Appendix 1 - Frequently Asked Questions to address often-raised concerns about the switch from iron and folic acid supplementation to multiple micronutrient supplementation.

The purpose of this document is to present an orderly summary of the most frequently asked technical questions and issues raised by decision-makers and operational managers trying to decide whether and how to add MMS to existing nutritional services.

1. **What are the specific health benefits of switching from taking iron and folic acid (IFA) to multiple micronutrient supplements (MMS) during pregnancy?**

Multiple micronutrient deficiencies co-exist among women and micronutrients requirements are increased in pregnancy. Inadequate intake of micronutrients can lead to adverse effects on the mother and developing fetus.

Multiple micronutrient supplementation (MMS) is demonstrated to improve birth outcomes, significantly, by reducing the risk of low birth weight, being born small-for-gestational age (SGA), and preterm births, as compared to use of iron and folic acid supplementation (IFA) alone.[1, 2]

While the benefits of the MMS on birth outcomes are found overall; women who are nutritionally vulnerable, that is, women who are anemic and/or underweight during their pregnancy experience even greater benefits. This includes a reduced risk of SGA, low birthweight, and 6-month mortality among infants born to anemic women and an even greater reduction in the risk of preterm birth among underweight women. Additionally, female infants born to mothers who received MMS, have a reduced risk of mortality throughout the first year of life.[2]

2. **What are the long-term benefits for children of giving prenatal MMS?**

To date, few studies have examined the long-term physical and developmental benefits of giving MMS during pregnancy, and findings are mixed.[3] *However, SGA and preterm birth have long-term effects (e.g., an increased risk stunting and mortality), so by preventing these condition one can postulate long-term benefits of MMS use.*

3. **What are the proxy measures for nutritional deficiencies among pregnant women?**

In general, nutritional deficiencies among women of reproductive age (WRA) are relatively common in LMICs. While data on specific countries is often limited, there are a number of data

sources that can help indicate the prevalence of nutritional deficiencies. Ideally, micronutrient biomarker data from a representative sample of WRA will provide the most direct and quantitative assessment of nutritional deficiencies. However, should these data not be available, the prevalence of anemia, dietary intake data, dietary diversity scores, and the Hidden Hunger Index can be used to assess nutritional status. Prevalence of adverse birth outcomes can also be used as a proxy measure for poor nutritional status. For example, a high prevalence of LBW, SGA and preterm births would suggest nutritional deficiencies.

4. What is the rationale for the UNIMMAP formulation?

Building on the considerable experience and documented, positive effect of IFA on pregnant women with nutritional deficiencies, the potential utility and formulation of a multiple micronutrient supplementation program for pregnant women arose as a consensus. This consensus was built around a recognition that multiple micronutrient deficiencies co-exist among women of vulnerable populations combined with three additional facts, including knowledge that: i) "improvements in diet are difficult to achieve over a short time span" for vulnerable populations; ii) several nations have worked to achieve fortification of basic foodstuffs on a large-scale, yet fortification goals are often not fully realized for the most vulnerable populations; and iii)"the high nutrient needs of pregnancy are almost impossible to cover through dietary intake alone".[6] To address the need for a standardized MMS that could meet the increased micronutrient requirements of pregnant women, and be used in clinical trials to test the efficacy of MMS vs IFA, an expert group was assembled in July of 1999. The work of that expert group resulted in identification of the United Nations International Multi-micronutrient Antenatal Preparation – otherwise known as the UNIMMAP formulation.

The selection of nutrients for the UNIMMAP formulation was based on nutrient requirements, risk of nutrient deficiencies, potential nutrient toxicities, and on the potential interactions between nutrients if combined into one tablet. Other considerations included cost, size of the resulting supplement, and possible side effects. Based on these criteria, the resulting formulation included 15 micronutrients (vitamins A, C, D, E, B1 (thiamine), B2 (riboflavin), B3 (niacin), B6, B12, folic acid, Fe, Zn, Cu, I, Se).[6 (p. ii)] See Table 1 for the full description of the technical specifications of the UNIMMAP formulation.

