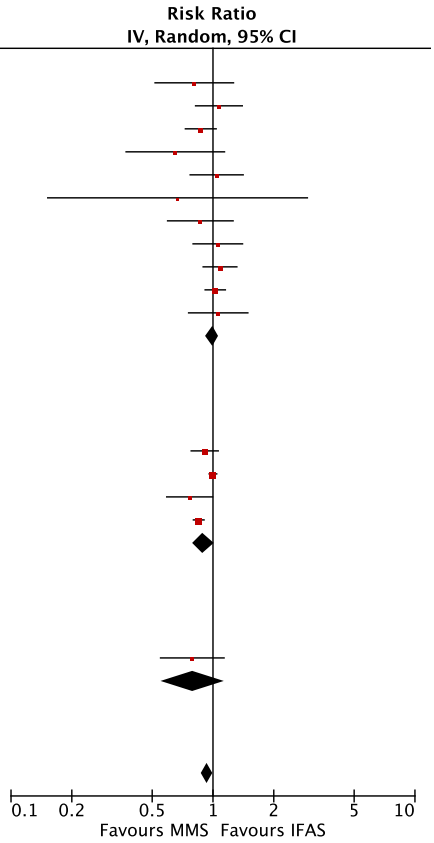
(1) Control arm received 60 mg iron and 0.25 mg folic acid

(2) Control arm received 27 mg iron and 0.6 mg folic acid

(3) Iron and folic acid provided as separate supplements in both arms

f. Preterm birth

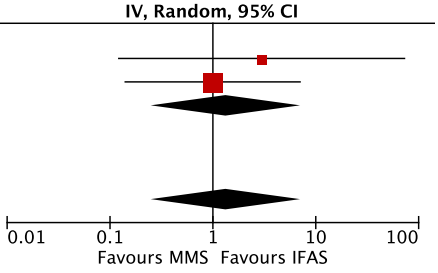
Study or Subgroup	log[Risk Ratio]	SE	MMS Total	IFAS Total	Weight	Risk Ratio IV, Random, 95% CI
1.6.1 MMS vs IFAS with 60 mg iron						
Ashorn 2010	-0.2132	0.2281	466	463	1.9%	0.81 [0.52, 1.26]
Bhutta 2009a	0.0677	0.1358	1148	1230	4.6%	1.07 [0.82, 1.40]
Christian 2003	-0.1393	0.0895	1050	957	8.1%	0.87 [0.73, 1.04]
Dewey 2009	-0.4296	0.2862	439	441	1.3%	0.65 [0.37, 1.14]
Kaestel 2005	0.0421	0.1541	1392	708	3.8%	1.04 [0.77, 1.41]
Moore 2009	-0.4039	0.7551	164	146	0.2%	0.67 [0.15, 2.93]
Osrin 2005	-0.1441	0.1905	600	600	2.7%	0.87 [0.60, 1.26]
Roberfroid 2008	0.055	0.1438	714	712	4.2%	1.06 [0.80, 1.40]
Sunawang 2009 (1)	0.0801	0.098	432	411	7.2%	1.08 [0.89, 1.31]
Zagre 2007	0.0259	0.0587	1893	1777	12.0%	1.03 [0.91, 1.15]
Zeng 2008	0.0598	0.1723	1899	1912	3.2%	1.06 [0.76, 1.49]
Subtotal (95% CI)			**10197**	**9357**	**49.2%**	**0.99 [0.92, 1.07]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.82$, df = 10 (P = 0.65); $I^2 = 0\%$						
Test for overall effect: Z = 0.20 (P = 0.84)						
1.6.2 MMS vs IFAS with 30 mg iron						
Lui 2013	-0.0943	0.0786	6252	6266	9.3%	0.91 [0.78, 1.06]
SUMMIT 2008	-0.0005	0.0219	15804	15486	17.6%	1.00 [0.96, 1.04]
Tofail 2008	-0.2663	0.1333	1224	1248	4.8%	0.77 [0.59, 0.99]
West 2014 (2)	-0.1625	0.0309	22500	22500	16.4%	0.85 [0.80, 0.90]
Subtotal (95% CI)			**45780**	**45500**	**48.0%**	**0.90 [0.80, 1.01]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 20.97$, df = 3 (P = 0.0001); $I^2 = 86\%$						
Test for overall effect: Z = 1.77 (P = 0.08)						
1.6.3 Iron dose not specified						
Friis 2004 (3)	-0.2357	0.1847	837	832	2.8%	0.79 [0.55, 1.13]
Subtotal (95% CI)			**837**	**832**	**2.8%**	**0.79 [0.55, 1.13]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.28 (P = 0.20)						
Total (95% CI)			**56814**	**55689**	**100.0%**	**0.94 [0.88, 1.00]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 31.53$, df = 15 (P = 0.007); $I^2 = 52\%$						
Test for overall effect: Z = 1.86 (P = 0.06)						
Test for subgroup differences: $Chi^2 = 3.17$, df = 2 (P = 0.20), $I^2 = 37.0\%$						



Footnotes
(1) Control arm received 60 mg iron and 0.25 mg folic acid
(2) Control arm received 27 mg iron and 0.6 mg folic acid
(3) Iron and folic acid provided as separate supplements in both arms

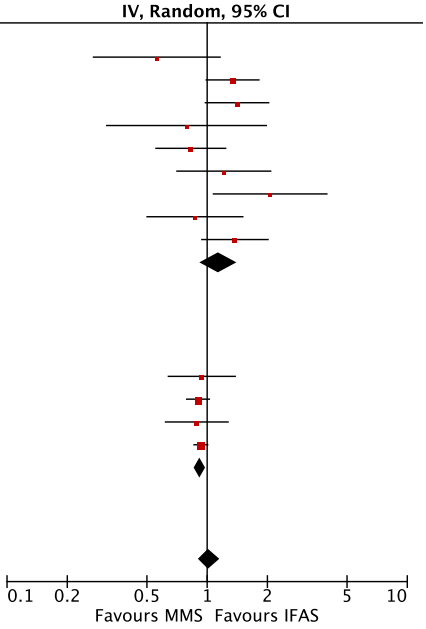
g. Congenital anomalies

Study or Subgroup	log[Risk Ratio]	SE	MMS Total	IFAS Total	Weight	Risk Ratio IV, Random, 95% CI
1.7.1 MMS vs IFAS with 60 mg iron						
Dewey 2009	1.0913	1.6314	439	441	27.2%	2.98 [0.12, 72.88]
Osrin 2005	-0.0053	0.9982	600	600	72.8%	0.99 [0.14, 7.04]
Subtotal (95% CI)			**1039**	**1041**	**100.0%**	**1.34 [0.25, 7.12]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.33$, df = 1 (P = 0.57); $I^2 = 0\%$						
Test for overall effect: Z = 0.34 (P = 0.73)						
Total (95% CI)			**1039**	**1041**	**100.0%**	**1.34 [0.25, 7.12]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.33$, df = 1 (P = 0.57); $I^2 = 0\%$						
Test for overall effect: Z = 0.34 (P = 0.73)						
Test for subgroup differences: Not applicable						



