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Nutritional interventions update: zinc supplements during pregnancy

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Acronyms and abbreviations

ANC	antenatal care
CI	confidence interval
DECIDE	Developing and Evaluating Communication strategies to Support Informed Decisions and Practice based on Evidence
DOI	declaration of interest
ERG	External Review Group
EtD	evidence-to-decision
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRADE-CERQual	Confidence in the Evidence from Reviews of Qualitative research
GSG	Guideline Steering Group
HRP	UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction
ICM	International Confederation of Midwives
LMICs	low- and middle-income countries
MCA	Department of Maternal, Newborn, Child and Adolescent Health and Ageing
NFS	Department of Nutrition and Food Safety
RCT	randomized controlled trial
RR	risk ratio
SRH	Department of Sexual and Reproductive Health and Research
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
US$	United States dollar
USAID	United States Agency for International Development
WHO	World Health Organization

Executive summary

Introduction

Evidence from a systematic review on antenatal zinc supplementation was evaluated as part of the World Health Organization (WHO) antenatal care (ANC) guideline development process in 2016, and the following recommendation on zinc supplementation was made: "Zinc supplementation for pregnant women is only recommended in the context of rigorous research." The Guideline Development Group (GDG) made this recommendation because it felt that the evidence on the intervention was incomplete and that more research was necessary.

Since the publication of the systematic review, four additional randomized controlled trials have been published; therefore, in April 2019, the Executive Guideline Steering Group (GSG) prioritized the WHO recommendation on antenatal zinc supplementation for updating.

Zinc is a trace element found in many foods, particularly in meat, but also in dairy products, legumes and unrefined cereals. It plays an important role in many biological processes that contribute to human growth and development, and also to immunity. As it is not stored in the body, it needs to be consumed regularly to prevent zinc deficiency, which is particularly common in low- and middle-income countries, where dietary intake of zinc-rich foods is often low. However, the effects of zinc deficiency in pregnancy have not been clearly established.

In January 2021, a WHO-convened GDG comprising most of the 2016 GDG members re-evaluated the evidence on antenatal zinc supplementation, updating the recommendation on zinc in accordance with WHO's living guidelines approach.

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, nutritionists 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*. These involve: (i) identification of the priority question 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 recommendation; and (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendation. The scientific evidence supporting the recommendation 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. An up-to-date systematic review was used to prepare an evidence profile 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, an international group of experts that was convened for this process during an online GDG meeting on 13 January 2021. For consistency and continuity, the GDG, including the chair, comprised most of the same members as the ANC guideline GDG.

Recommendations

The WHO meeting led to the retention of the 2016 recommendation on antenatal zinc supplementation (Table 1). The GDG had the option to recommend the intervention, not recommend the intervention or recommend the intervention under certain conditions (in specific contexts, with targeted monitoring and evaluation, in the context of rigorous research). The GDG experts also provided additional remarks that they considered necessary

in the understanding and implementation of the recommendation. 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.

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

Table 1. The WHO recommendation on antenatal zinc supplementation for a positive pregnancy experience

Zinc supplementation for pregnant women is recommended only in the context of rigorous research.
Remarks
• The Guideline Development Group agreed to retain the WHO recommendation found in the 2016 WHO antenatal care (ANC) guideline. • WHO does not recommend zinc supplementation as part of routine ANC. It is recommended in the context of rigorous research to improve our knowledge of its effect on maternal and newborn health outcomes. Research is particularly needed on how zinc status is impacted by other nutritional supplementation (e.g. iron and/or calcium) given as part of routine ANC. Additionally, research is needed on the efficacy of zinc supplementation, provided either alone or with other nutritional supplements (e.g. iron and folic acid, calcium, according to national guidelines/standard of care), on maternal and neonatal outcomes. Multiple doses of zinc, iron and/or calcium may need to be evaluated based on the current national standard of care. Research on the effectiveness or the implementation of zinc supplementation is not identified as a priority at this time. • Pregnant women should be encouraged and supported to receive adequate nutrition, which is best achieved through consumption of a healthy, balanced diet, and to refer to guidelines on healthy eating.

1 Introduction

1.1 Background

Zinc supplementation in pregnancy

Zinc is a trace element found in many foods, particularly in meat, but also in dairy products, legumes and unrefined cereals; diets low in bioavailable zinc are those in which animal protein is low and intake of cereals is high *(1)*. Zinc is not stored in the body, so physiological needs must be met by dietary intake alone *(2)*. In pregnant women, the average physiological requirement of zinc is estimated to double in the third trimester and almost triple during lactation *(2)*. Therefore, many pregnant women are potentially at risk of zinc deficiency through inadequate dietary intake, exacerbated by the increased nutritional demands of pregnancy and lactation. In addition, routine iron supplementation may prevent women from meeting their zinc requirements by competing with zinc for absorption *(3)*. This may also occur with calcium supplements and foods fortified with inorganic calcium salts *(1)*.