The benefits of the UNIMMAP formulation vs. IFA alone on birth outcomes has been demonstrated.[1, 2]

5. Is the iron in the MMS formulation readily bioavailable?

No recommendation for the optimal form(s) of iron to use in MMS currently exists. Currently, different forms are used by different manufacturers. However, when comparing different oral preparations using a human intestinal model, results demonstrate that there are differences in dissolution times and iron uptake, with varying physical characteristics of the preparation (e.g., tablet, capsule, syrup) and iron form (e.g. sulfate, fumarate, and gluconate), and, whether iron is alone or with vitamins, minerals, or both.[8] This issue requires further study; however, major

manufacturers of MMS in the U.S. and Europe currently use the ferrous fumarate or ferrous sulfate forms of iron.

6. Why does the UNIMMAP formulation contain 30 mg of iron while IFA usually contains 60 mg of iron?

The original rationale for the UNIMMAP formulation, which specifies 30 mg of iron (rather than 60 mg) was based on, among other things, the following:[6 (p. 12)]

- *Iron absorption in the UNIMMAP formulation is enhanced (as compared to the IFA) due to the inclusion of vitamin C, vitamin A, and riboflavin.*
- *Most pregnant women suffer from mild or moderate anemia, which is able to be addressed with 30 mg of iron.*
- *Larger amounts of zinc may be needed if 60 mg of iron were used to counteract the possible negative influence of higher amounts of iron on zinc absorption.*
- *Increased risk of side effects caused by higher amounts of iron, which may reduce adherence to supplementation*

The current rationale for retaining 30 mg of iron in the UNIMMAP formulation is that it is consistent with the recent WHO Antenatal Guidelines, which state that iron supplementation should be between 30-60 mg/day.

7. What is the optimal amount of iron for women during pregnancy?

The following guidance can be helpful:

- *Generally in settings where maternal anemia is present, 30 – 60 mg of supplemental iron is sufficient to optimize birth outcomes.*
- *In individual cases of severe anemia (as defined by local health authorities), treatment should be undertaken by giving 120 mg of iron until hemoglobin level rises to normal or through use of IFA tablets (administered with MMS) to achieve a rapid increase in hemoglobin concentration.*[7 (p. 23).]
- *It should be noted by the Institute of Medicine in the US, that the Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake likely to pose no adverse health effects. For iron the UL is 45 mg/day,* which was set based on the highest dose least likely to cause gastrointestinal side effects. While toxicity from iron overdose can occur, these have only been reported at much higher doses.*[9]

**Note: There is no globally accepted UL for iron, as recognized by multiple regulatory authorities (e.g., the European Food Safety Authority (hyperlink to reference: FSA UL for iron). However, some regulatory authorities do state an UL for iron. For example, the US Institute of Medicine and the Australia Ministry of Health state 45 mg/day during pregnancy as UL (hyperlinks to references: US UL for iron, Australia UL for iron)*

8. **Can MMS and IFA be taken simultaneously? What side-effects can be expected with simultaneous use of MMS + IFA?**

While the MMS is sufficient for most pregnant women, in individual cases where treatment of severe anemia is indicated, MMS can be used in conjunction with IFA tablets to achieve a more rapid increase in hemoglobin concentration.[6, p. 12]

The evidence shows that the most common complaints among women consuming IFA (60 mg iron) or MMS include constipation, nausea, vomiting, and diarrhea.[1, 10, 11, 12] *If MMS and IFA are taken simultaneously, it would result in an intake of a 90 mg/day, with some increased risk of gastrointestinal side effects.*

9. **Does MMS use lead to larger birth size, especially for boys? Could this lead to birth complications in pregnancy for women of short stature?**

While some research suggests that MMS may significantly increase the risk of being born large-for-gestational-age (LGA) based on the Intergrowth standard, [2 (p. e1096 – e1098)] *the risk of LGA with MMS use* ***does not*** *vary by sex of offspring and* ***does not*** *increase the subsequent risk of stillbirth or neonatal mortality.*

Conclusion: Large-scale deployment should be implemented, even among populations of with a high prevalence of maternal stunting.[2 (p. e1096 – e1098)]

Note: WHO's recommendation for maternal and child health services is for the global use of skilled birth attendance to ensure optimal health conditions for both mother and baby.