h. Perinatal mortality

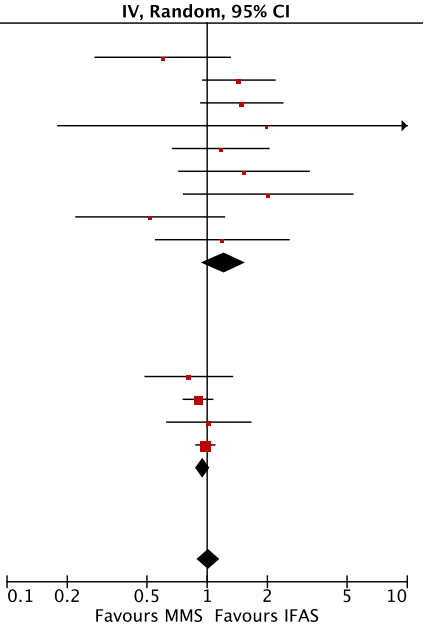
Study or Subgroup	log[Risk Ratio]	SE	MMS Total	IFAS Total	Weight	Risk Ratio IV, Random, 95% CI
1.8.1 MMS vs IFAS with 60 mg iron						
Ashorn 2010	−0.5793	0.3715	466	463	2.5%	0.56 [0.27, 1.16]
Bhutta 2009a	0.2927	0.1545	1148	1230	9.5%	1.34 [0.99, 1.81]
Christian 2003	0.3436	0.1856	1050	957	7.5%	1.41 [0.98, 2.03]
Dewey 2009	−0.2374	0.4683	439	441	1.6%	0.79 [0.31, 1.97]
Kaestel 2005	−0.1884	0.2044	1392	708	6.6%	0.83 [0.55, 1.24]
Osrin 2005	0.1914	0.2751	600	600	4.2%	1.21 [0.71, 2.08]
Roberfroid 2008	0.7245	0.3329	714	712	3.0%	2.06 [1.07, 3.96]
Sunawang 2009 (1)	−0.1406	0.281	432	411	4.0%	0.87 [0.50, 1.51]
Zeng 2008	0.3195	0.1942	1899	1912	7.1%	1.38 [0.94, 2.01]
Subtotal (95% CI)			**8140**	**7434**	**46.1%**	**1.15 [0.93, 1.42]**
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 14.00$, df = 8 (P = 0.08); $I^2 = 43\%$						
Test for overall effect: Z = 1.27 (P = 0.20)						
1.8.2 MMS vs IFAS with 30 mg iron						
Lui 2013	−0.0619	0.1961	6252	6266	7.0%	0.94 [0.64, 1.38]
SUMMIT 2008	−0.10536	0.06651	15804	15486	18.2%	0.90 [0.79, 1.03]
Tofail 2008	−0.1195	0.1834	1224	1248	7.7%	0.89 [0.62, 1.27]
West 2014 (2)	−0.0726	0.0399	22500	22500	21.0%	0.93 [0.86, 1.01]
Subtotal (95% CI)			**45780**	**45500**	**53.9%**	**0.92 [0.86, 0.98]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.23$, df = 3 (P = 0.97); $I^2 = 0\%$						
Test for overall effect: Z = 2.47 (P = 0.01)						
Total (95% CI)			**53920**	**52934**	**100.0%**	**1.02 [0.90, 1.15]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 23.08$, df = 12 (P = 0.03); $I^2 = 48\%$						
Test for overall effect: Z = 0.35 (P = 0.72)						
Test for subgroup differences: $Chi^2 = 3.76$, df = 1 (P = 0.05), $I^2 = 73.4\%$						



Footnotes
(1) Control arm received 60 mg iron and 0.25 mg folic acid
(2) Control arm received 27 mg iron and 0.6 mg folic acid