Zinc plays an important role in many biological processes that contribute to human growth and development. Among children, the prevalence of stunting has been used as an indicator of zinc deficiency *(1, 3)*. Zinc deficiency increases susceptibility to infections, and supplementing zinc among children in disadvantaged populations has been shown to reduce the incidence of diarrhoea and pneumonia *(1–5)*. The World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) recommend zinc supplementation is given along with oral rehydration salts for the clinical management of diarrhoea in children *(6)*.

In pregnancy, zinc deficiency has been linked to prolonged labour, postpartum haemorrhage, pre-eclampsia, preterm birth and post-term pregnancies *(7)*; however, these associations have not been well established. This evidence-to-decision (EtD) framework presents research evidence on the effects and other considerations relevant to recommendations on antenatal zinc supplements compared with no zinc supplements or placebo.

The updated recommendation in the context of the WHO antenatal care guideline

In 2016, the following recommendation on antenatal zinc supplementation was made: "Zinc supplementation for pregnant women is only recommended in the context of rigorous research"*(8)*. The Guideline Development Group (GDG) made this recommendation because it felt that the evidence on the intervention was incomplete and that more research was necessary. Since the publication of the 2016 WHO antenatal care (ANC) guideline, the systematic review, on which the 2016 recommendation was based, has been updated to include four additional trials *(9)*; hence the need to re-evaluate the evidence.

1.2 Rationale and objectives

As part of the WHO's normative work on supporting evidence-informed policies and practices and its living guidelines approach *(10)*, the Department of Sexual and Reproductive Health and Research (SHR), the Department of Maternal, Newborn, Child and Adolescent Health and Ageing (MCA) and the Department of Nutrition and Food Safety (NFS) prioritized the updating of this recommendation on zinc supplements following the advice of the Executive Guideline Steering Group (GSG) in response to the identification of updated evidence on this intervention.

1.3 Target audience

The recommendation in this global guideline is intended to inform the development of relevant national and local 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, nutritionists and general medical practitioners), researchers, and academic staff involved in training health professionals.

1.4 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 fetuses and newborns. The guideline question was prioritized during the WHO 2016 ANC guideline development process. In 2019, the recommendation was prioritized for updating in the context of WHO's living guideline commitment *(10)*. The outcomes of interests are, therefore, the same as those prioritized for the ANC guideline relevant to nutritional interventions (Box 1).

Box 1: Outcomes of interest in antenatal care nutritional interventions

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	

2 Methods

This recommendation is an update of one of 49 recommendations that were published in *WHO recommendations on antenatal care for a positive pregnancy experience (8)*. The recommendation was developed initially using the standardized operating procedures described in the *WHO handbook for guideline development (11)*. In summary, the process included: (i) identification of priority question and outcomes, (ii) retrieval of evidence, (iii) assessment and synthesis of the evidence, (iv) formulation of recommendation, 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 this question.

2.1 Contributors to the guideline

Executive Guideline Steering Group

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 as the WHO ANC guideline of 2016 (see Annex 1 for the list of members). The WHO Steering Group drafted the priority question in PICO (population, intervention, comparator, outcome) format and identified individuals to be invited to participate as guideline methodologists, and in the guideline development and external review groups. In addition, the WHO Steering Group supervised the evidence retrieval and synthesis, organized the technical consultation and finalized the guideline document. Additionally, WHO regional office representatives for sexual and reproductive health were invited to all GDG sessions and provided comments on the updated recommendation document. The WHO Steering Group in collaboration with WHO regional offices will oversee the dissemination of the updated recommendation.

Guideline Development Group

The WHO Steering Group identified and invited 12 external experts and stakeholders from the six WHO regions to constitute the GDG, ensuring representation, gender balance and no important conflicts of interest. These experts also served in the GDG for the WHO ANC guideline's nutrition recommendations of 2016. They were a diverse group of individuals with expertise in research, guideline development methods and clinical policy and programmes relating to ANC interventions, plus 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 13 January 2021. 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

The External Review Group (ERG) was a geographically and gender-balanced group with no important conflicts of interest (see Annex 2). There were four members, including technical experts and other stakeholders with interests in the provision of evidence-informed ANC. This group peer-reviewed the draft version of the guideline document to identify any factual errors and 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 people 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 the recommendation 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. Working closely with the WHO Steering Group, methodologists from The Evidence-based Medicine Consultancy in the United Kingdom of Great Britain and Northern Ireland appraised the quantitative evidence using WHO's standardized operating procedures for GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology *(12)*. 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

Six representatives of the ICM, UNFPA, USAID, 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 the WHO in guideline dissemination and implementation. Observers do not participate in the formulation of recommendations.

