Multiple Micronutrient Supplements (MMS) for Pregnant Women

Immediate and Long-Term Supply of MMS for National Programs (including Local Sourcing/Manufacturing)

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Topics

• Identify recommendations and guidance from WHO, UNICEF and the global MMS – TAG helping to shape decision-making pertaining to MMS supplies for national programs

• Describe how national programs are beginning to think about synchronizing MMS supply with program implementation

• Answer frequently asked questions about MMS supplies, with a focus on local & global manufacturing
Current Recommendations and Guidance

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

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 UNIMMAM-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.3
2. MMS containing 30 mg of iron are as effective as IFA containing 60 mg of iron in preventing maternal anemia.4
3. MMS is a low cost and highly cost-effective intervention in comparison with IFA.5,6
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.4

Key recommendation is to introduce MMS in the context of antenatal care services informed by implementation research.
Current Recommendations and Guidance

• What does it mean to introduce MMS “informed by implementation research” (IR)

• Implementation research
  - Identifies implementation challenges related to supply, demand and delivery, and is an approach that helps to find solutions to those challenges

• IR in its simplest form typically consists of 3 phases (see diagram)

ROADMAP = IMPLEMENTATION RESEARCH

Phase 1: Creating an Enabling Environment
Phase 2: Design & Testing Implementation Strategies
Phase 3: Scaling

Average time to complete 3 phases = 3 - 4 years

Hurley et al. Field Exchange. 2020
Current Recommendations and Guidance

MMS product-related issues in global recommendations and guidance for national consideration:

- **Use a UNIMMAP formulated MMS product for national programs** – UNIMMAP being the *United Nations International Multiple Micronutrient Antenatal Preparation* designed for populations with characteristics including those found in LMICs.

- **Provide 180 doses of MMS** during pregnancy as a *preventive* intervention (i.e., not a treatment regimen); and start MMS as early in pregnancy as possible, and

- **Ensure an uninterrupted supply of MMS manufactured to accepted quality standards** which can include thoughtfully planned local manufacturing where feasible.

**UNIMMAP Composition**

<table>
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<tr>
<th>Nutrient</th>
<th>Amount</th>
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<tr>
<td>Vitamin A</td>
<td>800 µg</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>200 IU</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>10 mg</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>70 mg</td>
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<tr>
<td>Thiamine</td>
<td>1.4 mg</td>
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<tr>
<td>Riboflavin</td>
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</tr>
<tr>
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<td>18 mg</td>
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<tr>
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</tr>
<tr>
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<tr>
<td>Selenium</td>
<td>65 µg</td>
</tr>
<tr>
<td>Zinc</td>
<td>15 mg</td>
</tr>
</tbody>
</table>
Current Recommendations and Guidance

The guidance documents also suggest practical, operational tips for national programs:

• Plan to use a UNIMMAP – MMS product as formulated without variation:
  - Commercially, it is the evidence-based MMS product most widely available
  - Even small formula changes are not advised; because they will translate into delayed program activation & incremental cost attributable to more product development needed to create a re-formulated product *

• Don’t let the “perfect” be the enemy of the good:
  - Engaging in clinical research to find a “better” nutritional supplement for pregnant women is of global interest, but should not serve as a reason to delay use of the existing, proven UNIMMAP – MMS nutritional supplement in regular service delivery settings

• Introduction & scaling of UNIMMAP – MMS using an implementation research approach requires early attention and accommodation by regulatory authorities and procurement systems (as compared to other medicines/nutritional supplements already in regular use) because UNIMMAP – MMS is new, is not on any essential medicines list, is not locally available, and is not available off-the-shelf
How to Synchronize MMS Supply with Program Implementation

Given application of an implementation research model, what actions are needed in each phase to synchronize MMS supply with program implementation?
How to Synchronize MMS Supply with Program Implementation

Phase 1: The Focus is on:

