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# **UNIMMAP MMS for National Health Systems: Considerations for Developing a Supply Strategy**

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November 2022, Version 1

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## Contributors and Acknowledgements

While the opinions expressed in this paper represent only the views of the authors, the authors wish to recognize individuals for their contributions to this paper and/or to acknowledge individuals for their efforts to review this paper and provide thoughtful comments:

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### Acknowledgements

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Dr. Douglas Call, The Bill & Melinda Gates Foundation  
Dr. Jack Clift, Eleanor Crook Foundation  
Dr. Kristen Hurley, The Vitamin Angel Alliance  
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Editorial support provided by GMMB

*This paper has been made possible through the generous sponsorship of Kirk Humanitarian.*

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## Foreword

The observations and recommendations presented in this resource document derive from the early programmatic experiences of eight countries in which UNIMMAP MMS is being introduced (or considered for introduction) into antenatal care (ANC) services informed by implementation science. Source materials used for this paper include reports generated from national activities undertaken to raise awareness and build consensus for UNIMMAP MMS introduction; country-level landscaping of the national environments into which UNIMMAP MMS is being introduced; results from Supply Readiness Assessments – SRAs (*Sight and Life*) and Supply Context Assessments – SCAs (The Vitamin Angel Alliance) either completed or underway in several countries\*; activities associated with initiating selected implementation research projects; and early contracting experiences with suppliers in the United States, Europe, and Asia.

This paper is intended for stakeholders including national governments, multi- and bi-lateral organizations, nutrition philanthropies, global technical advisory groups, non-governmental organizations (NGOs), and current and prospective suppliers. Its purpose is to capture lessons learned and key operational considerations derived from country experiences that may be helpful to stakeholders developing a national strategy for securing short- and long-term UNIMMAP MMS availability and access, whether from national, regional, or global suppliers.

The authors note that not all high-volume manufacturers across all regions of the world have been fully identified or assessed for their manufacturing capacity. Additionally, this paper and the experiences among the eight countries included in this analysis do not include a full analysis of the contributions that could be made by private sector deployment of UNIMMAP MMS. While it is anticipated that the primary distribution channel for UNIMMAP MMS is likely to be through national health services, private sector contributions to supply and demand could provide many benefits to complement the efforts of national governments. Further landscaping and analysis – along with private sector experimentation – are needed before the contribution of private sector deployment of UNIMMAP MMS to supply and demand can be planned or assessed.

Finally, this document was developed in the spirit of contributing to the formation of a strategy for developing/securing UNIMMAP MMS supplies for national health services that might eventually be agreed upon by a range of stakeholders and serve as the basis for collective action. Thus, we invite other key stakeholders to contribute additional information that might lead to the creation of a consensus strategy for developing/securing UNIMMAP MMS product supplies.

\* The Supply Readiness Assessment (SRA) was originally created by Sight and Life. The Supply Context Assessment (SCA) is based upon the SRA, and is similar, but the SCA assesses and analyzes additional information that is of special interest to national health systems.

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## Executive Summary

### *Background*

The United Nations International Multiple Micronutrient Antenatal Preparation Multiple Micronutrient Supplement (UNIMMAP MMS – **referred to throughout this paper as MMS**) is the most effective nutritional supplement for pregnant women proven to improve maternal health and pregnancy outcomes through extensive randomized clinical trials in several low- and middle-income countries (LMICs). Pregnant women using MMS (as compared to iron and folic acid supplements – IFAS) experience improved health and reduced risk for a range of pregnancy outcomes including stillbirth, infant mortality, low birth weight, pre-term birth, and fetal undernutrition expressed as being small for gestational age. Risk reduction for adverse pregnancy outcomes is even more favorable among pregnant women who are anemic or underweight. The available evidence (summarized in **ATTACHMENT I**) demonstrates MMS to be efficacious and safe. Combined with recent policy guidance and enabling actions that support MMS, increasing numbers of LMICs are considering or beginning introduction of MMS.

The approach to MMS introduction (recommended by UNICEF and others) is one informed by the application of implementation science (IS). Described in detail in **ATTACHMENT II**, IS provides a framework for generating information to guide nations on how to deliver MMS effectively, how to secure product access, and how to synchronize national program implementation with product availability and access. Application of IS has also yielded important insights into current and future global MMS supply and demand and the global manufacturing landscape. This resource document draws on information from early IS experiences to help shape national supply/demand strategies, which may require national, regional, or even global demand and supply coordination of MMS as it is introduced and scaled.