2.2 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 declaration of interests (WHO Experts) (13)*, all GDG 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 declaration of interest (DOI) was completed and signed by each expert. The WHO Steering Group reviewed all the DOI forms before finalizing experts' invitations to participate. Where any conflicts of interest were declared, the WHO 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 WHO Steering Group applied the criteria for assessing the severity of a conflict of interest in the *WHO handbook for guideline development (11).*

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 a 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. 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 in this guideline together, with a description of the objectives of relevant meetings, were made public ahead of the planned online GDG meeting, to allow time for public notice and comment.

2.3 Identifying priority questions and outcomes

The priority question and outcomes were aligned with those of the ANC guideline. This question and 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, and by a WHO-commissioned scoping qualitative review of what women want during pregnancy *(14).* 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.

2.4 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 systematic review was the primary source of evidence on the effectiveness of oral antenatal zinc supplementation. 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 assessments of the certainty of the evidence, for the comparisons of interest.

Two qualitative systematic reviews commissioned by the WHO Steering Group for the 2016 guideline development process informed the values, acceptability and feasibility criteria of the EtD frameworks to inform the recommendation (see below for more information, under section 2.6 – Preparation of the evidence summary) *(14, 15)*. Additionally, systematic reviews of cost-effectiveness were sought through PubMed searches of the literature.

2.5 Quality assessment and grading of the evidence

The GRADE approach *(12)* was used to appraise the certainty of quantitative evidence, 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 systematic 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 a qualitative evidence synthesis performed for the WHO 2016 ANC guideline *(14, 15)*. Previously subjected to a quality appraisal using the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative research) tool, the evidence was not regraded 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 qualitative evidence synthesis according to four components: methodological limitations of the individual studies, adequacy of data and coherence and relevance of the findings to the review question *(16)*.

2.6 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 *(17)*. 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. The certainty of the graded evidence on intervention effectiveness was systematically interpreted in EtD frameworks according to guidance from the Cochrane group on effective practice and organization of care *(18)*.

2.7 Formulation of the recommendation

GDG members and other participants were provided with the evidence summary in advance of the online GDG meeting held on 13 January 2021, organized by the WHO 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 intervention for each of the EtD criteria. GDG judgements were summarized in a table, before finalizing the recommendation and remarks. The intervention could be recommended, not recommended, or recommended only under certain conditions (in specific contexts, with targeted monitoring and evaluation, in the context of rigorous research).

2.8 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, if necessary, the context in which the recommendation would apply were confirmed by unanimous consensus (i.e. full agreement among all GDG members).

2.9 Guideline preparation and peer review

Following the online GDG meeting, members of the WHO Steering Group, assisted by methodologists, drafted a full guideline document to accurately reflect the deliberations and decisions of participants. A preliminary version of the document was sent electronically to the participants and the ERG for final review and technical comments. The WHO 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 WHO 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.

3 Evidence and recommendation on antenatal zinc supplementation

This section provides the WHO recommendation adopted by the GDG on antenatal zinc supplementation with its corresponding evidence summary. Evidence on the effectiveness of zinc supplementation is further detailed in GRADE tables in Annex 3. 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 zinc supplementation

Zinc supplementation for pregnant women is recommended only in the context of rigorous research.

Remarks

- This Guideline Development Group agreed to retain the WHO recommendation found in the 2016 WHO antenatal care guideline *(8)*.
- WHO does not recommend zinc supplementation as part of routine antenatal care. It is recommended only in the context of rigorous research to improve our knowledge of its effect on maternal and newborn health outcomes. Research is particularly needed on how zinc status is impacted by other nutritional supplementation (e.g. iron and/or calcium) given as part of routine antenatal care. Additionally, research is needed on the efficacy of zinc supplementation – provided either alone or with other nutritional supplements (e.g. iron, folic acid and calcium, according to national guidelines/standard of care) – on maternal and neonatal outcomes. Multiple doses of zinc, iron and/or calcium may need to be evaluated based on the current national standard of care. Research on the effectiveness or the implementation of zinc supplementation is not identified as a priority at this time.
- Pregnant women should be encouraged and supported to receive adequate nutrition, which is best achieved through a healthy, balanced diet, and to refer to guidelines on healthy eating *(19)*.

3.1 The priority question

For pregnant women (population), does zinc supplementation (intervention) compared with no zinc supplementation (comparator) improve maternal and perinatal health outcomes (outcome)?

3.2 Assessment

Effects of the intervention

What are the anticipated effects of antenatal zinc supplements compared with no zinc supplements (or placebo)?