i. Neonatal mortality

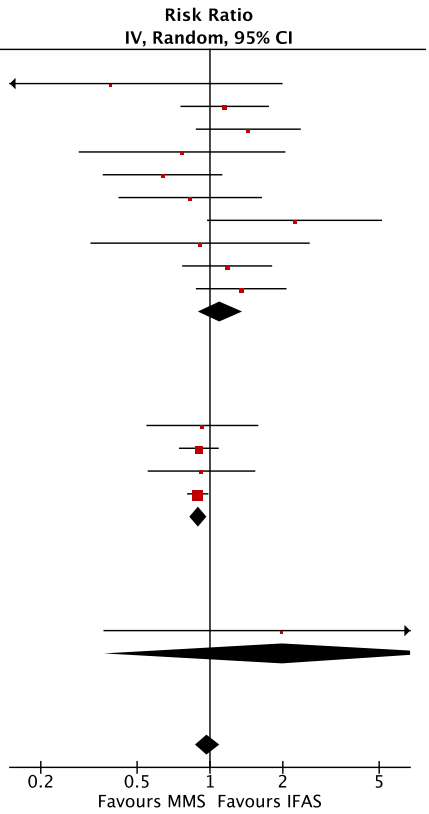
Study or Subgroup	log[Risk Ratio]	SE	MMS Total	IFAS Total	Weight	Risk Ratio IV, Random, 95% CI
1.9.1 MMS vs IFAS with 60 mg iron						
Ashorn 2010	−0.5113	0.3963	466	463	2.7%	0.60 [0.28, 1.30]
Bhutta 2009a	0.3646	0.2122	1148	1230	8.0%	1.44 [0.95, 2.18]
Christian 2003	0.3988	0.2405	1050	957	6.5%	1.49 [0.93, 2.39]
Dewey 2009	0.6789	1.2225	439	441	0.3%	1.97 [0.18, 21.65]
Kaestel 2005	0.1555	0.283	1392	708	4.9%	1.17 [0.67, 2.03]
Osrin 2005	0.4245	0.3823	600	600	2.8%	1.53 [0.72, 3.23]
Roberfroid 2008	0.7028	0.4967	714	712	1.7%	2.02 [0.76, 5.35]
Sunawang 2009 (1)	−0.6555	0.436	432	411	2.2%	0.52 [0.22, 1.22]
Zeng 2008	0.1743	0.3912	1899	1912	2.7%	1.19 [0.55, 2.56]
Subtotal (95% CI)			**8140**	**7434**	**31.8%**	**1.22 [0.94, 1.56]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 9.89$, df = 8 (P = 0.27); $I^2 = 19\%$						
Test for overall effect: Z = 1.51 (P = 0.13)						
1.9.2 MMS vs IFAS with 30 mg iron						
Lui 2013	−0.2107	0.2564	6252	6266	5.8%	0.81 [0.49, 1.34]
SUMMIT 2008	−0.1053	0.08626	15804	15486	24.2%	0.90 [0.76, 1.07]
Tofail 2008	0.0191	0.2466	1224	1248	6.2%	1.02 [0.63, 1.65]
West 2014 (2)	−0.0202	0.0549	22500	22500	31.9%	0.98 [0.88, 1.09]
Subtotal (95% CI)			**45780**	**45500**	**68.2%**	**0.95 [0.87, 1.04]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.17$, df = 3 (P = 0.76); $I^2 = 0\%$						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (95% CI)			**53920**	**52934**	**100.0%**	**1.02 [0.90, 1.17]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 15.91$, df = 12 (P = 0.20); $I^2 = 25\%$						
Test for overall effect: Z = 0.34 (P = 0.74)						
Test for subgroup differences: $Chi^2 = 3.16$, df = 1 (P = 0.08), $I^2 = 68.4\%$						



Footnotes
(1) Control arm received 60 mg iron and 0.25 mg folic acid
(2) Control arm received 27 mg iron and 0.6 mg folic acid

j. Stillbirth

Study or Subgroup	log[Risk Ratio]	SE	MMS Total	IFAS Total	Weight	Risk Ratio IV, Random, 95% CI
1.10.1 MMS vs IFAS with 60 mg iron						
Ashorn 2010	−0.9491	0.8333	466	463	0.5%	0.39 [0.08, 1.98]
Bhutta 2009a	0.1398	0.2113	1148	1230	6.7%	1.15 [0.76, 1.74]
Christian 2003	0.3646	0.2513	1050	957	4.9%	1.44 [0.88, 2.36]
Dewey 2009	−0.2655	0.4982	439	441	1.4%	0.77 [0.29, 2.04]
Kaestel 2005	−0.4513	0.2869	1392	708	3.9%	0.64 [0.36, 1.12]
Osrin 2005	−0.1875	0.3446	600	600	2.8%	0.83 [0.42, 1.63]
Roberfroid 2008	0.8046	0.4212	714	712	1.9%	2.24 [0.98, 5.10]
Sunawang 2009 (1)	−0.0941	0.5286	432	411	1.2%	0.91 [0.32, 2.56]
Zagre 2007	0.1635	0.215	1893	1777	6.5%	1.18 [0.77, 1.79]
Zeng 2008	0.297	0.2166	1899	1912	6.4%	1.35 [0.88, 2.06]
Subtotal (95% CI)			**10033**	**9211**	**36.2%**	**1.11 [0.89, 1.37]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 11.47$, df = 9 (P = 0.24); $I^2 = 22\%$						
Test for overall effect: Z = 0.93 (P = 0.35)						
1.10.2 MMS vs IFAS with 30 mg iron						
Lui 2013	−0.0726	0.268	6252	6266	4.4%	0.93 [0.55, 1.57]
SUMMIT 2008	−0.1053	0.09302	15804	15486	20.9%	0.90 [0.75, 1.08]
Tofail 2008	−0.0807	0.2576	1224	1248	4.7%	0.92 [0.56, 1.53]
West 2014 (2)	−0.1165	0.0481	22500	22500	33.4%	0.89 [0.81, 0.98]
Subtotal (95% CI)			**45780**	**45500**	**63.4%**	**0.89 [0.82, 0.97]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.05$, df = 3 (P = 1.00); $I^2 = 0\%$						
Test for overall effect: Z = 2.70 (P = 0.007)						
1.10.3 Iron dose not specified						
Friis 2004 (3)	0.6849	0.8628	837	832	0.5%	1.98 [0.37, 10.76]
Subtotal (95% CI)			**837**	**832**	**0.5%**	**1.98 [0.37, 10.76]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						
Total (95% CI)			**56650**	**55543**	**100.0%**	**0.98 [0.87, 1.10]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 17.33$, df = 14 (P = 0.24); $I^2 = 19\%$						
Test for overall effect: Z = 0.42 (P = 0.68)						
Test for subgroup differences: $Chi^2 = 4.12$, df = 2 (P = 0.13), $I^2 = 51.5\%$						



Footnotes

(1) Control arm received 60 mg iron and 0.25 mg folic acid

(2) Control arm received 27 mg iron and 0.6 mg folic acid

(3) Iron and folic acid provided as separate supplements in both arms

GRADE tables for effects of MMS vs IFAS: Comparison 2

Question: Antenatal MMS with UNIMMAP (containing 30 mg iron/0.4 mg folic acid) compared with iron (30 mg or 60 mg) and folic acid supplements.

Setting: Low- and middle-income countries.