### *Summary of Analysis*

Analysis of initial data indicates that there is currently sufficient manufacturing capacity to support introduction of MMS informed by IS. However, in anticipation of increased short-term demand for MMS (for IS-driven introduction in years to come), more must be done to build global/regional manufacturing capacity and to coordinate procurement and deployment actions associated with donated MMS supplies. To meet long-term demand, work must be done now to ensure regional and global manufacturers initiate product development and manufacturing capacity to support procurement in 2025 when demand, including early demand expected from government purchases, is likely to begin to outstrip available supply. This call to action is urgent given established manufacturers producing MMS for the first time will take an estimated minimum of three years to develop, test, and certify a quality product for market.

### *Conclusions*

The authors conclude that key stakeholders – national governments, multi- and bi-lateral organizations, nutrition philanthropies, global technical advisory groups, non-governmental organizations (NGOs), and suppliers and prospective suppliers – should invest time and resources on the following:

- **Gain consensus on an overall approach for positioning, building, and allocating resources to expand manufacturing capacity that will meet short- and long-term needs.** Most LMICs do not have a capacity (i.e., either technical and/or manufacturer volume) for local manufacture of MMS and/or a sufficient local MMS demand to optimize manufacturing cost-efficiency to achieve an affordable price point for governments. Using donor supplied product appears to be the most efficient way to manage and assure short-term supply needed to accommodate an IS approach to introduction – during the application of which national (and global/regional) stakeholders identify and execute upon a strategy to secure product supplies to meet long-term demand. More manufacturers are needed to close the supply/demand gap over the next 3-5 years.

- **Build a product supply strategy to manufacture and deploy MMS commensurate with demand in 2025 and beyond.** Meeting future demand will require a combination of global/regional-national suppliers that can serve both domestic and export markets. Any MMS supply strategy should be informed by a systematic landscaping of global manufacturing capability, viewed from a regional perspective. This will lead to enhanced supply/demand forecasting models.
- **Coordinate procurement and deployment of donated product supplies.** Improved coordination among groups donating available product will accelerate opportunities to activate exploratory initiatives and to plan and activate MMS introduction while making more efficient use of available product supplies.
- **Identify and activate strategies to finance both incremental advance purchases by existing donors to expand product availability and anticipated regular purchases by governments scaling their transition from IFAS to MMS.** Financing of product manufacturing is emerging as an issue given existing donors are not expected to significantly scale their purchases in the next 2-3 years. Starting after 2025, incremental financing is projected to be needed to grow the supplies of donated product. Additionally, as governments begin to scale their transition from IFAS to MMS, individual nations importing will need financing or access to foreign exchange to make their initial purchases until their procurement systems transition to purchase MMS.
- **Acknowledge the importance of achieving a common approach to producing MMS that regularly meets quality standards.** Effort is needed, starting with the current donor agencies that procure MMS, to align on product specifications for the MMS tablet, regional standardization that benefits trade among regional partners, a common approach to building quality into product development and manufacturing, developing an approach to ongoing supply management, and technical engagement with key high-volume manufacturers. Such actions could speed product availability and lower costs while optimizing benefits for manufacturers, purchasers, and consumers.

To review the full conclusion of this report, click [here](#). To review recommended next steps, click [here](#).

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## Acronyms and Definitions

ANC	Antenatal care
cGMP	Current Good Manufacturing Process
HMHB	Healthy Mothers Healthy Babies Consortium hosted by the Micronutrient Forum
IFAS	Iron and folic acid supplement (or supplementation)
IS	Implementation Science
LMIC	Low- and middle-income country
MCH	Maternal and Child Health
MMS	Multiple micronutrient supplement (or supplementation)
MMS – Task Force	Multiple Micronutrient Supplementation Task Force hosted by New York Academy of Sciences
MMS – TAG	Multiple Micronutrient Supplementation Technical Advisory Group hosted by New York Academy of Sciences
Open-Access Consensus Specification	Expert consensus on an open-access product specification for MMS for pregnant women
Product Specification	A technical document that provides a detailed description of the product to be manufactured
RFP	Request for Proposal
SRA and SCA	Supply Readiness Assessment and Supply Context Assessment
UNICEF	United Nations Children’s Fund
UNIMMAP	United Nations International Multiple Micronutrient Antenatal Preparation
WHO	World Health Organization