Research evidence

The following evidence was derived from a systematic review *(9)* that updated evidence from a review published in 2015 *(7)*. The updated review includes data from four additional trials, so that there was a total of 25 RCTs, involving more than 18 000 pregnant women. Studies were carried out in Bangladesh (two studies), Chile, China, Denmark, Egypt, Ghana, Indonesia (two studies), the Islamic Republic of Iran (three studies), Nepal, Pakistan, Peru (two studies), South Africa, United Republic of Tanzania, the United Kingdom (three studies) and the United States of America (four studies). The dose of daily zinc supplementation ranged from 5 mg to 50 mg of zinc per day, although in one trial some women received up to 90 mg of zinc per day. Eleven trials compared zinc supplementation with placebo. There was a wide variation in the size of trials (56 women recruited in the smallest, 4926 women in the largest) and in women's nutritional and zinc status at trial entry. Women's gestational age at recruitment and the duration of supplementation also varied across trials (before conception in one trial, in the first or second trimester in most trials, after 26 weeks' gestation in two trials, and up to 6 months postpartum in one trial), as did compliance with treatment.

Maternal outcomes

Pre-eclampsia: The evidence suggests that zinc supplementation may make little or no difference to pre-eclampsia compared with no zinc supplements (six trials, 2568 women; risk ratio, RR, 0.93, 95% confidence interval, CI, 0.62 to 1.42; *low-certainty evidence, downgraded due to design limitations and imprecision*).

Maternal infection: The evidence suggests that zinc supplementation may make little or no difference to maternal infection compared with no zinc supplements (four trials, 1891 women; RR 0.94, 95% CI 0.72 to 1.23; *low-certainty evidence, downgraded due to design limitations and imprecision*).

Side-effects: Side-effects were not generally reported in trials.

The evidence on caesarean section was of very low certainty and there were no relevant data on maternal anaemia, maternal mortality, gestational diabetes mellitus or positive pregnancy experience.

Fetal/neonatal outcomes

Small for gestational age: Zinc supplementation probably makes little or no difference to the small for gestational age outcome compared with no zinc supplements (nine trials, 5330 babies; RR, 1.02, 95% confidence interval, CI, 0.92 to 1.12; *moderate-certainty evidence, downgraded due to design limitations*).

Low birthweight: Zinc supplementation probably makes little or no difference to low birthweight compared with no zinc supplements (17 trials, 7399 babies; RR 0.94, 95% CI 0.79 to 1.13; *moderate-certainty evidence, downgraded due to design limitations*).

Preterm birth: Zinc supplementation probably makes little or no difference to preterm birth compared with no zinc supplements (20 trials, 9454 babies; RR 0.90, 95% CI 0.78 to 1.04; *moderate-certainty evidence, downgraded due to design limitations*).

Neonatal mortality: Zinc supplementation may make little or no difference to neonatal mortality compared with no zinc supplements (three trials, 1965 babies; RR 2.24, 95% CI 0.40 to 14.83; *low-certainty evidence, downgraded due to design limitations and imprecision*).

Stillbirth: Zinc supplementation may make little or no difference to stillbirth compared with no zinc supplements (six trials, 2898 babies; RR 1.32, 95% CI 0.85 to 2.04; *low-certainty evidence, downgraded due to design limitations and imprecision*).

Perinatal mortality: Zinc supplementation may make little or no difference to perinatal mortality compared with no zinc supplements (two trials, 2489 babies; RR 1.10, 95% CI 0.81 to 1.51; *low-certainty evidence, downgraded due to design limitations and imprecision*).

Congenital anomalies: Zinc supplementation may make little or no difference to congenital malformation compared with no zinc supplements (five trials, 1106 babies; RR 0.67, 95% CI 0.33 to 1.35; *low-certainty evidence, downgraded due to design limitations and imprecision*).

Neonatal infection: Zinc supplementation may make little or no difference to neonatal sepsis compared with no zinc supplements (two trials, 736 babies; RR 0.17, 95% CI 0.03 to 1.01; *low-certainty evidence, downgraded due to design limitations and imprecision*).

Summary of effects

Low-certainty evidence suggests that zinc supplementation may have little or no effect on pre-eclampsia and maternal infections; there is insufficient evidence available for other maternal outcomes. In addition, low-certainty evidence suggests that supplementation may have little or no effect on any of the important fetal and neonatal outcomes.

Additional considerations

- WHO recommends iron and folic acid supplementation containing 30 mg to 60 mg of iron and 0.4 mg of folic acid for all pregnant women, and calcium supplementation for women with low dietary intake and those at risk of pre-eclampsia; these supplements may potentially reduce the bioavailability of zinc (1).

Desirable effects

How substantial are the desirable anticipated effects of zinc supplements compared with no zinc supplements?

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

Rationale for judgement: There appears to be no clear improvement in pregnancy outcomes.

Undesirable effects

How substantial are the undesirable anticipated effects of zinc supplements compared with no zinc supplements?

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

Rationale for judgement: There was no evidence suggesting harm but adverse events were generally not reported in the studies.