10. **Should there be variations of the UNIMMAP formula? Does possible benefit outweigh the likely cost?**

The UNIMMAP formulation was carefully formulated based on a rigorous multi-level criteria (see Q. 4),[6 (p. 1& 7-10)] and the benefits of using UNIMMAP and similar MMS formulations have been demonstrated across multiple countries.[1, 2] Regional or country specific variations of MMS are unlikely to have robust evidence of added benefit to the UNIMMAP formulation, and can't currently be recommended in place of the UNIMMAP formulation.

There is ongoing consideration being given to enhance the UNIMMAP formulation. However, if, a different formulation is eventually agreed to, it would take years to achieve the level of safety and efficacy for a new formulation; and there would need to be an examination of the additional costs and/or feasibility issues related to manufacturing and procurement of the new product. Health services should not wait to deploy the UNIMMAP MMS product in hopes that a new formulation of MMS will be made readily available in the foreseeable future.

11. Is it likely that the UNIMMAP formulation will be re-formulated and if so, what changes are expected?

UNIMMAP may be re-formulated over time to reflect changes in nutrient requirements and recommendations (e.g., RDAs), but the current UNIMMAP formulation is likely to remain unchanged for the foreseeable future. The benefits of the current MMS formulation versus IFA alone on birth outcome has been demonstrated.[1, 2] Combined with the lengthy period of time to formulate, manufacture and establish stability data needed for label claims, any new "custom" formulation is several years away. Thus, waiting for a re-formulated MMS product, should not factor into any decision about using the existing UNIMMAP MMS product.

12. Is the level of any of the micronutrients in the UNIMMAP formulation teratogenic (e.g., vit A)?

No, none of the micronutrient concentrations in the UNIMMAP formulation are teratogenic. The UL is the highest level of daily intake that is likely to pose no risk of adverse health effects in almost all individuals of a specified life stage. ***Across all 15 ingredients in the UNIMMAP formulation, <u>none</u> exceed the UL for the target age groups (see Table 1).***

With regards to vitamin A specifically, although normal embryonic and fetal development require sufficient maternal vitamin A intake, consumption of excess preformed vitamin A during pregnancy causes birth defects, especially during the first trimester. An increased risk of vitamin A-associated birth defects has not been observed at supplemental doses below 3,000 µg (10,000 IU)/day of preformed vitamin.[9] Thus the UL of vitamin A for pregnant women ≤ 18 years is 2,800 µg and for those 19-50 years is 3,000 µg. The amount of vitamin A in the UNIMMAP formulation is 800 µg (2,667 IU)/day which is only 29% and 27% of the UL for these age groups, respectively. Even if a pregnant woman consumed the RDA for vitamin A (750 µg retinol activity equivalents/day), and took the UNIMMAP supplement, she would still be below the UL for vitamin A.

13. What is the recommended number of MMS tablets to be taken during pregnancy?

Optimally, one MMS tablet would be taken on each day during pregnancy. However, it is not known with any precision what the minimum number of MMS tablets are needed to accrue the benefits of MMS use for a positive birth outcome. Data from the clinical trials suggest that greater adherence (≥95%) to MMS significantly reduces the risk of neonatal mortality and infant mortality compared to those who had lower adherence.

Complicating this issue is that MMS use, as for IFA use, is unlikely to occur starting on the date of conception, and that pregnant women generally don't have their first antenatal care visit until well into their first trimester – both of which impedes optimal initiation of MMS or IFA use.

Moreover, the cost of both MMS and IFA, which is now about the same, is still a factor regarding decision-making about the number and format of MMS tablet packaging. Currently, where there is no local research that suggests otherwise, the expert consensus (of the Task Force for Multiple-micronutrient Supplementation for Pregnant Women) and practical field experience is that MMS tablets should be packaged in 180 count bottles, and that the full bottle should be given to the pregnant women at her first antenatal care visit or at the time she is first contacted by a community-based provider.

14. What is the best timing for initiating MMS use by pregnant women to optimize the known effect of MMS on SGA, pre-term babies, underweight, and stunting?