• **Assessing supply readiness** (see diagram below)
• **Engaging domestic manufacturers** to assess their interest, capacity, and qualifications
• **Identifying who is the ”buyer” of MMS from manufacturers for national health services**
• **Encouraging “influencers”** to explore use of MMS on a limited basis using **donated product** to support awareness-raising and consensus-building for MMS

**Figure 1. Framework for Global Assessment of MMS Supply Readiness**

**Phase 1:** Creating an Enabling Environment

**Phase 2:** Design & Testing Implementation Strategies

**Phase 3:** Scaling

**Phase 1**
- Desk Research
  - 2 weeks

**Phase 2**
- Market Assessment
  - 2 weeks

**Phase 3**
- Production Assessment
  - 3 weeks

**Phase 4**
- Regulation & Policy Assessment
  - 3 weeks

**Phase 5**
- Lab Testing of Samples
  - 6 months
Phase 1 Progress in Indonesia

Phase 1 supply related progress:

- Supply Readiness Assessment nearing completion
- Qualified local manufacturers were engaged to assess interest, capacity and qualifications starting in the period from June – August 2019
- Indonesia secured access to donated UNIMMAP – MMS imported under a research authority (for Hasanuddin & Airlangga Universities to explore MMS use) from:
  - Kirk Humanitarian (USA)
  - The Vitamin Angel Alliance (USA)
- Influencers with access to donated product have contributed to momentum to advance MMS use
How to Synchronize MMS Supply with Program Implementation

Phase 2: The focus is on:

- Ensuring continued access to *donated* MMS supplies needed to test implementation strategies
- Taking regulatory decisions needed to trigger manufacturers’ investment to develop a locally produced MMS product
- Harmonizing regulatory requirements & procurement system realities given a need for purchases from multiple suppliers that likely will require:
  - Initial purchases of MMS *imported in bulk to be re-packaged and sold by local suppliers on an interim basis* (including import of ingredients and pre-mixes)
  - Preferential purchases of MMS from *local manufacturers that agree to commence product development* for MMS to be delivered in phase 3 or sooner
  - Guaranteed annual purchases of a fixed amount of *locally produced product* from qualified manufacturers when available
- Work to place MMS on the national (and WHO) essential medicines lists
Phase 2 Progress in Indonesia

Phase 2 supply related progress:

- Indonesia secured a continuing commitment of donated UNIMMAP – MMS from phase 1 donors to support testing of specific implementation strategies.

- Specifically, the University of Indonesia and its partners are designing and preparing to test application of social behavior change communications combined with MMS packaging variations to determine effective strategies to ensure adherence to MMS dosing.

- Qualified local manufacturers:
  - Are negotiating to import MMS in bulk for re-packaging
  - Have identified regulatory actions to advance MMS product registration, and
  - Await regulatory decision-making needed to trigger their investments to develop a locally produced product.
How to Synchronize MMS Supply with Program Implementation

Phase 3: The focus is on:

- Expanding MMS supplies that keep pace with increased population coverage through issuance of government procurement notices for MMS supplies
Frequently Asked Questions

Why focus on MMS product supply early?

• **Product availability is a rate-limiting step to program activation**

• **MMS is needed** to support, potentially ≈207m pregnancies/yr in LMICs

• **Current global supply can support** ≈8 m pregnancies/yr, of which:
  - Product for ≈6.5 m pregnancies/yr originates as global donations from just 2 organizations other than UNICEF

• **Product demand is growing;** WHO’s recommendation will add demand

• **As a “custom” product,** national governments can expect a 2 - 3 year lead time for each new local manufacturer to define, test manufacture, and produce UNIMMAP – MMS commercially at volume
  - While global supplies are limited, **global supplier capacity is very scalable**

• **National programs can be assured of near- and intermediate-term availability** of MMS supplies from global suppliers, but national authorities and local manufacturers need to plan early and aggressively for phase 3 supplies – especially if they plan to transition to local purchase in phase 3
Is the publicly available formula for UNIMMAP – MMS sufficient to describe MMS in a procurement contract?