Certainty of the evidence

What is the overall certainty of the evidence of effects of zinc supplements compared with no zinc supplements?

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

Rationale for judgement: Low certainty was the most common GRADE rating.

Values

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

A scoping review of what women want from ANC informed the outcomes for the WHO ANC guideline *(14)*. Evidence showed that women from various resource settings valued having a positive pregnancy experience comprising three equally important components, namely 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: It is important to pregnant women that clinical practices are effective.

Balance of effects

Does the balance between desirable and undesirable effects favour zinc supplements or no zinc supplements?

Judgement						
☐ Don't know	☐ Varies	☐ Favours no zinc supplements	☐ Probably favours no zinc supplements	☒ Does not favour zinc supplements or no zinc supplements	☐ Probably favours zinc supplements	☐ Favours zinc supplements

Rationale for judgement: The low-certainty evidence suggests that there are neither benefits nor harms with zinc supplements.

3.3 Resources

How large are the resource requirements (costs)?

Research evidence

No research evidence on the costs and cost-effectiveness of implementing zinc supplementation was found.

Main resource requirements

The main resource requirement is probably the cost of the supplements. The UNICEF Supply Catalogue pricing accessed on 3 June 2021 gave an indicative price of US$ 1.34 for a blister pack of 100 tablets of 20 mg each, which is equivalent to US$ 3.20 for six-month supply *(20)*. However, to ensure that women received relevant and accurate information about the supplements, staff training would be required, which would also have cost implications.

Additional considerations
• The cost-effectiveness of zinc supplements for pregnant women is uncertain because the systematic review found no strong evidence of their effectiveness in relation to the pregnancy outcomes evaluated. • To have an impact on child mortality, it has been suggested that food fortification may be the most cost-effective strategy to supplement zinc among populations with a high prevalence of zinc deficiency *(3)*.

Resources required

How costly are the resources required for zinc supplements compared with no zinc supplements?

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

Rationale for judgement: The cost of zinc supplements is similar to that of iron and folic acid supplements, and, if implemented, may double the cost of micronutrient supplements provided to women during pregnancy.

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.

Cost-effectiveness

How cost-effective are zinc supplements compared with no zinc supplements?

Judgement						
☒ Don't know	☐ Varies	☐ Favours no zinc supplements	☐ Probably favours no zinc supplements	☐ Does not favour zinc supplements or no zinc supplements	☐ Probably favours zinc supplements	☐ Favours zinc supplements

Rationale for judgement: The evidence did not show zinc supplementation to be effective, so cost-effectiveness cannot be evaluated.

3.4 Equity

What would be the impact of zinc supplements compared with no zinc supplements on health equity?

Research evidence

None.

Additional considerations

- Nutritional deficiencies are common in low- and middle-income countries (LMICs). Effective interventions to improve the nutritional status of pregnant women and girls in these settings could help to address health inequalities by preventing illnesses related to vitamin and mineral deficiencies.

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

Rationale for judgement: There is no clear evidence of the effectiveness of zinc supplementation for pregnancy outcomes; the effectiveness of zinc supplementation on general maternal health in LMICs was not a prioritized guideline outcome.

3.5 Acceptability

Would zinc supplements be acceptable to key stakeholders?

Research evidence

A systematic review of qualitative research exploring women's views and experiences of ANC suggests that women 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) (15)*.

The same review explored health professionals' views of ANC, and suggests 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 the resources and time to deliver the service in the informative, supportive and caring manner that women want *(high confidence in the evidence) (15)*.

Additional considerations
None.

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

Rationale for judgement: If zinc supplementation improved pregnancy outcomes, supplementation would probably be acceptable. However, as there is no clear evidence of effectiveness, it may not be acceptable.

3.6 Feasibility

Would zinc supplementation be feasible to implement?

Research evidence

Evidence derived from a qualitative evidence synthesis conducted to support the WHO ANC guideline development shows that where there are likely to be additional costs associated with supplementation *(high confidence in the evidence)*, women may be less likely to engage with services *(15)*. In addition, in a number of LMIC settings, providers felt that a lack of resources, both in terms of the availability of recommended supplements and the lack of suitably trained staff to deliver nutritional information, was an issue, which may limit the implementation of this intervention *(high confidence in the evidence)*.

Additional considerations
• On the demand side, if zinc supplements are free and available, routine supplementation may be feasible. On the supply side, however, 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. • In addition, the lack of effectiveness of this intervention suggests that it would not be feasible in LMICs where health-care expenditure is constrained.

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

Rationale for judgement: There is no clear evidence of effectiveness.