Source: GDG-specified WHO analysis based on data found in *Keats EC, Haider BA, Tam E, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. Cochrane Database of Systematic Reviews. 2019;3(3):CD004905 (13).*

Certainty assessment							Number of participants		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Comparison 2: UNIMMAP	IFAS	Relative (95% CI)	Absolute (95% CI)		
Maternal anaemia (third trimester Hb <110 g/L)												
2	randomized trials	serious [a]	not serious	not serious	not serious	none	2499	2512	**RR 0.90** (0.77 to 1.05)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Maternal anaemia (third trimester Hb <110 g/L) – versus 60 mg iron plus folic acid												
2	randomized trials	serious [a]	not serious	not serious	not serious	none	2499	2512	**RR 0.90** (0.77 to 1.05)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Maternal anaemia (third trimester Hb <110 g/L) – versus 30 mg iron plus folic acid												
0 [b]							0	0	not pooled	not pooled	-	CRITICAL
Mode of delivery: Caesarean section												
3	randomized trials	serious [a]	not serious	not serious	serious [c]	none	2462	2542	**RR 1.06** (0.75 to 1.49)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Mode of delivery: Caesarean section – versus 60 mg iron plus folic acid												
3	randomized trials	serious [a]	not serious	not serious	serious [c]	none	2462	2542	**RR 1.06** (0.75 to 1.49)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL

Certainty assessment							Number of participants		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Comparison 2: UNIMMAP	IFAS	Relative (95% CI)	Absolute (95% CI)		
Mode of delivery: Caesarean section – versus 30 mg iron plus folic acid												
0 [b]							0	0	not pooled	not pooled	–	CRITICAL
Maternal mortality												
3	randomized trials	serious [a]	not serious	not serious	serious [c]	none	19 089	17 971	**RR 0.97** (0.63 to 1.48)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Maternal mortality – versus 60 mg iron plus folic acid												
2	randomized trials	serious [a]	not serious	not serious	serious [c]	none	3285	2485	**RR 0.77** (0.30 to 1.97)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Maternal mortality – versus 30 mg iron plus folic acid												
1	randomized trial	serious [a]	not serious	not serious	serious [c]	none	15 804	15 486	**RR 1.03** (0.64 to 1.66)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Small for gestational age												
9	randomized trials	serious [a]	not serious	not serious	not serious	none	25106	24084	**RR 0.91** (0.85 to 0.98)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Small for gestational age – versus 60 mg iron plus folic acid												
7	randomized trials	not serious	not serious	not serious	not serious	none	8078	7350	**RR 0.89** (0.81 to 0.97)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗⊗ HIGH	CRITICAL

Certainty assessment							Number of participants		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Comparison 2: UNIMMAP	IFAS	Relative (95% CI)	Absolute (95% CI)		
Small for gestational age – versus 30 mg iron plus folic acid												
2	randomized trials	serious [a]	not serious	not serious	not serious	none	17 028	16 734	**RR 0.95** (0.85 to 1.06)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Low birthweight												
10	randomized trials	serious [a]	not serious	not serious	not serious	none	31 358	30 350	**RR 0.87** (0.81 to 0.94)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Low birthweight – versus 60 mg iron plus folic acid												
7	randomized trials	serious [a]	not serious	not serious	not serious	none	8078	7350	**RR 0.84** (0.75 to 0.94)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Low birthweight – versus 30 mg iron plus folic acid												
3	randomized trials	serious [a]	not serious	not serious	not serious	none	23 280	23 000	**RR 0.89** (0.81 to 0.98)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Preterm births												
10	randomized trials	serious [a]	not serious	not serious	not serious	none	31 358	30 350	**RR 1.00** (0.96 to 1.03)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL

Certainty assessment							Number of participants		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Comparison 2: UNIMMAP	IFAS	Relative (95% CI)	Absolute (95% CI)		
Preterm births – versus 60 mg iron plus folic acid												
7	randomized trials	serious [a]	not serious	not serious	not serious	none	8078	7350	**RR 1.04** (0.96 to 1.12)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Preterm births – versus 30 mg iron plus folic acid												
3	randomized trials	serious [a]	serious [d]	not serious	not serious	none	23 280	23 000	**RR 0.93** (0.82 to 1.05)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Congenital anomalies – versus 60 mg iron plus folic acid												
1	randomized trial	serious [a]	not serious	not serious	serious [c]	none	600	600	**RR 0.99** (0.14 to 7.04)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Perinatal mortality												
9	randomized trials	serious [a]	not serious	not serious	not serious	serious [e]	29 465	28 573	Subgroup data not pooled (tests for subgroup differences $P = 0.03$, $I^2 = 77.9\%$)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	-	CRITICAL
Perinatal mortality – versus 60 mg iron plus folic acid												
6	randomized trials	not serious	not serious	not serious	serious [c]	none	6185	5573	**RR 1.20** (0.95 to 1.51)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Perinatal mortality – versus 30 mg iron plus folic acid												

Certainty assessment							Number of participants		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Comparison 2: UNIMMAP	IFAS	Relative (95% CI)	Absolute (95% CI)		
3	randomized trials	serious [a]	not serious	not serious	not serious	none	23 280	23 000	**RR 0.90** (0.80 to 1.01)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Neonatal mortality												
9	randomized trials	serious [a]	not serious	not serious	serious [c]	none	29 465	28 573	Subgroup data not pooled (tests for subgroup differences $P = 0.05$, $I^2 = 74.4\%$)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	-	CRITICAL
Neonatal mortality – versus 60 mg iron plus folic acid												
6	randomized trials	not serious	not serious	not serious	serious [c]	none	6185	5573	**RR 1.25** (0.94 to 1.67)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Neonatal mortality – versus 30 mg iron plus folic acid												
3	randomized trials	serious [a]	not serious	not serious	not serious	none	23 280	23 000	**RR 0.90** (0.78 to 1.05)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗⊗○ MODERATE	CRITICAL
Stillbirths												
10	randomized trials	serious [a]	not serious	not serious	not serious	publication bias strongly suspected [f]	31 358	30 350	**RR 1.00** (0.86 to 1.17)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Stillbirths – versus 60 mg iron plus folic acid												

Certainty assessment							Number of participants		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Comparison 2: UNIMMAP	IFAS	Relative (95% CI)	Absolute (95% CI)		
7	randomized trials	serious [a]	not serious	not serious	serious [c]	none	8078	7350	**RR 1.10** (0.86 to 1.41)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL
Stillbirths – versus 30 mg iron plus folic acid												
3	randomized trials	serious [a]	serious [g]	not serious	not serious	none	23 280	23 000	**RR 0.91** (0.77 to 1.07)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊗⊗○○ LOW	CRITICAL