- **No, a product specification is needed** to define:
  - Product formula, form of ingredients, and finished product characteristics
  - Label claims & regulatory requirements to be met and the certifications/documentation required to support label claims
  - Reference standards and methods to be used to verify product conformance with standards

- **The product specification** is appended to a purchase agreement; ensures both parties understand what product is being produced and how the finished product will be authenticated

- **An Expert Consensus Open-Access UNIMMAP – MMS Product Specification** is available for free to any purchaser or manufacturer
Expert Consensus on an Open-Access UNIMMAP-MMS Product Specification

Introduction

Micronutrient deficiencies can have debilitating impacts on maternal health and pregnancy outcomes. The United Nations International Multiple Micronutrient Antenatal Preparation–multiple micronutrient supplement (UNIMMAP-MMS) initiative has been shown to provide health benefits to both mother and baby, improving pregnancy and a healthy start to life in a safe and cost-effective manner. The strength of the evidence, combined with global advocacy and the availability of technical assistance, drove an increased demand globally for the UNIMMAP-MMS product. The World Health Organization (WHO) has supported the convening of a group of experts to lay the groundwork for the development of the UNIMMAP-MMS specification, which followed the Declaration of the Panel of International Experts, assembled in Washington, DC, November 11-12, 2019, convened by the NYAS and the Multi-Micronutrient Technical Advisory Group (MMTAG) of the New York Academy of Sciences.

https://www.nyas.org/media/21537/expert-consensus-on-an-open-access-unimmap-mms-prod-spec.pdf

Frequently Asked Questions

What’s the additional value of the Expert Consensus Open-Access UNIMMAP – MMS Product Specification?

• Streamlines and reduces cost of product development and manufacturing
• Adaptable for use in any region of the world that recognizes international standards
• Using the Consensus Specification can position local manufacturers as producers for the export market
Frequently Asked Questions

What is the benchmark price of UNIMMAP – MMS (i.e., lowest price & volume for MMS of international quality at which additional volume has no effect on price)?

- UNIMMAP – MMS should approximate price of an iron and folic acid supplement (IFAS)
- Benchmark price of IFAS is at least US$.01/dose (≈140 Rupiah)
- Benchmark price of UNIMMAP – MMS (assumes 1 bottle/pregnancy) is currently tiered:
  - US$0.014/dose (minimum order of 100,000 bottles) ≈198 Rupiah
  - US$0.012/dose: for 3 m bottles
  - US$0.011/dose: for 5 m bottles or ≈156 Rupiah/dose

MMS has achieved price parity with IFA at the global level
What Should UNIMMAP – MMS Cost

Sample IFAS pricing in Yogyakarta (NB: wide variances occur in IFA pricing across Indonesia)

IFAS vs. MMS

IFAS price stamped on foil:
10 Tablets @ 7,000 Rupiah, or 1 tablet @ 700 Rupiah

IFAS Price ≈ U.S. $0.05
MMS Price ≈ U.S. $0.01

Roughly 50-80% of IFAS price difference is probably attributable to Alu-Alu packaging

Blister packaging generally has the environmental disadvantage of being more costly to recycle

Depending on packaging, IFA and MMS can achieve price parity in Indonesia
Frequently Asked Questions

Can the Benchmark Price offered by global manufacturers be achieved by those manufacturing locally for a single domestic market:

• In most cases, no:
  - Few countries have annual product demand needed to achieve economies of scale in manufacturing (e.g., ≈ 3-5 million pregnancies)
  - Most manufacturers don’t have volume capacity needed to produce at economies of scale
  - Ingredients are generally not locally available; and associated import fees & excise taxes have a significant effect on final price

• Negotiations with local manufacturers should be informed by the benchmark price of MMS (produced to international quality standards), but adjusted for local factors that add cost

• To lower overall costs, where feasible, local manufacturers should be encouraged to produce to internationally recognized standards to facilitate their becoming a regional exporter
Closing Observations