Research suggests that early (< 20 weeks' gestation) and extended (> 20 weeks' gestation) adherence to a daily MMS regimen throughout the period of pregnancy decreases risk of preterm, SGA, LBW, and infant mortality.[2] *Thus, starting MMS as soon after conception as possible, and continuing MMS use throughout the pregnancy is the most optimal pattern of use to encourage. While it is optimal to start MMS supplementation as early as possible after conception, the evidence shows that it is still valuable to initiate MMS anytime in pregnancy.*

15. Is there any benefit for giving MMS during pre-conception?

More research is needed to determine benefits on birth outcomes of taking MMS during the pre-conceptual period. However, folic acid supplementation should be commenced as early as possible (ideally before conception) to prevent neural tube defects (NTD), which most often occur within the first few weeks of pregnancy.[7 (p. 23 footnote c)]

In populations considering switching from IFA to MMS completely, supplementation with MMS during the pre-conception period should be considered for the prevention of NTDs. If you give MMS or IFA only after pregnancy is identified, it will not prevent NTDs.

16. Is there any benefit for giving MMS during the period of lactation?

More research is needed to determine effects of MMS during the period of lactation. However, the expert committee that developed the UNIMMAP formulation also took lactating women into consideration. Due to the high nutrient demands during early lactation and to help support recovery after delivery, they suggest continuing the use of UNIMMAP into lactation. However,

when resources are limited, it is recommended that MMS be targeted towards pregnant women, given its impact during this lifestage has been clearly demonstrated on the mother and newborn.

17. Wouldn't populations be best served by focusing on overall improvement of diet rather than promotion of a "pill based" solution that could take resources away from efforts to improve diets?

While recognizing that these micronutrients should ideally be obtained from food, improvements in diet are difficult to achieve over a short time span for populations in most resource-poor countries. Some countries have established programs to increase micronutrient intake through food fortification, but many more have yet to achieve appropriate food fortification goals. Moreover, the increased micronutrient requirements posed by pregnancy are especially challenging to cover through dietary intake. In fact, in most industrialized countries, it is common for women to take MMS during pregnancy and lactation.

18. Is there any group or combination of groups that provides technical and/or financial assistance to demonstration activities to: i) advise on demonstration project design, ii) review planning for data analysis, iii) assist with interpretation of results, and/or iv) facilitate dissemination of findings

A Technical Advisory Committee will be created by the Sackler Institute for Nutrition Science with funding from the Bill & Melinda Gates Foundation. They will have 2 official meetings per year, in which they can discuss such issues. There will also be a website to help disseminate information to those who are interested in learning more about what the group is doing and planning to do.

19. What should a "Demonstration Project" for early adopters attempt to learn or achieve?

Demonstration projects are generally undertaken to identify information that will make large scale implementation occur more smoothly or to answer questions on how to optimize policies that guide implementation – but NOT for the purpose of replicating research to prove the worth of the intervention. The following suggested uses for a demonstration project for early adopters of MMS would be to determine:

- *Acceptance: Is acceptance improved or the same/worse with MMS as compared to IFA?*
- *Compliance: Is compliance improved or the same/worse with MMS as compared to IFA?*
- *Cost implications: What is the net cost of swapping MMS for IFA?*
- *Optimal answers to policy or operational implementation issues, including:*
  - *When is the earliest time during pregnancy that women can be reached to receive MMS in a given country?*
  - *What configuration of behavior change communication optimizes adherence/use in a given country?*
  - *What is the right packaging in terms of number of doses to dispense at a time (e.g., 180 tablets per bottle)?*
  - *What is the optimal supply amount to give at one time (e.g., give full supply all at once or as a monthly supply)?*
  - *What are the optimal points for accessing MMS (e.g., in-facility antenatal visits, family planning clinics, at the time of mandatory marriage counseling, etc.)?*

- *Can MMS distribution effectively reach eligible beneficiaries with the right dose at the right time, when scaled (e.g., reach, dose, adherence)?*

20. Should introduction and scaling of MMS always be based on the results of implementing a demonstration project?

No, the introduction and scaling does not always need to be based on the results of implementing a demonstration project, especially in cases where a functioning IFA platform exists and/or lessons from other demonstration projects can be applied.

