Interim Country-level Decision-making Guidance for Introducing Multiple Micronutrient Supplementation for Pregnant Women

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Key Messages Pertaining to the Interpretation of the 2020 *World Health Organization antenatal care recommendations for a positive pregnancy experience. Nutritional interventions update: Multiple micronutrient supplements during pregnancy*

1. There is clear and consistent evidence from clinical trials that multiple micronutrient supplements (MMS) provide additional benefits over iron and folic acid supplements (IFA) in reducing adverse pregnancy outcomes.
    - The World Health Organization (WHO) analysis finds UNIMMAP-MMS reduce the risk of low birthweight (LBW) and small for gestational age (SGA).[1]
    - An additional individual patient data (IPD) meta-analysis also finds MMS reduce the risk of stillbirth and preterm birth.[2]
    - Anemic women and underweight women derive even greater benefits with MMS.[2]
2. MMS containing 30 mg of iron are as effective as IFA containing 60 mg of iron in preventing maternal anemia.[1]
3. MMS is a low cost and highly cost-effective intervention in comparison with IFA.[3–5]
4. The updated WHO guidelines recommend MMS as "context specific – research", meaning:
    - Using MMS in the context of antenatal care (ANC) services informed by implementation research designed to optimize MMS introduction, and
    - Continuing clinical research as part of a global agenda to inform future WHO guidelines as they are updated.
5. In settings where dietary quality is poor, micronutrient deficiencies are common and anemia and low birthweight are public health problems, daily MMS with iron and folic acid can contribute to improved micronutrient intakes in pregnancy, prevent maternal anemia and reduce adverse pregnancy outcomes, including low birthweight.

Objective

This document aims to provide guidance to country-level decision makers who are interested in introducing MMS for pregnant women in ANC programs. Guidance provided here is contextualized to the 2020 update to the *WHO antenatal care recommendations for a positive pregnancy experience. Nutritional interventions update: Multiple micronutrient supplements during pregnancy*.[1]

Background – Importance of Adequate Nutrition during Pregnancy

Ensuring pregnant women and adolescent girls have nutritious diets along with routine access to ANC is fundamental not only to their survival and wellbeing but also that of their infants. However, for many pregnant women and adolescent girls in low- and middle-income countries (LMICs) poor quality diets are the norm and food intake is often insufficient to meet the unique needs of pregnancy, hence the risk of micronutrient deficiencies is high.[6]

Maternal malnutrition is a key determinant of poor pregnancy outcomes. It not only increases the risk of maternal morbidity and mortality but also the risk of giving birth to infants who are LBW, either due to being born SGA or premature birth. Starting life with LBW puts infants on a trajectory of potentially long-term negative consequences ranging from impaired growth and development in early childhood through chronic diseases in adulthood.[7] Twenty percent of all stunting and 30 percent of all wasting in children under 5-years old is associated with being born SGA.[8]

Iron deficiency anemia is the most commonly known micronutrient deficiency. However, intakes of other vitamins and minerals such thiamine, riboflavin, niacin, vitamins B-6 and B-12 and zinc are often low among pregnant women in LMICs and have been associated with adverse pregnancy outcomes.[6] MMS represent a safe way to meet many micronutrient requirements of pregnancy that poor diets cannot meet.[9]

The United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) is an established multiple micronutrient formulation containing 15 vitamins and minerals, including iron and folic acid in recommended dosages.[10] This formulation was specifically developed to improve pregnancy outcomes and has been widely tested in efficacy and effectiveness trials across multiple regions. UNIMMAP-MMS was demonstrated to confer similar benefits for the prevention of anemia compared with IFA and larger impacts on other pregnancy outcomes compared with IFA.[2,11]

UNIMMAP Composition	
Vitamin A	800 µg
Vitamin D	200 IU
Vitamin E	10 mg
Vitamin C	70 mg
Thiamine	1.4 mg
Riboflavin	1.4 mg
Niacin	18 mg
Vitamin B6	1.9 mg
Folic Acid	400 µg
Vitamin B12	2.6 µg
Copper	2 mg
Iodine	150 µg
Iron	30 mg
Selenium	65 µg
Zinc	15 mg

Summary of the Updated WHO Recommendation

The 2020 update to the *WHO antenatal care recommendations for a positive pregnancy experience. Nutritional interventions update: Multiple micronutrient supplements during pregnancy*[1] recommends the use of MMS containing iron and folic acid in the context of rigorous research (context-specific recommendation – research) and supersedes the 2016 WHO ANC guidance.[1,12] At a program level, MMS are recommended in the context of implementation research, while additional research is recommended to address remaining clinical questions.