CI: confidence interval; **RR:** risk ratio

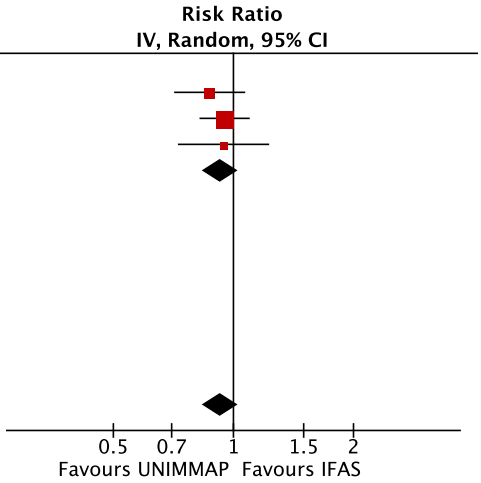
Explanations

a. Most of the pooled effect provided by studies with some risk of bias but without a substantial proportion (i.e. < 50%) from studies with a high risk of bias ("C" studies).
b. No studies were found that included data for this subgroup analysis.
c. Wide CI crossing the line of no effect.
d. Serious unexplained heterogeneity ($I^2 = 60\%$).
e. Substantial subgroup differences.
f. Evident asymmetry in funnel plot.
g. Serious unexplained heterogeneity ($Chi^2 = 0.02$).

Forest plots for effects of UNIMMAP vs IFAS: Comparison 2

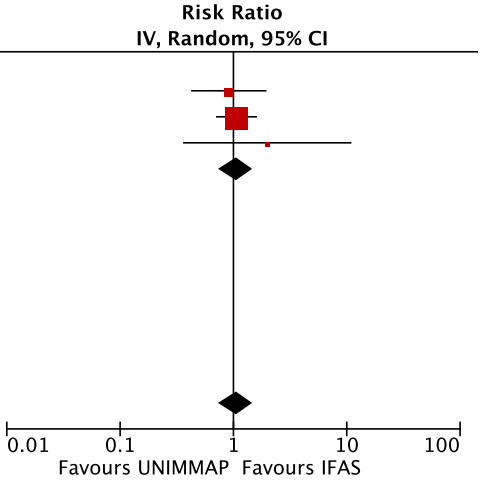
a. Anaemia

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 UNIMMAP vs IFAS with 60 mg iron				
Osrin 2005	−0.1373	0.1023	27.4%	0.87 [0.71, 1.07]
Roberfroid 2008	−0.0509	0.0715	56.1%	0.95 [0.83, 1.09]
Zeng 2008	−0.0571	0.1319	16.5%	0.94 [0.73, 1.22]
Subtotal (95% CI)			**100.0%**	**0.93 [0.83, 1.03]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.50$, df = 2 (P = 0.78); $I^2 = 0\%$				
Test for overall effect: Z = 1.41 (P = 0.16)				
2.1.2 UNIMMAP vs IFAS with 30 mg iron				
Subtotal (95% CI)				**Not estimable**
Heterogeneity: Not applicable				
Test for overall effect: Not applicable				
Total (95% CI)			**100.0%**	**0.93 [0.83, 1.03]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.50$, df = 2 (P = 0.78); $I^2 = 0\%$				
Test for overall effect: Z = 1.41 (P = 0.16)				
Test for subgroup differences: Not applicable				



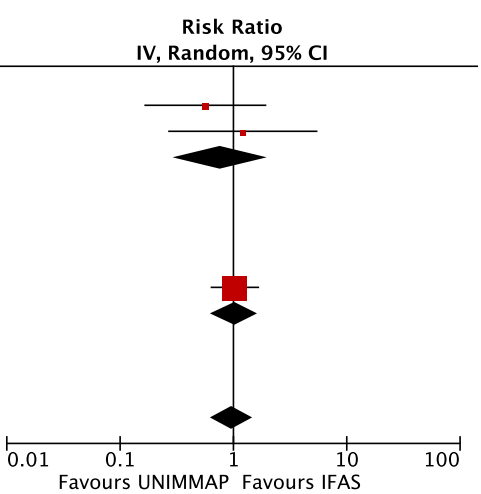
b. Caesarean section

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
2.2.1 UNIMMAP vs IFAS with 60 mg iron				
Bhutta 2009a	−0.0943	0.3825	21.2%	0.91 [0.43, 1.93]
Osrin 2005	0.0621	0.2036	74.7%	1.06 [0.71, 1.59]
Roberfroid 2008	0.6868	0.8642	4.1%	1.99 [0.37, 10.81]
Subtotal (95% CI)			**100.0%**	**1.06 [0.75, 1.49]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.69$, df = 2 (P = 0.71); $I^2 = 0\%$				
Test for overall effect: Z = 0.31 (P = 0.76)				
2.2.2 UNIMMAP vs IFAS with 30 mg iron				
Subtotal (95% CI)				**Not estimable**
Heterogeneity: Not applicable				
Test for overall effect: Not applicable				
Total (95% CI)			**100.0%**	**1.06 [0.75, 1.49]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.69$, df = 2 (P = 0.71); $I^2 = 0\%$				
Test for overall effect: Z = 0.31 (P = 0.76)				
Test for subgroup differences: Not applicable				



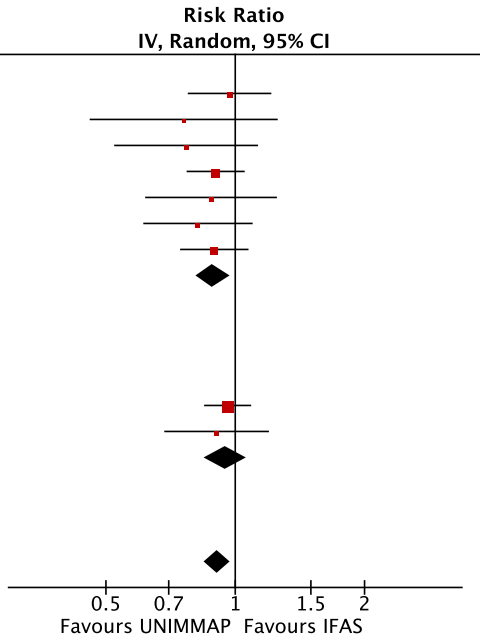
c. Maternal mortality

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
2.3.1 UNIMMAP vs IFAS with 60 mg iron				
Kaestel 2005	−0.5711	0.6236	12.1%	0.56 [0.17, 1.92]
Zagre 2007	0.1906	0.7652	8.0%	1.21 [0.27, 5.42]
Subtotal (95% CI)			**20.1%**	**0.77 [0.30, 1.97]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.60$, df = 1 (P = 0.44); $I^2 = 0\%$				
Test for overall effect: Z = 0.55 (P = 0.58)				
2.3.2 UNIMMAP vs IFAS with 30 mg iron				
SUMMIT 2008	0.02955	0.2427	79.9%	1.03 [0.64, 1.66]
Subtotal (95% CI)			**79.9%**	**1.03 [0.64, 1.66]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.12 (P = 0.90)				
Total (95% CI)			**100.0%**	**0.97 [0.63, 1.48]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.90$, df = 2 (P = 0.64); $I^2 = 0\%$				
Test for overall effect: Z = 0.14 (P = 0.89)				
Test for subgroup differences: $Chi^2 = 0.30$, df = 1 (P = 0.58), $I^2 = 0\%$				