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# 1. Understanding Current National Context

## 1.1. Overview

The observations, findings, and recommendations presented in this paper stem from an examination of early programmatic experiences in eight of 24 countries shown in bold in **FIGURES 1** and **2**.<sup>1</sup> Source materials used for this paper include: reports generated from national activities undertaken to raise awareness and build consensus for MMS introduction; country-level landscaping of the national environments into which MMS is being introduced; results from Supply Readiness Assessments – SRAs (*Sight and Life*) and Supply Context Assessments – SCAs (The Vitamin Angel Alliance) that include key informant interviews, either completed or under way in several countries; activities associated with initiating selected implementation research projects; and early contracting experiences with suppliers in the United States, Europe, and Asia.<sup>2</sup>

National stakeholders within the eight countries perceived the following key barriers to introduction and scaling MMS: product availability and accessibility, affordability, regulatory issues affecting manufacturing, and specific issues affecting delivery.

## 1.2. Product Availability and Accessibility

**Product availability** is defined as ensuring an adequate quantity of quality product is produced for commercial sale. **Product accessibility** is defined as ensuring the product being produced can be secured in adequate quantities to meet demand through purchase or donation.

Within the eight countries examined, product availability and accessibility were among the most frequently identified barriers expressed as a reason for deferring exploration of MMS introduction. When governments, champions, and influencers initiated discussions to introduce MMS, they were generally unaware of the availability of MMS product supplies for IS activities from global sources, and participants assumed product could be locally manufactured quickly.

National stakeholders noted that through dialogue with local, regional, and international experts, national decision-makers recognized that initial *introduction* of MMS can be achieved by importing product, either by government purchase or donation, and that national decision-makers' focus is best placed on how to secure MMS product supplies for long-term scaling and program maintenance. Among the donation programs, Kirk Humanitarian (a U.S.-based foundation), UNICEF, and The Vitamin Angel Alliance (a U.S.-based, nutrition-focused NGO with global operations) all donate product for well-designed MMS introduction initiatives constructed around an IS approach. Securing access to product to fulfill long-term needs requires significant information-gathering and analysis. Undertaking an assessment of UNIMMAP MMS supply context within the IS approach to introduction will provide the necessary decision-making information. Importantly, an IS approach can facilitate decision-making regarding whether to purchase imported MMS (which comes with foreign exchange requirements), manufacture MMS locally (which also comes with a foreign exchange requirement to purchase ingredients) or use some combination of the two. Application of IS in this regard is detailed in **SECTION 4.2.2**.

**TIP:** National decision-makers should separate procurement decisions into **short-term** and **long-term** needs. This will provide decision-makers with the time and space needed to make informed, strategic decisions about long-term product availability and access.



### 1.3. Product Affordability

Early adopter governments have generally used one of two models to determine affordability of health interventions. In the first model, government seeks to understand the absolute cost of a new intervention compared to the cost of an existing intervention. In the second model, government uses a cost-benefit analysis for decision-making. Generally, ministries of finance tend to focus on cost, while ministries of health focus on cost-benefit.

Comparing the price and affordability of MMS relative to IFAS can be confusing depending upon the interpretation of the following:

- **Recommended MMS and IFAS dosing schedules.** Governments may not interpret the recommended dosing schedule for IFAS and MMS consistently when comparing costs. The World Health Organization (WHO) does not explicitly define the number of tablets to be used in a pregnancy for IFAS or MMS. Both products are technically recommended to be used daily throughout pregnancy (for preventive purposes). This should translate into a practical assumption of 180 doses per pregnancy for both products, taking into consideration when a pregnancy is recognized and when antenatal care is engaged. In practice, the number of IFAS tablets offered to the pregnant women may be 90 or 180 doses depending upon how governments interpret WHO guidelines, while the recommendation for MMS is generally acknowledged to be 180 doses during pregnancy as used in clinical efficacy trials comparing IFAS to MMS and as implied in UNICEF guidance which recommends daily dosing for 6 months during pregnancy.<sup>3,4</sup> If the existing standard for IFAS is variable, it is easy to see how a ministry of finance may view transition to MMS (at 180 tablets per pregnancy) as being prohibitively (or at least, more) expensive. Simultaneously, a ministry of health might conclude, based upon a cost-benefit ratio, that MMS is “highly cost-effective,” regardless of whether 90 or 180 IFAS or MMS tablets are used, or if the price of MMS is greater than IFAS per tablet. Consumer adherence to the dosing regimen established by national authorities is assumed to occur at high levels (but may not be true in fact) in cost-benefit analysis and underscores the need for IS to find effective strategies to ensure adherence.
- **Benchmark pricing.** The benchmark price is the lowest price achievable and below which there is no further meaningful reduction in price for a product of a defined quality, irrespective of volume purchased. Understanding the benchmark price for MMS is difficult as production globally has not yet reached scale. The benchmark price may not be achievable by any manufacturer that seeks to manufacture MMS for a single market – as discussed in **SECTION 4.4: PRICING EXPERIENCE FOR UNIMMAP MMS.**