Evidence Base

There is now a strong evidence base of randomized controlled trials that have demonstrated the benefits of using MMS over IFA.[2,11] This includes a 2019 Cochrane review, and an individual patient data (IPD) meta-analysis was conducted as well. Most of the trials in the IPD were also in the Cochrane review.

The WHO guideline is based on the 2019 Cochrane review of clinical trials comparing MMS to IFA alone. WHO further analyzed the evidence by making two comparisons: one using MMS containing 13 to 15

micronutrients compared with IFA supplements, and a second comparison with the trials that only used the UNIMMAP-MMS formulation in comparison with IFA. This second comparison is presented here because UNIMMAP-MMS were the most commonly used formulation in the clinical trials and is readily available This analysis showed:

LBW: UNIMMAP-MMS reduce the risk of LBW by 13% in comparison with IFA.

SGA: UNIMMAP-MMS reduce the risk of being born SGA by 9% in comparison with IFA.

Preterm birth: There is little or no difference in preterm birth between UNIMMAP-MMS and IFA.

Perinatal mortality: Outcomes for perinatal mortality vary by the dose of iron (30 or 60 mg) in the IFA but are not statistically significant for UNIMMAP-MMS.

Maternal anemia: UNIMMAP-MMS containing 30 mg of iron offer similar benefits on maternal anemia compared with IFA (containing 30mg or 60mg of iron).

Table 1. The WHO summary of the evidence from trials comparing MMS with IFA; significant effects of risk reduction are in **bold** and favor the use of MMS. Non-significant effects suggest no difference between IFA and MMS.

Outcome	*MMS trials 13-15 Micronutrients*	*UNIMMAP-MMS trials*
LBW	**RR: 0.88** **95% CI 0.86 to 0.91** **16 trials**	**RR: 0.87** **95% CI: 0.81 to 0.94** **10 trials**
SGA	RR: 0.98 95% CI: 0.96 to 1.00 15 trials	**RR: 0.91** **95% CI: 0.85 to 0.98** **9 trials**
Preterm birth	RR: 0.94 95% CI: 0.88 to 1.00 16 trials	RR: 1.00 95% CI: 0.96 to 1.03 10 trials
Perinatal mortality (30 mg iron in IFA)	**RR 0.92** **95% CI: 0.86 to 0.98** **4 trials**	RR: 0.90 95% CI 0.80 to 1.01 3 trials
Perinatal mortality (60 mg iron in IFA)	RR: 1.15 95% CI: 0.93 to 1.42 9 trials	RR: 1.2 95% CI: 0.95 to 1.51 6 trials
Maternal anemia	RR 1.03 95% CI:0.92 to 1.15 8 trials	RR: 0.90 95% CI 0.77-1.05 2 trials

IPD meta-analysis: This analysis found similar results to the Cochrane review but also included a number of sub-group analyses with statistically significant effects of MMS and are summarized in Table 2. Importantly, this meta-analysis showed that MMS have a greater beneficial effect among anemic and underweight pregnant women.[2]

Cost-effectiveness: Two cost-effectiveness analyses found MMS to be very cost-effective compared with IFA, yielding a high return on investment.[3,4] As noted in the updated WHO guideline, Nutrition International modelled the data from the estimates in the WHO sub-analysis using the Online MMS Cost Benefit Tool. Applying statistically significant effects of LBW and SGA from the WHO sub-analysis, MMS

remained very cost effective in all scenarios.[13] The NI MMS Cost–Benefit Tool estimates between 7.8 M[11] and 28.6 M[2] additional DALYs can be averted by MMS compared to IFA across 32 LMICs.[14*]

Table 2. Summary of significant subgroup differences with significantly reduced risks of adverse outcomes associated with the use of MMS (vs IFA).[2]

Outcome	*Overall population*	*Anemic women*	*Underweight women*	*Female infants*
LBW	-12%	-19%	-	-
SGA	-3%	-8%	-	-
Preterm birth	-8%	-	-16%	-
Stillbirth	-8%	-21%	-	-
6-month mortality	-	-29%	-	-15%