d. Small for gestational age

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
2.4.1 UNIMMAP vs IFAS with 60 mg iron				
Bhutta 2009a	-0.0305	0.112	10.0%	0.97 [0.78, 1.21]
Kaestel 2005	-0.2763	0.2549	1.9%	0.76 [0.46, 1.25]
Osrin 2005	-0.2634	0.1945	3.3%	0.77 [0.52, 1.13]
Roberfroid 2008	-0.1051	0.0772	21.1%	0.90 [0.77, 1.05]
Sunawang 2009 (1)	-0.1299	0.178	4.0%	0.88 [0.62, 1.24]
Zagre 2007	-0.1998	0.1473	5.8%	0.82 [0.61, 1.09]
Zeng 2008	-0.1122	0.0913	15.1%	0.89 [0.75, 1.07]
Subtotal (95% CI)			**61.1%**	**0.89 [0.81, 0.97]**
Heterogeneity: Tau² = 0.00; Chi² = 1.90, df = 6 (P = 0.93); I² = 0%				
Test for overall effect: Z = 2.63 (P = 0.009)				
2.4.2 UNIMMAP vs IFAS with 30 mg iron				
SUMMIT 2008	-0.0408	0.0621	32.6%	0.96 [0.85, 1.08]
Tofail 2008	-0.1	0.1409	6.3%	0.90 [0.69, 1.19]
Subtotal (95% CI)			**38.9%**	**0.95 [0.85, 1.06]**
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%				
Test for overall effect: Z = 0.89 (P = 0.37)				
Total (95% CI)			**100.0%**	**0.91 [0.85, 0.98]**
Heterogeneity: Tau² = 0.00; Chi² = 2.94, df = 8 (P = 0.94); I² = 0%				
Test for overall effect: Z = 2.61 (P = 0.009)				
Test for subgroup differences: Chi² = 0.90, df = 1 (P = 0.34), I² = 0%				

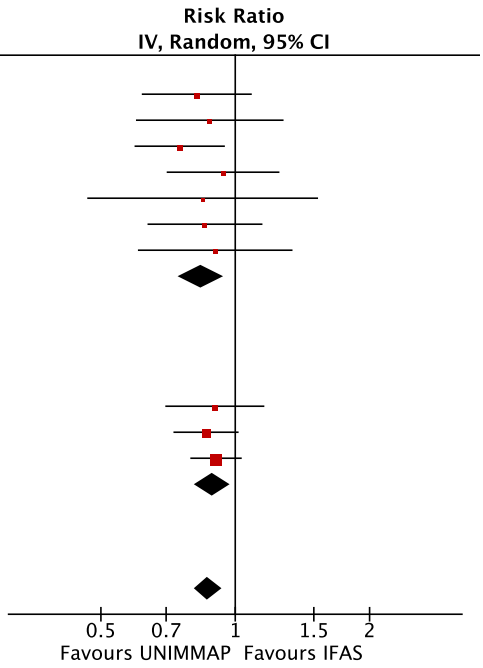


Footnotes

(1) Control group received 60 mg iron and 0.25 mg folic acid

e. Low birthweight

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
2.5.1 UNIMMAP vs IFAS with 60 mg iron				
Bhutta 2009a	-0.1985	0.1426	6.9%	0.82 [0.62, 1.08]
Kaestel 2005	-0.1315	0.1921	3.8%	0.88 [0.60, 1.28]
Osrin 2005	-0.2866	0.1167	10.3%	0.75 [0.60, 0.94]
Roberfroid 2008	-0.0629	0.1462	6.6%	0.94 [0.71, 1.25]
Sunawang 2009 (1)	-0.1682	0.3016	1.5%	0.85 [0.47, 1.53]
Zagre 2007	-0.1562	0.1491	6.3%	0.86 [0.64, 1.15]
Zeng 2008	-0.1034	0.2013	3.5%	0.90 [0.61, 1.34]
Subtotal (95% CI)			**38.8%**	**0.84 [0.75, 0.94]**
Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 6 (P = 0.94); I² = 0%				
Test for overall effect: Z = 2.93 (P = 0.003)				
2.5.2 UNIMMAP vs IFAS with 30 mg iron				
Lui 2013	-0.1054	0.1282	8.5%	0.90 [0.70, 1.16]
SUMMIT 2008	-0.1508	0.0836	20.0%	0.86 [0.73, 1.01]
Tofail 2008	-0.0992	0.0655	32.6%	0.91 [0.80, 1.03]
Subtotal (95% CI)			**61.2%**	**0.89 [0.81, 0.98]**
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 2 (P = 0.88); I² = 0%				
Test for overall effect: Z = 2.44 (P = 0.01)				
Total (95% CI)			**100.0%**	**0.87 [0.81, 0.94]**
Heterogeneity: Tau² = 0.00; Chi² = 2.56, df = 9 (P = 0.98); I² = 0%				
Test for overall effect: Z = 3.74 (P = 0.0002)				
Test for subgroup differences: Chi² = 0.59, df = 1 (P = 0.44), I² = 0%				