**TIP:** Defining “affordability” for national stakeholders is nearly always a country-specific task. [Nutrition International’s Cost-Benefit Tool](#) is very helpful for national stakeholders to understand the highly cost-effective nature of UNIMMAP MMS.

Affordability should weigh both price (which reflects the local business case for importation or local manufacturing) and cost-benefit together when implementation is established at scale. MMS can arguably be a much better value than IFAS after recognizing that the price of MMS and IFAS can be about the same on a **per dose basis**, and MMS is among the MCH interventions with the highest cost-benefit ratio. Current country experience demonstrates that both SRAs and SCAs assist ministries of finance and health gain an understanding of affordability. Key points of persuasion are generally associated with the overall cost-benefit of the intervention (including transition costs) and/or that the cost (and price) per MMS tablet is relatively close to that of IFAS. The result is both ministries of health and finance conclude the product is affordable.

### 1.4. Understanding the Regulatory Framework and Product Standards

As national stakeholders become more familiar with MMS and envision its incorporation into services of the

national health system, they begin to envision how to secure a sustainable supply of MMS. Whether the MMS product is eventually secured from national suppliers or imported, before routine access to MMS can be achieved, suppliers need to know how national regulatory authorities will regulate MMS. Understanding the regulatory framework is critical, especially when local manufacturing is feasible, since local manufacturers, generally, will be unwilling to begin product development until they know the applicable product and manufacturing requirements laid out in a regulatory framework.

In conjunction with the regulatory framework, there is parallel interest among national authorities and manufacturers to know what are the product standards necessary to ensure a high-quality product acceptable to national authorities.

## 1.5. Understanding Impact of Adherence and Product Packaging Preferences on Manufacturing

A key concern of national stakeholders is ensuring that adherence to MMS is improved over that achieved with IFAS. Among the important factors that can affect adherence to MMS is product packaging – which becomes an important manufacturing issue and cost factor. For MMS, packaging choice has been generally based on preferences of health care providers – often rooted in a generalized belief that 30 and 90 count packaging encourages women to attend future follow-up ANC visits. MMS packaging, increasingly, is also driven by consumer marketing research to ascertain “consumer appeal.” More recently, national stakeholders have become more aware that finished product packaging options have very significant cost- and environmental-implications, driving packaging analysis to be included in IS initiatives.<sup>5</sup>

Experience does not support definitive statements about optimal MMS packaging. Decision-makers must look to ongoing and future IS to balance competing packaging demands, needs, and preferences from a range of stakeholders against programmatic and manufacturing costs, environmental impact, and uptake and adherence. Country experience shows these competing interests are a central focus of ongoing IS in which various packaging options are being configured with optimized social and behavior change communications to achieve improved adherence at reduced cost and reduced environmental impact. Such investment can help shape future guidance on more standardized packaging for donated product used in introduction, and product procured for scaling and maintenance of MMS. **SECTION 4.5** provides more consideration of product packaging.

**TIP:** There is a need for investment not only to evaluate packaging options in the context of addressing preferences and program imperatives, but in innovation in packaging, and further assessment of the implications of packaging choices on the environment.

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## 2. Current Supply and Demand

### 2.1. The Nature and Level of Current Demand

Today, demand for MMS production is driven primarily from procurement by foundations, non-profits, and multilateral institutions to support an IS approach to country introduction of MMS, including initial exploratory activities, or to begin initial scale up of services.

Currently, there are a total of 15 countries (**FIGURE 1**) in which MMS product supplies are being used to support IS-informed introduction of MMS. Based on inquiries and activities, the additional nine countries shown in **FIGURE 2** are working toward formal IS-informed introduction of MMS by 2024. These activities are

documented in an interactive “World Map of MMS Activities” produced by the Healthy Mothers Healthy Babies (HMHB) Consortium hosted by the Micronutrient Forum and posted to its website.<sup>6</sup> The countries identified in **bold** are ones from which information was used to help create this report. The countries marked with a double asterisk (\*\*) have introduction programs sponsored by UNICEF.