- UNIMMAP – MMS can be used effectively and without modification in national health services, including in Indonesia
- Indonesia is making progress examining MMS barriers, not just in supply, but in demand, and delivery using an implementation research model for introduction and scaling
- A model for synchronizing UNIMMAP – MMS supply with program implementation has emerged and includes:
  - **Initial Phase 1 dependence on donated UNIMMAP – MMS product** imported under research authority & given to universities/national authorities
  - **Interim Phase 2 dependence primarily on donated product (and possibly some purchased product)** using imported product re-packaged by local manufacturers while local manufacturers develop a locally produced product
  - **Transition (in late Phase 2 and early Phase 3) to procurement of a locally produced product** once approved and commercially available
- This model can assure immediate and long-term access to MMS supplies that enables immediate program activation in Indonesia
Thank You

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References

References:


2 Review of the Evidence Regarding the Use of Antenatal Multiple Micronutrient Supplementation in Low- and Middle-Income Countries. Annals of the New York Academy of Sciences, 2019
Which MMS Product and Why?

Selenium in the UNIMMAP – MMS product

- Indonesian RDA for selenium is 60 ug; UNIMMAP contains 65 ug
- International experts suggest this variance is not meaningful given the sparse evidence base originally used to determine the Se requirement
- Recent Indonesian study (Yustiyanty Monoarfa et.al.) suggests use of 65 ug Se (in the UNIMMAP – MMS) reduces risk of pre-eclampsia as compared to IFA
- Indonesian regulatory authorities will need to weight costs and benefits of using the recommended UNIMMAP formula as is vs. adjusting it for Indonesia keeping in mind:
  - Eleven randomized clinical trials used UNIMMAP – MMS formula – all showing significantly increased benefit beyond IFAS w/o adverse consequences
  - **Re-formulation of UNIMMAP – MMS would halt program implementation**, and incur a significant additional delay to permit completion of at least a new product development cycle
  - Re-formulation is not advised if local companies are manufacturing for export
Additional Resources

Resources: Quality and Supply Readiness Tools

Kirk Humanitarian’s White Paper: Understanding Product Quality

Understanding Product Quality
As Applied to UNIMMAP-MMS Product
Donated by Kirk Humanitarian

John R. Kruger, Ph.D. | September 2020

Key Takeaways

- Quality is the single most important consideration for both purchasers and beneficiaries of a United Nations International Multiple Mission Activity Program (UNIMMAP) multiple micronutrient supplement (MMS) product.
- A key challenge in collecting data on the quality of UNIMMAP-MMS products is the lack of a clear, comprehensive, and uniform dataset to capture the data across all participating agencies.
- The Kirk Humanitarian’s UNIMMAP-MMS product contains the minimal quality parameters that are critical for ensuring the safety and performance benefits of such fortified products.
- Kirk Humanitarian requires that the current manufacturer provide a UNIMMAP MMS Project Evaluation Report (PER), which details the specifics, including the quality assurance program.
- Kirk Humanitarian requires that the current manufacturer provide a UNIMMAP MMS Project Evaluation Report (PER), which details the specifics, including the quality assurance program.

Kirk Humanitarian’s White Paper: Understanding Product Quality


Sight and Life’s Toolkit for Assessing Supply Readiness

Procurement and Production of Multiple Micronutrient Supplements for Pregnant Women

A country assessment toolkit.

Katarzyna Froncisz, Prio Schaffner von Steffeln
April 29, 2020

For example:

- The toolkit will help you assess the quality and functionality of all the processes involved in the procurement, production, and distribution of multiple micronutrient supplements.
- The toolkit will help you identify areas for improvement and set targets for improvement.
- The toolkit will help you document and share best practices.