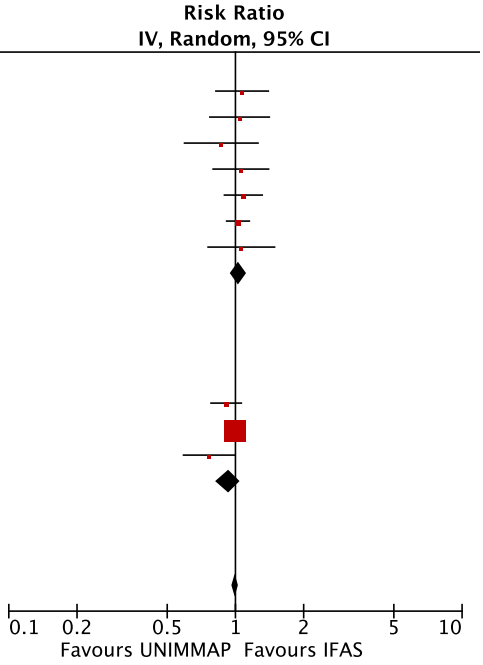


Footnotes

(1) Control arm received 60 mg iron and 0.25 mg folic acid

f. Preterm birth

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
2.6.1 UNIMMAP vs IFAS with 60 mg iron				
Bhutta 2009a	0.0677	0.1358	1.9%	1.07 [0.82, 1.40]
Kaestel 2005	0.0421	0.1541	1.5%	1.04 [0.77, 1.41]
Osrin 2005	−0.1441	0.1905	0.9%	0.87 [0.60, 1.26]
Roberfroid 2008	0.055	0.1438	1.7%	1.06 [0.80, 1.40]
Sunawang 2009 (1)	0.0801	0.098	3.6%	1.08 [0.89, 1.31]
Zagre 2007	0.0259	0.0587	10.0%	1.03 [0.91, 1.15]
Zeng 2008	0.0598	0.1723	1.2%	1.06 [0.76, 1.49]
Subtotal (95% CI)			**20.7%**	**1.04 [0.96, 1.12]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.22$, df = 6 (P = 0.98); $I^2 = 0\%$				
Test for overall effect: Z = 0.90 (P = 0.37)				
2.6.2 UNIMMAP vs IFAS with 30 mg iron				
Lui 2013	−0.0943	0.0786	5.6%	0.91 [0.78, 1.06]
SUMMIT 2008	−0.0005	0.0219	71.8%	1.00 [0.96, 1.04]
Tofail 2008	−0.2663	0.1333	1.9%	0.77 [0.59, 0.99]
Subtotal (95% CI)			**79.3%**	**0.93 [0.82, 1.05]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.01$, df = 2 (P = 0.08); $I^2 = 60\%$				
Test for overall effect: Z = 1.13 (P = 0.26)				
Total (95% CI)			**100.0%**	**1.00 [0.96, 1.03]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.43$, df = 9 (P = 0.59); $I^2 = 0\%$				
Test for overall effect: Z = 0.17 (P = 0.86)				
Test for subgroup differences: $Chi^2 = 2.07$, df = 1 (P = 0.15), $I^2 = 51.7\%$				

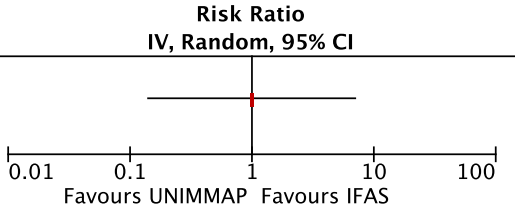


Footnotes

(1) Control arm received 60 mg iron and 0.25 mg folic acid

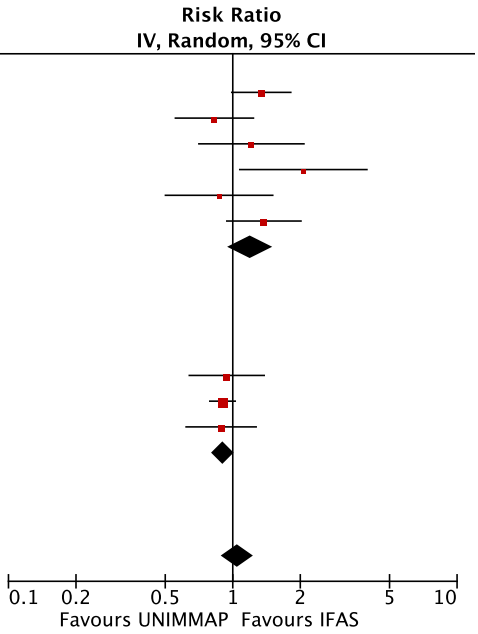
g. Congenital anomalies

Study or Subgroup	log[Risk Ratio]	SE	Risk Ratio IV, Random, 95% CI
2.7.1 UNIMMAP vs IFAS with 60 mg iron			
Osrin 2005	−0.0053	0.9982	0.99 [0.14, 7.04]



h. Perinatal mortality

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
2.8.1 UNIMMAP vs IFAS with 60 mg iron				
Bhutta 2009a	0.2927	0.1545	14.1%	1.34 [0.99, 1.81]
Kaestel 2005	-0.1884	0.2044	10.4%	0.83 [0.55, 1.24]
Osrin 2005	0.1914	0.2751	7.0%	1.21 [0.71, 2.08]
Roberfroid 2008	0.7245	0.3329	5.2%	2.06 [1.07, 3.96]
Sunawang 2009 (1)	-0.1406	0.281	6.8%	0.87 [0.50, 1.51]
Zeng 2008	0.3195	0.1942	11.1%	1.38 [0.94, 2.01]
Subtotal (95% CI)			**54.7%**	**1.20 [0.95, 1.51]**
Heterogeneity: Tau² = 0.03; Chi² = 8.27, df = 5 (P = 0.14); I² = 40%				
Test for overall effect: Z = 1.52 (P = 0.13)				
2.8.2 UNIMMAP vs IFAS with 30 mg iron				
Lui 2013	-0.0619	0.1961	11.0%	0.94 [0.64, 1.38]
SUMMIT 2008	-0.10536	0.06651	22.5%	0.90 [0.79, 1.03]
Tofail 2008	-0.1195	0.1834	11.8%	0.89 [0.62, 1.27]
Subtotal (95% CI)			**45.3%**	**0.90 [0.80, 1.01]**
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 2 (P = 0.97); I² = 0%				
Test for overall effect: Z = 1.73 (P = 0.08)				
Total (95% CI)			**100.0%**	**1.06 [0.89, 1.25]**
Heterogeneity: Tau² = 0.03; Chi² = 15.58, df = 8 (P = 0.05); I² = 49%				
Test for overall effect: Z = 0.63 (P = 0.53)				
Test for subgroup differences: Chi² = 4.54, df = 1 (P = 0.03), I² = 77.9%				

