The Evidence Base
Reviewing the Evidence and Promoting the Adoption of Multiple Micronutrient Supplements

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Key messages

- Micronutrient deficiencies are common during pregnancies; they can have deleterious effects on multiple antenatal and perinatal outcomes.
- Evidence outlined in this paper shows that multiple micronutrient supplements (MMS) are a highly cost-effective way to prevent many adverse antenatal and perinatal outcomes.
- A Technical Advisory Group (TAG) has been created to further support the adoption and implementation of MMS, to advance knowledge and to serve as a communications hub to all MMS stakeholders.

The importance of micronutrients in pregnancy

Global pregnancy-related mortality and morbidity of both mothers and infants remain unacceptably high.¹,² A key determinant of perinatal outcomes is maternal nutrition: a woman’s diet during pregnancy should include an adequate intake of energy, protein, essential fatty acids and vitamins and minerals (micronutrients) to meet maternal and fetal needs. Micronutrients are essential for positive pregnancy outcomes because they play a critical role in the successive phases of fetal development, from the formation of the placenta, to the organ and neurological development, tissue deposition and body composition of the offspring.³

Programmatic responses to micronutrient deficiencies in pregnancy

Public health programs have long promoted dietary change and the use of dietary supplements – particularly iron and folic acid (IFA) – to prevent micronutrient deficiencies during pregnancy. However, those interventions alone are generally insufficient to fill the various micronutrient gaps that may exist. This prompted the United Nations Children’s Fund (UNICEF), along with the World Health Organization (WHO) and the United Nations University, to develop the United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) in 1999 to provide the Recommended Daily Allowance (RDA) of 15 micronutrients, including IFA, and offer a cost-effective strategy to address a broad spectrum of micronutrient deficiencies (Box 1). To date, more than 20 trials have used the UNIMMAP formulation or similar formulations in comparison with IFA alone. In 2016, WHO considered the 2016 Cochrane Review of 15 of these trials when developing its guidelines on antenatal care (ANC), but found that further evidence was needed on the benefits, risks and costs of MMS to universally recommend these supplements over IFA.⁴,⁵ Subsequently, WHO reaffirmed its recommendation of IFA for routine use in pregnancy, with the caveat that countries with a high prevalence of nutritional deficiencies may want to consider MMS over IFA.

Box 1: UNIMMAP Micronutrient formula

- Iron 30 mg
- Zinc 15 mg
- Copper 2 mg
- Selenium 65 µg
- Iodine 150 µg
- Vitamin A 800 µg retinol equivalent (RE)
- Vitamin B₁ 1.4 mg
- Vitamin B₂ 1.4 mg
- Vitamin B₃ (niacin) 18 mg
- Vitamin B₆ 1.9 mg
- Vitamin B₉ (folic acid) 400 µg
- Vitamin B₁₂ 2.6 µg
- Vitamin C 70 mg
- Vitamin D 200 IU
- Vitamin E 10 mg

MMS or IFA? Comparing the evidence

To help countries understand the WHO guidelines and assess emerging evidence around MMS during pregnancy, the New York Academy of Sciences (NYAS), with support from the Bill & Melinda Gates Foundation (BMGF), assembled a Task Force in 2017. In particular, the group aimed to assess: the prevalence of micronutrient deficiencies among women of reproductive age and pregnant
women; the prevalence of adverse birth outcomes; and the safety considerations, side effects, adherence and cost-effectiveness of MMS. To this end, the Task Force compiled the latest scientific evidence on the prevalence of micronutrient deficiencies from literature reviews of national and regional surveys. The Task Force used new meta-analyses published after the release of the 2016 WHO ANC Guidelines, inclusive of an individual person data (IPD) analysis. This data reiterated the high prevalence of micronutrient deficiencies among pregnant women and women of reproductive age. For example, it reported that 63.2 percent of women of reproductive age in low- and middle-income countries (LMICs) are vitamin-D-deficient, 41.4 percent are zinc-deficient and 15.9 percent are vitamin-A-deficient (Figure 1). These deficiencies put the mothers and their infants at increased risk of adverse birth outcomes. Indeed, the prevalence of adverse birth outcomes for both the infants and their mothers remains unacceptably high, as shown by evidence compiled by the Task Force: 34.2 percent of newborns in South Asia are small for gestational age, and maternal mortality is as high as 546 women per 100,000 live births in sub-Saharan Africa. Adequate nutrition, including the provision of micronutrients, is an important and well-documented way to mitigate these adverse effects.

The IPD meta-analysis reaffirmed the findings of the Cochrane Review that MMS during pregnancy can reduce the risk of low birth weight, small-for-gestational-age birth and preterm birth when compared with IFA. However, the IPD meta-analysis also deepened our understanding of the data by conducting several subgroup analyses based on individual data. This is in contrast to the Cochrane Review analysis, in which only the trial average (i.e., maternal body mass index or hemoglobin) is used in the subgroup analyses. As a result, the IPD meta-analysis was able to identify subgroups that could have greater benefit with MMS, including underweight women, anemic women and female infants whose mothers received MMS during pregnancy.
It was also important to the Task Force to examine the potential risk of the excess intake of micronutrients in order to address any potential safety concerns. An analysis performed by Gernand showed that there is relatively little risk associated with the excess intake of any of the micronutrients included in UNIMMAP. Additionally, a 2019 analysis by Schulze et al. shows that even with MMS, many women in Bangladesh remain micronutrient-deficient. Similarly, the Task Force examined the side effects and adherence that were reported by the trials comparing MMS with IFA because this would be an important consideration for the uptake of the intervention. While the trial data reported these outcomes in a variety of ways, there was no apparent change in the side effects or adherence rates between the two supplements across the trials.