**FIGURE 1. Countries receiving MMS product supplies in 2021 in support of an implementation science approach to introduction.**

<b>ASIA</b>
1. Bangladesh**
<b>2. Indonesia</b>
<b>3. Pakistan</b>
<b>4. Philippines</b>
5. Vietnam
<b>AFRICA</b>
7. Burkina Faso**
<b>8. Democratic Republic of Congo</b>
9. Madagascar**
10. Mali
<b>11. South Africa</b>
12. Tanzania**
13. Uganda
14. Zimbabwe
<b>LATIN AMERICA</b>
<b>15. Haiti</b>
<b>16. Mexico</b>

**FIGURE 2. Countries anticipated to adopt an implementation science approach to introduction of MMS by 2024.**

<b>ASIA</b>
<b>1. Cambodia</b>
2. Nepal
3. Thailand
<b>AFRICA</b>
4. Botswana
5. Ethiopia
6. Ghana
7. Malawi
8. Zambia
9. Zimbabwe

**Table 1** represents the approximate number of pregnancies supported worldwide in 2021 and 2022 from product procured by three key product donors and used to support IS-led introduction efforts in the countries listed in **Figures 1** and **2**. Product available from some of these same donors is also being used to facilitate very early exploratory initiatives in at least 50 additional countries.

**TABLE 1. Current number of pregnancies supported by MMS purchased by key product donors**

DONOR	2021	2022
<b>KIRK HUMANITARIAN</b>	6.9 m	9.6 m
<b>VITAMIN ANGEL ALLIANCE</b>	1.0 m	1.0 m
<b>UNICEF*</b>	1.5 m	1.5 m
<b>TOTAL</b>	<b>9.4 m</b>	<b>12.1 m</b>

\*Estimated based upon historical procurement, and public records of contracts awarded.

## 2.2. Current Suppliers

As of December 2021, there are only 13 manufacturers around the world currently able or close to being able to produce a commercially available finished UNIMMAP MMS product. Among these, only five actively manufacture MMS, and one currently produces about 80% of the total annual available supply (Contract Pharmacal Corporation). Manufacturers known to be building capacity or actively delivering product are shown in **TABLE 2** with the active suppliers highlighted in orange.

**TABLE 2. Manufacturers currently known to have capacity to manufacture UNIMMAP MMS**

COUNTRY	SUPPLIER/ MANUFACTURER	PRODUCT FORM	REGION OF MMS SUPPLY	ACTIVE SUPPLIER	COMMENTS
CANADA	Noor	Capsules	Regional	Yes	Active Supplier
BANGLADESH	Beximco	Tablets	Regional	Yes	Ongoing production only for local clinical trials
	Renata	Tablets	Regional	Yes	Capable, but no export sales yet, unknown pricing
DENMARK	Lekapharm / Bioplus	Tablets	Global	Yes	Contract manufacturing by Bioplus, India
GERMANY	Lomapharm	Tablets	Global	Yes	Active Supplier
INDIA	Bioplus	Tablets	Global	Yes	Active supplier to Lekapharm
	Hexagon	Tablets	–	–	Requires further inquiry
	Manisha Pharmoplast	Tablets	–	–	Requires further inquiry
	Mepro	Tablets	–	–	Under development
INDONESIA	To be named	Tablets	–	–	Under development, contract negotiations in progress
SOUTH AFRICA	DSM / Wrapsa	Tablets	–	–	Under development
UNITED STATES	Contract Pharmacal Corp	Tablets	Global	Yes	Active Supplier
	ProCaps Laboratories	Capsules	Global	Yes	Active Supplier

### 3. Future Demand and Supply Forecasts

#### 3.1. Forecasting Demand

As shown in **TABLE 1**, in 2021 and 2022, donated MMS supported an estimated 9.4 million and 12.1 million pregnancies in countries introducing MMS. From 2023 through 2024, demand for product supplies (attributable to donor purchases) is projected to increase as shown in **TABLE 3** below.