Sight and Life’s Toolkit for Assessing Supply Readiness

# UNIMMAP Multiple Micronutrient Supplements (MMS) for Pregnant Women

**Packaging Options, Cost and Environmental Impact**

<table>
<thead>
<tr>
<th>Packaging Features</th>
<th>180 Count</th>
<th>30 Count</th>
<th>30 Count</th>
<th>Bulk¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-resistant cap and tamper evident seal HDPE bottle</td>
<td>Child-resistant and tamper-proof HDPE bottle</td>
<td>Child-resistant and tamper-proof acrylic film with foil</td>
<td>No child-resistant or tamper-proof features</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product Cost</th>
<th>180 Count</th>
<th>30 Count</th>
<th>30 Count</th>
<th>Bulk¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per tablet²,³</td>
<td>1.1 cents Palletization costs an added .05 cents per bottle.</td>
<td>2 cents Palletization costs an added .01 cent per bottle.</td>
<td>1.7 cents Palletization costs an added .01 cent per card.</td>
<td>0.9 cents Repackaging costs are variable.</td>
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<table>
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<th>30 Count</th>
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<tr>
<td>Total waste⁴:</td>
<td>22,900 kg</td>
<td>98,400 kg</td>
<td>38,856 kg</td>
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<table>
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<th>30 Count</th>
<th>Bulk¹</th>
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</thead>
<tbody>
<tr>
<td>Available now. Approved in the U.S. and commercially available now.</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

¹ MMS shipped in bulk requires repackaging before dissemination (business-to-business (B2B) option).
² Prices are based on a high-volume guarantee. The product cost is higher for customers who buy the MOQ (minimum order quantity) of 100,000 bottles.
³ The current MMS Taskforce recommendation for MMS dosing is 180 tablets per pregnancy beginning as early as possible.
⁴ Data provided by Contract Pharmacal Corporation (CPC), 2019.
⁵ It is more difficult and more costly to recycle acrylic film and foil than it is to recycle HDPE bottles.

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**COURTESY OF**

**Kirk Humanitarian**

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UNIMMAP multiple micronutrient supplements (MMS) contain 15 vitamins and minerals consistent with antenatal micronutrient standards that women need to help ensure a healthy pregnancy and a healthy baby.
MMS – TAG Resources

The MMS – TAG has a range of resources available to support efforts to introduce MMS:

• **General:** [https://www.nyas.org/programs/multiple-micronutrient-supplements-in-pregnancy/?tab=resources](https://www.nyas.org/programs/multiple-micronutrient-supplements-in-pregnancy/?tab=resources)

• **Evidence – Key Scientific Papers:**
  - [2016 WHO Guidelines for Antenatal Care](https://www.nyas.org/programs/multiple-micronutrient-supplements-in-pregnancy/?tab=resources)
  - [2017 Cochrane Review](https://www.nyas.org/programs/multiple-micronutrient-supplements-in-pregnancy/?tab=resources)
  - [Review of the evidence regarding the use of MMS in low- and middle-income countries](https://www.nyas.org/programs/multiple-micronutrient-supplements-in-pregnancy/?tab=resources)
  - [Replacing IFA with MMS among pregnant women in Bangladesh and Burkina Faso: costs, impacts, and cost-effectiveness](https://www.nyas.org/programs/multiple-micronutrient-supplements-in-pregnancy/?tab=resources)
  - [The upper level: examining the risk of excess micronutrient intake in pregnancy from antenatal supplements](https://www.nyas.org/programs/multiple-micronutrient-supplements-in-pregnancy/?tab=resources)
  - [Benefits of MMS supplementation in pregnancy](https://www.nyas.org/programs/multiple-micronutrient-supplements-in-pregnancy/?tab=resources)
MMS – TAG Resources

The MMS – TAG has a range of resources available to support efforts to introduce MMS:

• Technical Resource Materials:
  - TRM I: Technical Brief for Policy Makers
  - TRM II: Training Materials
  - TRM III: Logistics of Implementation
  - FAQ

• Manufacturing Resources:
  - Open-Access UNIMMAP – MMS Product Specification

• Implementation Research priorities:
  - Child Health & Research Initiative methodology CHNRI exercise
  - Publication of the PROSPERO protocol for the ongoing systematic review on interventions to increase adherence to micronutrient supplementation during pregnancy