One of the concerns highlighted in the WHO ANC Guidelines was the increased cost of MMS compared with IFA. At the time of the WHO analysis, MMS was about three times the cost of IFA, using costs from UNICEF’s supply catalogue. However, the costs have been dramatically reduced in recent years and will likely decline further as demand increases. More importantly, MMS was shown to be a highly cost-effective intervention compared with IFA, even when allowing for the increased costs, as discussed in greater detail elsewhere in this Sight and Life special report.

“MMS was shown to be a highly cost-effective intervention compared with IFA”

Based on these findings, the Task Force concluded that countries having a high prevalence of maternal micronutrient deficiencies should consider using MMS instead of IFA to reduce the risk of micronutrient deficiencies and adverse birth outcomes. A more detailed account of the Task Force’s conclusions was published in a special issue of the Annals of the New York Academy of Sciences.

A number of articles in this Sight and Life Special Report introduce and expand upon these Task Force products.

The MMS Technical Advisory Group (TAG)

To consolidate the strong scientific basis established by the Task Force, UNICEF, with support from the BMGF, is currently Reviewing the Evidence and Promoting the Adoption of Multiple Micronutrient Supplements.
implementing the MMS strategy in four country demonstration programs (Bangladesh, Burkina Faso, Tanzania and Madagascar). Separately, Vitamin Angels and Kirk Humanitarian, consistent with Task Force findings, are supporting a country demonstration program in collaboration with the Haitian Ministry of Population and Public Health. In conjunction with these efforts, NYAS is facilitating the global coordination of MMS actors via the creation of a TAG. Activities under the TAG include: the establishment of a communications hub to advise and document global program implementation; the production of generic technical reference materials that could be adapted to the context of adopting countries; and the provision of technical support when needed to address issues that emerge. The activities of the MMS TAG, since its creation in November 2018, are described below.

Technical reference materials and policy briefs for adopting countries

A series of technical reference materials was prepared to support countries aiming to adopt MMS in their ANC programs. The documents include generic pre- and in-service training materials for medical professionals and frontline health workers. In addition, FAQs and job aids are available. Further, country-specific policy briefs were prepared for Bangladesh and India, to explain in simple terms the potential benefits of MMS compared with IFA, taking into account the burden of maternal micronutrient deficiencies evident in these countries. These documents are available on the MMS TAG website (see below).

Identification of key implementation knowledge gaps

A research prioritization exercise using a methodology known as the Child Health and Nutrition Research Initiative identified key knowledge gaps in the implementation of MMS interventions. This approach involved bringing together a group of international experts to specify and rank which research questions most urgently need to be resolved in order for prenatal MMS interventions to be successfully implemented. Thirty-five consolidated research questions were identified and scored, yielding a ranking of 10 priority research topics. These range from strategies to increase antenatal care attendance and MMS adherence, to methods needed to identify populations more likely to benefit from MMS interventions, to issues such as the potential benefit of extending MMS through lactation.

Organization of an MMS product specification workshop

While the formulation of UNIMMAP is not currently being revisited, standard manufacturing specifications have not yet been proposed for the fabrication of MMS products. To address this, NYAS and the Micronutrient Forum co-hosted an expert technical consultation in November 2019 to generate an MMS product specification document that can be used by any manufacturer or buyer seeking to manufacture or procure an MMS product. This document described on page 102 of this Special Report is a broader quality manual on the production of MMS that includes variances in aspects such as packaging and unit count, which may vary between countries and manufacturers.

“Although the efficacy of MMS is now well established, the effectiveness of this intervention will only materialize if pregnant women adhere to the supplementation regimen”

Preparation of a systematic review on adherence to MMS

Although the efficacy of MMS is now well established, the effectiveness of this intervention to decrease adverse pregnancy and birth outcomes will only materialize if pregnant women adhere to the supplementation regimen. Adherence, defined as “the extent to which a patient’s behavior matches the agreed recommendations from a healthcare provider,” appears to be poor. Based on Demographic and Health Surveys data from 22 countries with IFA programs, coverage of IFA is often higher than 80 percent, but only 8 percent of the targeted recipients consume the recommended dose (180 tablets or more). The MMS TAG is currently carrying out a systematic review to assess the effectiveness of interventions designed to increase adherence to MMS in pregnant women. Results from this review will be available later in 2020.

Creation of an MMS website

A website platform (www.nyas.org/mms) was created to broadly represent MMS TAG activities to the public. The website is continually updated, and visitors can download key documents prepared by the expert group, consult a repository of information on the issue and request technical assistance in the implementation of MMS programs.

Conclusion

MMS offers a highly cost-effective intervention to improve a variety of antenatal outcomes. Promoted by actions such as the BMGF Goalkeepers Accelerator Initiative, the approach is rapidly gaining interest from national- and international-level stakeholders. Several technical issues remain to be answered, but this rapidly evolving field of knowledge is well served by the solid technical support provided by the MMS TAG and associated groups, as described in this Sight and Life Special Report.
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References


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