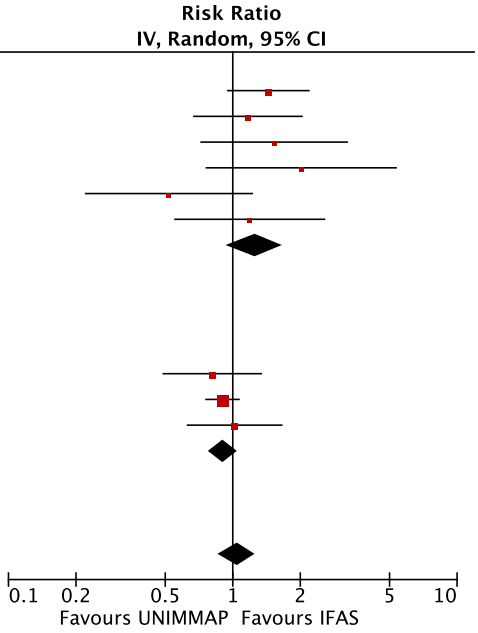


Footnotes

(1) Control arm received 60 mg iron and 0.25 mg folic acid

i. Neonatal mortality

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
2.9.1 UNIMMAP vs IFAS with 60 mg iron				
Bhutta 2009a	0.3646	0.2122	14.6%	1.44 [0.95, 2.18]
Kaestel 2005	0.1555	0.283	9.6%	1.17 [0.67, 2.03]
Osrin 2005	0.4245	0.3823	5.8%	1.53 [0.72, 3.23]
Roberfroid 2008	0.7028	0.4967	3.7%	2.02 [0.76, 5.35]
Sunawang 2009 (1)	-0.6555	0.436	4.6%	0.52 [0.22, 1.22]
Zeng 2008	0.1743	0.3912	5.6%	1.19 [0.55, 2.56]
Subtotal (95% CI)			**44.0%**	**1.25 [0.94, 1.67]**
Heterogeneity: Tau² = 0.02; Chi² = 5.78, df = 5 (P = 0.33); I² = 13%				
Test for overall effect: Z = 1.54 (P = 0.12)				
2.9.2 UNIMMAP vs IFAS with 30 mg iron				
Lui 2013	-0.2107	0.2564	11.2%	0.81 [0.49, 1.34]
SUMMIT 2008	-0.1053	0.08626	33.0%	0.90 [0.76, 1.07]
Tofail 2008	0.0191	0.2466	11.8%	1.02 [0.63, 1.65]
Subtotal (95% CI)			**56.0%**	**0.90 [0.78, 1.05]**
Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 2 (P = 0.81); I² = 0%				
Test for overall effect: Z = 1.32 (P = 0.19)				
Total (95% CI)			**100.0%**	**1.04 [0.86, 1.27]**
Heterogeneity: Tau² = 0.02; Chi² = 11.06, df = 8 (P = 0.20); I² = 28%				
Test for overall effect: Z = 0.42 (P = 0.67)				
Test for subgroup differences: Chi² = 3.91, df = 1 (P = 0.05), I² = 74.4%				

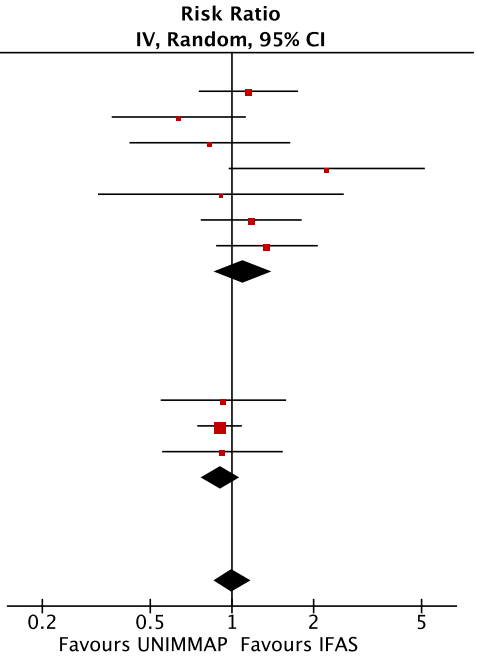


Footnotes

(1) Control arm received 60 mg iron and 0.25 mg folic acid

j. Stillbirth

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
2.10.1 UNIMMAP vs IFAS with 60 mg iron				
Bhutta 2009a	0.1398	0.2113	11.4%	1.15 [0.76, 1.74]
Kaestel 2005	−0.4513	0.2869	6.8%	0.64 [0.36, 1.12]
Osrin 2005	−0.1875	0.3446	4.8%	0.83 [0.42, 1.63]
Roberfroid 2008	0.8046	0.4212	3.3%	2.24 [0.98, 5.10]
Sunawang 2009 (1)	−0.0941	0.5286	2.2%	0.91 [0.32, 2.56]
Zagre 2007	0.1635	0.215	11.1%	1.18 [0.77, 1.79]
Zeng 2008	0.297	0.2166	11.0%	1.35 [0.88, 2.06]
Subtotal (95% CI)			**50.6%**	**1.10 [0.86, 1.41]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 8.27$, df = 6 (P = 0.22); $I^2 = 27\%$				
Test for overall effect: Z = 0.78 (P = 0.43)				
2.10.2 UNIMMAP vs IFAS with 30 mg iron				
Lui 2013	−0.0726	0.268	7.6%	0.93 [0.55, 1.57]
SUMMIT 2008	−0.1053	0.09302	33.6%	0.90 [0.75, 1.08]
Tofail 2008	−0.0807	0.2576	8.2%	0.92 [0.56, 1.53]
Subtotal (95% CI)			**49.4%**	**0.91 [0.77, 1.07]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 2 (P = 0.99); $I^2 = 0\%$				
Test for overall effect: Z = 1.20 (P = 0.23)				
Total (95% CI)			**100.0%**	**1.00 [0.86, 1.17]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 10.72$, df = 9 (P = 0.30); $I^2 = 16\%$				
Test for overall effect: Z = 0.05 (P = 0.96)				
Test for subgroup differences: $Chi^2 = 1.72$, df = 1 (P = 0.19), $I^2 = 42.0\%$				



Footnotes

(1) Control arm received 60 mg iron and 0.25 mg folic acid

World Health Organization

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