3.7 Summary of GDG judgements on antenatal zinc supplementation *(18)*

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 no zinc supplements	☐ Probably favours no zinc supplements	☑ Does not favour zinc supplements or no zinc supplements	☐ Probably favours zinc supplements	☐ Favours zinc supplements
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 no zinc supplements	☐ Probably favours no zinc supplements	☐ Does not favour zinc supplements or no zinc supplements	☐ Probably favours zinc supplements	☐ Favours zinc supplements
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

3.8 Conclusions

Recommendation

Zinc supplementation for pregnant women is recommended only in the context of rigorous research.

Judgement		
We do not recommend the intervention ☐	We recommend considering the intervention only ☐ in specific contexts ☐ with targeted monitoring and evaluation ☒ in the context of rigorous research	We recommend the intervention ☐

Remarks

- This GDG agreed to retain the WHO recommendation found in the 2016 WHO ANC guideline *(8)*.
- WHO does not recommend zinc supplementation as part of routine ANC. Zinc supplementation is recommended only in the context of rigorous research to improve our knowledge of its effect in pregnant women. Research is particularly needed on how zinc status is impacted by other nutritional supplementation (e.g. iron and/or calcium) given as part of routine ANC. Additionally, research is needed on the efficacy of zinc supplementation – provided either alone or with other nutritional supplements (e.g. iron and folic acid, calcium, according to national guidelines/standard of care) – on maternal and neonatal outcomes. Multiple doses of zinc, iron and/or calcium may need to be evaluated based on the current national standard of care. Research on the effectiveness or the implementation of zinc supplementation is not identified as a priority at this time.
- Pregnant women should be encouraged and supported to receive adequate nutrition, which is best achieved through a healthy, balanced diet, and to refer to guidelines on healthy eating *(19)*.

Draft implementation considerations

Not applicable.

Research gaps

- The GDG agreed that more research on the efficacy of zinc supplementation in pregnancy was needed and that trials of zinc supplementation should consider other nutritional supplements (e.g. iron and/or calcium) that women may be receiving as part of routine ANC. As iron supplementation is recommended in all settings, and calcium supplementation is recommended in settings with low dietary intake as part of routine ANC, research is needed to evaluate the interactions among these nutrients in relation to maternal and newborn outcomes.
- In settings providing iron and folic acid as part of routine ANC, trials on zinc supplementation should include several doses of zinc along with either 30 mg and/or 60 mg of elemental iron, according to national guidance.
- Information should be recorded carefully on the timing of the different supplements, whether taken at the same time or different times of the day, along with an assessment of the feasibility and acceptability of taking multiple supplements at different times in these trials.

4 Dissemination and implementation of the recommendation

4.1 Recommendation dissemination

This updated global guideline will be available online for download and also as a printed publication. Online versions will be available on the WHO websites and other online platforms developed by the WHO Departments of SRH, NFS and MCA, and through the WHO ANC portal[1] and the WHO Reproductive Health Library and WHO e-Library of Evidence for Nutrition Actions.[2] Print versions will be distributed to WHO regional and country offices, ministries of health, WHO collaborating centres, nongovernmental organization partners, among others, using the same distribution list that was developed for the WHO ANC guideline. 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 *(21)*. Social media channels will also be used. The executive summary and recommendation from this publication will be translated into the six United Nations languages for dissemination through the WHO regional offices and during meetings organized or attended by WHO staff.

4.2 Implementation considerations and applicability issues

This updated recommendation supersedes the WHO ANC guideline recommendation on zinc supplementation that was issued in 2016 (recommendation A6) *(8)*. The GDG agreed that there were no new implementation considerations or applicability issues specific to this recommendation, as it was recommended in a research context. Monitoring of the uptake and impact of this updated recommendation will be integrated into that of the 2016 WHO ANC guideline *(8)*. For implementation considerations related to *WHO recommendations on antenatal care for a positive pregnancy experience* in general, please refer to this guideline and associated derivative products, which are available on the WHO websites.

5 Research implications

The GDG agreed that more research on the efficacy of zinc supplementation in pregnancy is needed and that trials of zinc supplementation should consider other nutritional supplements (e.g. iron and/or calcium) that women may be receiving as part of routine ANC. As iron supplementation is recommended in all settings and calcium supplementation is recommended in settings with low dietary intake as part of routine ANC, research is needed to evaluate the interactions among these nutrients in relation to maternal and newborn outcomes.

In settings providing iron and folic acid as part of routine ANC, trials on zinc supplementation should include several doses of zinc along with 30 mg and/or 60 mg of elemental iron, according to national guidance.

Information should be recorded carefully on the timing of the different supplements, whether taken at the same time or different times of the day, along with an assessment of the feasibility and acceptability of taking multiple supplements at different times in these trials.

6 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. WHO will monitor the publication of new randomized trials on this topic. Any concern about the validity of the recommendation will be promptly communicated via the guideline website,[3] 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[4] file customized for priority outcomes, and the basis for quality ratings within the GRADE process, will be archived in the departmental shared folder for future reference and use.