References

1. Haider BA, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD004905. DOI: 10.1002/14651858.CD004905.pub5.
2. Smith ER, 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 Health 2017; 5: e1090–100.
3. Patrick I, et al. Impact of nutritional supplements on cognitive development of children in developing countries: A meta-analysis, Scientific Reports 2017, 7: 10611 | DOI:10.1038/s41598-017-11023-4.
4. Ruel-Bergeron JC, Stevens GA, Sugimoto JD, Roos FF, Ezzati M, Black RE, et al. (2015) Global Update and Trends of Hidden Hunger, 1995-2011: The Hidden Hunger Index. PLoS ONE 10(12): e0143497. doi:10.1371/journal.pone.0143497
5. Muthayya S, Rah JH, Sugimoto JD, Roos FF, Kraemer K, et al. (2013) The Global Hidden Hunger Indices and Maps: An Advocacy Tool for Action. PLoS ONE 8(6): e67860. doi:10.1371/journal.pone.0067860
6. UNICEF, WHO, UNU. Composition of a multiple-micronutrient supplement to be used in pilot programmes among pregnant women in developing countries, 1999.
7. World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience, 2016.
8. Zariwala MG, et al. Comparison study of oral iron preparations using a human intestinal model. Sci Pharm. 2013 Jun 21;81(4):1123-39. doi: 10.3797/scipharm.1304-03.
9. Food and Nutrition Board, Institute of Medicine. Vitamin A. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, D.C.: National Academy Press; 2001:290-393.
10. Oriji VK, Enyindah CE, Nyeche S. Factors determining compliance to routine iron supplementation in pregnancy at the University of Portharcout Teaching Hospital. Nigerian Journal of Medicine 2011; 20(1):131–4.
11. Seck BC, Jackson RT. Determinants of compliance with iron supplementation among pregnant women in Senegal. Public Health Nutrition 2008;11(6):596–605.
12. Rybo G, Solvell L. 1971. Side-effect studies on a new sustained release iron preparation. Scand J Haemato l 8:257–264.

Table 1. Finished Product Specifications

MMS Tablets or Capsules—Vitamins and Minerals for Pregnant Women

(UNIMMAP per WHO, UNICEF, & UNU[1])

Ingredient/Form[2]	**Label Claim UNIMMAP**	Tolerable Upper Levels (ULs)			
		14-18 y		19+y	
		UL	% UL	UL	%UL
Vitamin A	800 µg RE (2667 IU)	2,800 µg	29%	3,000 µg	27%
Vitamin C	70 mg	1,800 mg	3.9%	2,000 mg	3.5%
Vitamin D	200 IU (5 µg)	100 µg	5%	100 µg	5%
Vitamin E (10 mg α-TE)	10 mg (15 IU)	800 mg	1.3%	1,000 mg	1%
Vitamin B1	1.4 mg	ND	ND	ND	ND
Vitamin B2	1.4 mg	ND	ND	ND	ND
Vitamin B3	18.0 mg	30	60%	35	51.4%
Vitamin B6	1.9 mg	80	2.34%	100	1.9%
Folic Acid	400 µg	800 µg	50%	1000 µg	40%
Vitamin B12	2.6 µg	ND	ND	ND	ND
Iron	30 mg	45 mg	67%	45 mg	67%
Iodine	150.0 µg	900 µg	16.7%	1,100 µg	13.64%
Zinc	15.0 mg	34 mg	44.1%	40 mg	37.5%
Selenium	65.0 µg	400 µg	16.25%	400 µg	16.25%
Copper	2.0 mg	8.0 mg	25%	10.0 mg	20%

[1] Composition of MMS for pregnant women is formulated to provide the daily Recommended Dietary Allowance (RDA) of each nutrient. From Report of a United Nations Children's Fund (UNICEF), World Health Organization (WHO), United Nations University (UNU) Workshop, *Composition of a multi-micronutrient supplement to be used in pilot programmes among pregnant women in developing countries. Report of a Workshop. New York, UNICEF, 1999.*

[2] Several forms of each ingredient may be appropriate for use. It is necessary to refer to WHO specifications (when available, e.g., iron) and the manufacturer