30 vs 60 mg of Iron: Many of the MMS trials contained 30 mg of iron in the MMS group and were found to have a similar impact on the *prevention* of maternal anemia when compared with IFA, even when the IFA contained 60 mg of iron. The rationale for 30 mg of iron in the UNIMMAP formulation is that the presence of vitamin C, vitamin A and riboflavin increase the absorption of iron. In a setting where anemia is a severe public health problem (≥40% among pregnant women), countries can introduce MMS containing 30 mg of iron in the context of implementation research as a universal *preventive* intervention.

Research Recommendations

While there is ample evidence of the added benefits of MMS, there remain opportunities to expand the evidence base and learn from the implementation of MMS to ensure good coverage and adherence. To this end, the guideline refers to two types of research that would help support program effectiveness and expand the evidence base for MMS:

Implementation Research: Implementation research is the systematic approach to understanding and addressing barriers to effective and quality implementation of health interventions, strategies and policies. The WHO guideline recommends implementation research where MMS programs are being considered to optimize the impact of switching from IFA to MMS, including an evaluation of acceptability, feasibility, sustainability, equity and cost-effectiveness. At an operational or programmatic level within each country, the recommendation means introducing MMS in conjunction with implementation research to ensure effective implementation, the lessons from which, are used to inform future scaling of MMS within ANC services.

Clinical Research: The WHO guideline recommends "controlled clinical trials in which early pregnancy ultrasound is used to establish gestational age with certainty, with assessment of critical maternal and perinatal outcomes," such as SGA and preterm birth. They also recommend the "follow-up of infants sustained into childhood," which is currently being done by some of the clinical trials that form the evidence base for the recommendation. The global nutrition community will develop a global research agenda and are included in a forthcoming document, which is intended for researchers with an interest to build on the evidence base and inform a global research agenda. The outcomes of the ongoing clinical research will help inform future WHO guidelines as they are updated.

* *Please note this analysis assumes 30% coverage of supplements; 180 supplements per pregnancy and program implementation over 10 years. The analysis only includes significant health effects from the cited systematic*

Programmatic considerations for introducing MMS

Based on the existing evidence, countries where anemia and/or LBW are public health problems may want to consider introducing MMS within the context of ANC services and informed by implementation research. In doing so, there are several programmatic considerations for introducing MMS:

1. *Create an enabling environment to support implementation research.* To ensure long-term success of efforts to incorporate MMS into healthcare systems, creating an enabling environment is an essential first step during which national stakeholders (e.g., champions, influencers, and decision-makers) are identified and engaged to: i) raise awareness about MMS and advocate for its use; ii) facilitate an understanding of the evidence as it relates to the benefits of MMS over IFA, and a consensus around the evidence and about what issues may need further examination (e.g., issues related to supply and demand) in a national program to ensure sustainability and impact; and iii) develop a consensus on the need, feasibility, and plan to introduce MMS.

2. *Analyze key determinants of anemia.* Given the variable etiologies of anemia, countries should analyze data on the magnitude and distribution of anemia and its determinants (e.g. iron and other micronutrient deficiencies, malaria or soil transmitted helminthic (STH) infections). Where malaria and STH infections are endemic and anemia is a severe public health problem (≥40% among pregnant women), measures to prevent, diagnose and treat these infections should be implemented concomitantly with MMS as per the WHO and/or national ANC guidelines.

3. *Introduce MMS as part of comprehensive ANC.* The updated WHO guideline offers an opportunity for countries to introduce MMS as part of a strategy to improve the access to and quality of nutrition services in ANC. The WHO guideline recommends that women have eight ANC contacts, including those through the community, potentially offering additional opportunities to deliver MMS. Countries should undertake an analysis of ANC barriers based on which effective strategies can be identified to improve ANC services and MMS coverage/adherence, thereby forming the basis of implementation research. In some countries there may be opportunities to test the use of MMS as part of social protection schemes and market-based approaches.