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Annex 2. Summary of declarations of interest from the Guideline Development Group members, observers and External Review Group members and how they were managed

Name	Gender	Expertise	Disclosure of interest	Conflict of interest and management
Dr Niveen Abu-Rmeileh	Female	Community and public health, statistical epidemiology	None declared	None declared
Professor Lorena Binfa	Female	Midwifery, Director of of the WHO collaborating centre for Developing Midwifery	None declared	None declared
Dr Nita Dalmiya	Female	United Nations Children's Fund New York City, New York, United States of America (USA)	None declared	None declared
Dr Lindy Fenlason	Female	United States Agency for International Development	None declared	Not applicable
Dr Atf Ghérissi	Female	Systematic reviews, qualitative evidence, maternal and perinatal health, community health	None declared	Not applicable
Mrs Gill Gyte	Female	Consumer representative, pregnancy and childbirth	None declared	Not applicable
Professor Tamar Kabakian	Female	Health Promotion and Community Health	None declared	None declared
Professor Jim Neilson	Male	General obstetrics, perinatology, gynaecology, systematic reviews, evidence synthesis and guideline development using GRADE	None declared	Not applicable
Dr Lisa Noguchi	Female	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 PNC.	The conflict was not considered serious enough to affect Guideline Development Group (GDG) membership or participation in the GDG meeting.

Name	Gender	Expertise	Disclosure of interest	Conflict of interest and management
Professor Nafissa Osman	Female	Obstetrics and gynaecology, implementation research	None declared	Not applicable
Professor Erika Ota	Female	Nutrition, evidence synthesis, guideline development	None declared	Not applicable
Professor Bob Pattinson	Male	Obstetrics and gynaecology, delivery of care, evidence synthesis	None declared	Not applicable
Professor Kathleen Rasmussen	Female	Professor of maternal and child nutrition	None declared	Not applicable
Ms Bhavya Reddy	Female	Maternal and child health, gender and health equity, community health	None declared	None declared
Professor Harshpal Singh Sachdev	Male	Paediatrics, nutrition, systematic reviews	Contributed data from India to subsequent meta-analyses and contributed to a published opinion paper on the subject of zincs in pregnancy. Was involved in the epidemiological design and analysis of this paper; however, did not receive funding for this work	The conflict was not considered serious enough to affect GDG membership or participation in the GDG meeting.
Ms Rusidah Selamat	Female	Maternal and infant nutrition, community-based programmes, implementation research	None declared	Not applicable
Dr Mary Ellen Stanton	Female	United States Agency for International Development	None declared	Not applicable
Dr Petra Ten Hoope-Bender	Female	United Nations Population Fund	None declared	Not applicable
Dr Alison Tumilowicz	Female	Bill & Melinda Gates Foundation	None declared	Not applicable
Dr Petr Velebil	Male	Obstetrics and gynaecology	None declared	None declared
Dr Charlotte Warren	Female	Maternal and perinatal health, systematic reviews, implementation research	None declared	Not applicable
Dr Florence West	Female	International Confederation of Midwives	None declared	Not applicable

Annex 3. Zinc supplementation: GRADE tables

Question: Should zinc supplementation versus no zinc supplementation (with or without placebo) be used for pregnant women?

Settings: Bangladesh, Chile, China, Denmark, Indonesia, Islamic Republic of Iran, United Kingdom of Great Britain and Northern Ireland, United Republic of Tanzania, United States of America.

Bibliography: Carducci B, Keats EC, Bhutta ZA. Zinc supplementation for improving pregnancy and infant outcome. Cochrane Database Syst Rev. 2021; 3:CD000230. doi:10.1002/14651858.CD000230.pub6.

Maternal outcomes

Certainty assessment							Number of women		Effect		Certainty	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zinc supplementation	No zinc (with or without placebo)	Relative (95% CI)	Absolute		
Caesarean section												
7	randomized trials	serious[a]	serious[b]	no serious indirectness	serious[c]	none	150/1132 (13.3%)	143/1079 (13.3%)	RR 0.87 (0.58 to 1.29)	17 fewer per 1000 (from 56 fewer to 38 more)	⊗○○○ VERY LOW	CRITICAL
								31.8%		41 fewer per 1000 (from 134 fewer to 92 more)		
Instrumental vaginal birth												
1	randomized trial	serious[d]	no serious inconsistency	no serious indirectness	serious[c]	none	58/585 (9.9%)	55/621 (8.9%)	RR 1.12 (0.79 to 1.59)	11 more per 1000 (from 19 fewer to 52 more)	⊗⊗○○ LOW	CRITICAL
								8.9%		11 more per 1000 (from 19 fewer to 53 more)		

CI = confidence interval, RR = risk ratio

Certainty assessment							Number of women		Effect		Certainty	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zinc supplementation	No zinc (with or without placebo)	Relative (95% CI)	Absolute		
Pre-eclampsia												
6	randomized trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	41/1265 (3.2%)	45/1303 (3.5%)	RR 0.93 (0.62 to 1.42)	2 fewer per 1000 (from 13 fewer to 15 more)	⊗⊗○○ LOW	CRITICAL
								4.4%		3 fewer per 1000 (from 17 fewer to 18 more)		
Any maternal infection												
4	randomized trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	86/930 (9.2%)	96/961 (10%)	RR 0.94 (0.72 to 1.23)	6 fewer per 1000 (from 28 fewer to 23 more)	⊗⊗○○ LOW	CRITICAL
								5.4%		3 fewer per 1000 (from 15 fewer to 12 more)		
								18.2%		47 fewer per 1000 (from 116 fewer to 91 more)		

[a] Most of the pooled effect was provided by studies with moderate risk of bias and design limitations.
[b] Inconsistency between studies contributing data (I2 = 72%) (size and direction of effect inconsistent).
[c] Confidence interval is imprecise.
[d] Evidence from a single study with moderate risk of bias and design limitations.

Fetal and neonatal outcomes

Certainty assessment							Number of women		Effect		Certainty	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zinc supplementation	No zinc (with or without placebo)	Relative (95% CI)	Absolute		
Small for gestational age or intrauterine growth restriction												
9	randomized trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	609/2 695 (22.6%)	590/2 635 (22.4%)	RR 1.02 (0.92 to 1.12)	4 more per 1000 (from 18 fewer to 27 more)	⊗⊗⊗○ MODERATE	CRITICAL
								14%		3 more per 1000 (from 11 fewer to 17 more)		
Low birthweight (< 2500 g)												
17	randomized trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	499/3 755 (13.3%)	483/3 644 (13.3%)	RR 0.94 (0.79 to 1.13)	8 fewer per 1000 (from 28 fewer to 17 more)	⊗⊗⊗○ MODERATE	CRITICAL
								8.3%		5 fewer per 1000 (from 17 fewer to 11 more)		
Preterm birth (< 37 weeks)												
20	randomized trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	557/4 756 (11.7%)	599/4 698 (12.8%)	RR 0.9 (0.78 to 1.04)	13 fewer per 1000 (from 28 fewer to 5 more)	⊗⊗⊗○ MODERATE	CRITICAL
								8.9%		9 fewer per 1000 (from 20 fewer to 4 more)		

Certainty assessment							Number of women		Effect		Certainty	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zinc supplementation	No zinc (with or without placebo)	Relative (95% CI)	Absolute		
Perinatal death												
2	randomized trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	81/1272 (6.4%)	70/1217 (5.8%)	RR 1.1 (0.81 to 1.51)	6 more per 1000 (from 11 fewer to 29 more)	⊗⊗○○ LOW	CRITICAL
								5.7%		6 more per 1000 (from 11 fewer to 29 more)		
Neonatal death												
3	randomized trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	36/1013 (3.6%)	23/952 (2.4%)	RR 2.44 (0.4 to 14.83)	35 more per 1000 (from 14 fewer to 334 more)	⊗⊗○○ LOW	CRITICAL
								0%		-		
Stillbirth												
6	randomized trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	48/1450 (3.3%)	35/1448 (2.4%)	RR 1.32 (0.85 to 2.04)	8 more per 1000 (from 4 fewer to 25 more)	⊗⊗○○ LOW	CRITICAL
								2.3%		7 more per 1000 (from 3 fewer to 24 more)		

Certainty assessment							Number of women		Effect		Certainty	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zinc supplementation	No zinc (with or without placebo)	Relative (95% CI)	Absolute		
Congenital malformation												
5	randomized trials	serious[c]	no serious inconsistency	no serious indirectness	serious[b]	none	13/595 (2.2%)	18/511 (3.5%)	RR 0.67 (0.33 to 1.35)	12 fewer per 1000 (from 24 fewer to 12 more)	⊗⊗○○ LOW	CRITICAL
								3.2%		11 fewer per 1000 (from 21 fewer to 11 more)		
Neonatal sepsis												
2	randomized trials	serious[a]	no serious inconsistency	no serious indirectness	serious[d]	none	1/410 (0.24%)	6/326 (1.8%)	RR 0.17 (0.03 to 1.01)	15 fewer per 1000 (from 0 fewer to 18 fewer)	⊗⊗○○ LOW	CRITICAL
								2.1%		17 fewer per 1000 (from 0 fewer to 20 fewer)		

[a] Evidence from studies with moderate risk of bias and design limitations.
[b] Confidence interval is imprecise.
[c] More than 50% of the pooled effect from studies with moderate risk of bias and design limitations.
[d] Estimate based on low event rate.

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