4. *Ensure uninterrupted quality MMS supplies.* Ensuring an uninterrupted and quality supply of MMS is necessary for women to harness its benefits. Countries should undertake a supply chain analysis to identify and remove impediments to MMS access at health facilities especially where IFA stockouts are routinely reported. Some countries may be interested in establishing local manufacturing capacities for MMS for which an analysis of local production capacities and regulatory aspects of MMS is important. Where local production is not feasible, understanding the regulatory landscape can help to identify barriers and solutions to facilitate MMS importation.

5. *Strengthen health worker capacities to effectively deliver, counsel and support women to receive and consume MMS.* Investing in training of the health workers is essential for a smooth transition from IFA to MMS. Improving the quality of nutrition counselling and communications is also key to ensuring effective distribution and adherence to MMS. This includes training health workers and community workers on the benefits of MMS, managing side-effects, and strategies on how to remember to take MMS daily throughout pregnancy, along with counselling on nutritious diets.

6. *Counsel women and adolescent girls, and key influencers on the importance of MMS and nutritious diets in pregnancy.* Ensuring pregnant women and adolescent girls have an enabling environment that supports MMS use is critical. This requires attention to social behavior change communications, which are tailored to the specific needs of pregnant women and adolescent girls and key influencers (e.g.

husbands, mothers-in-law, grandmothers, community members) on the importance of nutritious diets, including the routine use of MMS. Formative research can be instrumental in identifying social and cultural barriers, social norms and key influencers to target and overcome issues of MMS and can be used to promote acceptance and adherence that may affect MMS uptake.

7. *Identify and treat anemic pregnant women and adolescent girls.* A critical component of ANC is routine screening and treatment of anemic women. The WHO guideline recommends routinely testing women for anemia at ANC contact 1 (12 weeks), 3 (26 weeks) and 6 (36 weeks), and treating women with low hemoglobin as per the WHO and/or national protocols.

8. *Integrate MMS coverage into routine monitoring systems.* Many administrative reporting systems such as health management information systems (HMIS) collect information on the provision of iron containing supplements to pregnant women during ANC contacts. Increasingly this information is integrated into District Health Information Systems. In countries introducing MMS it is imperative that MMS monitoring is integrated into the HMIS. Furthermore, there may be opportunities to introduce MMS monitoring into health facility assessments and household surveys (e.g. Demographic Health Surveys).

COVID-19 Pandemic: The COVID-19 pandemic risks impacting the quality of diets and has disrupted access to ANC services, making it more difficult to achieve adequate nutrition during pregnancy. Introducing MMS as part of the pandemic response is important for improving the nutrient intakes of pregnant women. WFP/UNICEF/Global Nutrition Cluster/Nutrition GTAM guidance on *Protecting Maternal Diets and Nutrition Services and Practices in the Context of COVID-19* recommends the use of MMS in pregnancy to ensure adequate micronutrient intake in populations with a high prevalence of nutritional deficiencies or where food distribution is disrupted in the context of the COVID-19 response.[15–17]

Conclusion

MMS is a safe, cost-effective intervention that holds significant potential to improve women's nutrition and wellbeing, as well as their offspring. Such a commitment to introduce MMS holds the promise of accelerating country- and global-level progress towards the prevention of maternal anemia, low birthweight, stunting and wasting in children and the achievement of the related Sustainable Development Goal targets. Over the coming years, the implementation of MMS is essential to broaden the evidence base and help inform future programs and guidelines.

If you would like to provide feedback on this document or have additional questions, please contact Megan Bourassa at mbourassa@nyas.org.

References

(1) World Health Organization. *WHO Antenatal Care Recommendations for a Positive Pregnancy Experience. Nutritional Interventions Update: Multiple Micronutrient Supplements during Pregnancy*; Geneva, 2020.

(2) Smith, E. R.; Shankar, A. H.; Wu, L. S.-F.; Aboud, S.; Adu-Afarwuah, S.; Ali, H.; Agustina, R.; Arifeen, S.; Ashorn, P.; Bhutta, Z. A.; et al. Modifiers of the Effect of Maternal Multiple Micronutrient Supplementation on Stillbirth, Birth Outcomes, and Infant Mortality: A Meta-Analysis of Individual Patient Data from 17 Randomised Trials in Low-Income and Middle-Income Countries. *Lancet Glob. Heal.* **2017**, *5* (11), e1090–e1100.

(3) Kashi, B.; M Godin, C.; Kurzawa, Z. A.; Verney, A. M. J.; Busch-Hallen, J. F.; De-Regil, L. M. Multiple Micronutrient Supplements Are More Cost-Effective than Iron and Folic Acid: Modeling Results from 3 High-Burden Asian Countries. *J. Nutr.* **2019**, *149* (7), 1222–1229.

(4) Engle-Stone, R.; Kumordzie, S.; Meinzen-Dick, L.; Vosti, S. A.; Engle-Stone, R.; Vosti, S. A. Replacing Iron-Folic Acid with Multiple Micronutrient Supplements among Pregnant Women in Bangladesh and Burkina Faso: Single-Year Assessment of Costs, Impacts, and Cost-Effectiveness. *Ann. N. Y. Acad. Sci.* **2019**, *1444* (1), 35–51.

(5) Nutrition International. *Policy Brief - Cost-Effectiveness of Transitioning from Iron and Folic Acid to Multiple Micronutrient Supplementation for Pregnancy*; Ottawa, 2019.

(6) Bourassa, M. W.; Osendarp, S. J. M. M.; Adu-Afarwuah, S.; Ahmed, S.; Ajello, C.; Bergeron, G.; Black, R.; Christian, P.; Cousens, S.; Pee, S. de; et al. Review of the Evidence Regarding the Use of Antenatal Multiple Micronutrient Supplementation in Low- and Middle-Income Countries. *Ann. N. Y. Acad. Sci.* **2019**, *1444* (1), 6–21.

(7) UNICEF; World Health Organization. *Low Birthweight Estimates: Levels and Trends 2000-2015*; Geneva, 2019.

(8) Christian, P.; Lee, S. E.; Donahue Angel, M.; Adair, L. S.; Arifeen, S. E.; Ashorn, P.; Barros, F. C.; Fall, C. H. D.; Fawzi, W. W.; Hao, W. Risk of Childhood Undernutrition Related to Small-for-Gestational Age and Preterm Birth in Low-and Middle-Income Countries. *Int. J. Epidemiol.* **2013**, *42* (5), 1340–1355.

(9) Black, R. E.; Dewey, K. G. Benefits of Supplementation with Multiple Micronutrients in Pregnancy. *Ann. N. Y. Acad. Sci.* **2019**, *1444* (1), 3–5.

(10) World Health Organization; UNICEF; United Nations University. *Composition of a Multi-Micronutrient Supplement to Be Used in Pilot Programmes among Pregnant Women in Developing Countries*; New York, 1999.

(11) Keats, E. C.; Haider, B. A.; Tam, E.; Bhutta, Z. A. Multiple-micronutrient Supplementation for Women during Pregnancy. *Cochrane Database Syst. Rev.* **2019**, *3*, CD004905.

(12) World Health Organization. *World Health Orgaization Recommendations on Antenatal Care for a Positive Pregnancy Experience.*; Geneva, 2016.

(13) Nutrition International. *Cost-Effectiveness Analyses for the WHO Review on Multiple Micronutrient Supplements during Pregnancy: Technical Report.*; Ottawa, 2020.

(14) Nutrition International. MMS Cost-Benefit Tool https://www.nutritionintl.org/knowledge-centre/mms-cost-benefit-tool/ (accessed Nov 11, 2020).

(15) UNICEF; World Food Programme; Global Nutrition Cluster; Nutrition GTAM. *Protecting Maternal Diets and Nutrition Services and Practices in the Context of COVID-19*; 2020.

(16) World Health Organization. *COVID-19: Operational Guidance for Maintaining Essential Health Services during an Outbreak*; Geneva, 2020.

(17) World Health Organization; UNICEF; World Food Programme. Preventing and Controlling Micronutrient Deficiencies in Populations Affected by an Emergency. *Bull. World Heal. Organ.* **2007**, *1*, 5–6.

Acronyms

ANC	antenatal care
GTAM	Global Technical Assistance Mechanism for Nutrition
HMIS	Health Management Information Systems
IFA	iron and folic acid supplements
IPD	individual patient data
LBW	low birthweight
LMIC	low- and middle-income country
MMS	multiple micronutrient supplements
SGA	small for gestational age
STH	soil transmitted helminthic
UNICEF	United Nations Children's Fund
UNIMMAP	United Nations International Multiple Micronutrient Antenatal Preparation
WHO	World Health Organization