**TABLE 3. Forecasted number of pregnancies able to be supported by donated supplies of MMS product purchased by key product donors**

ALL DONORS	2021	2022	2023	2024
TOTAL	9.4 m	12.1 m	14.5 m	15.5 m

The estimates through 2024 are based on modest increases in product needs driven, almost exclusively, by purchases of MMS product by the same donors shown in **TABLE 1**. This product will be used to fulfill demand from IS initiatives designed to introduce MMS, including anticipated new exploratory efforts in additional countries.

Beyond 2024, the factors influencing demand become much harder to predict. The author’s modeling for a future demand forecast would have been driven, preferably, by the number of *pregnancies* by country each year. However, *live births* by country projected into the future have been used. This decision was made primarily because information on live births by country are more readily available from recognized sources (for all countries) as identified in the footnotes.<sup>7</sup> Numbers of pregnancies are not readily available for all countries. Using live births, the resulting data set includes:

- 132 nations among 235 member states of the UN that are classified by the UN Development Group as LMICs based upon income and development status. China is excluded from the number of LMICs and from the overall demand analysis.
- For the 132 LMIC nations included in the analysis, there are an estimated **115.2 million** live births annually, representing women eligible to use MMS.<sup>8</sup> For the purposes of forecasting here, the same birth rate is assumed in all years starting from 2025 through 2030 to generate the numbers of live births.

The demand forecast modeling assumptions are described in full in **FIGURE 3**.

Based on the assumptions in **FIGURE 3**, analysis results in an estimate of demand (from both donor and government procurement) from 2025 to 2030 (**TABLE 4**) that increases from 15.5 million pregnancies in 2024 to 61.8 million pregnancies annually by 2030.

**FIGURE 3. Demand modeling assumptions**

- Countries embrace an IS approach to the introduction of MMS into antenatal care services.
- Countries pass through **approximately four years** of various “exploration and introduction” activities deemed part of an **evidence-based** approach to introduction.
- **During each year of exploration/introduction**, nations require sufficient MMS product for an average of 250,000 to 300,000 pregnancies per year. This assumption is based upon actual deliveries of MMS product supplies globally to most of the early adopter countries identified in **Figure 2**. These countries use product for both early exploration of MMS in ANC settings, and for testing of various implementation strategies.
- Model assumes no country will begin to scale MMS before 2024. Beginning in 2024, between 2 and 5 countries per year will begin scaling activities as an outcome of IS efforts in country. Countries selected are based on known IS activities planned or underway as of the writing of this paper.
- Between 2024 and 2030, in selected countries determined by the authors, governments begin phased scaling at a rate consistent with serving no more than 60% of pregnancies within 4 to 7 years. Additional support for scaling, incremental to national government scaling efforts, is provided in the form of donated product targeting traditionally underserved women (estimated at 20%) is included in the calculation of total demand.
- During years when national governments are scaling MMS, countries already purchasing IFAS commit to begin to redirect those funds to purchase MMS not later than scale has been reached (typically year 4). For comparison, on average, IFAS reach by government health services is assumed on average 70% with adherence in the low double digits.
- Throughout the government timeline for scaling, donations will continue. At the end of the national scale-up, use of donated MMS product will not exceed 20% of pregnant women and supports only hard-to-reach, vulnerable women not served by government systems. Population growth is assumed to be static for the purposes of this analysis.
- Demand that might be generated by the private sector is not considered in this model (Note: Private sector landscaping needs to be undertaken and results considered in future forecasting as feasible; and it is anticipated that once MMS is incorporated into government policy, they will encourage deployment of branded and/or generic MMS products through private sector channels such as retail pharmacy chains and social marketing schemes).

**TABLE 4. Anticipated demand 2024 through 2030 (based upon live birth rates)**

YEAR	2024	2025	2026	2027	2028	2029	2030
ESTIMATED NUMBER OF PREGNANCIES SUPPORTED	15.5 m	17.4 m	24.5 m	35.7 m	44.7 m	52.2 m	61.8 m

The authors recognize the demand estimates in **TABLE 4** are conservative (i.e., underestimated) for at least two reasons:

- As countries begin to design and test implementation strategies, some governments choose to accelerate the start of initial scaling before IS is completed. This action creates an increased level of demand earlier than expected that is not incorporated into our forecast.<sup>9</sup> Governments’ rationale for this acceleration derives from effective consensus-building leading up to testing of implementation strategies. While

governments understand that information needed to identify and demonstrate effective implementation strategies takes time to establish, they may also view the proven benefits of MMS for pregnancy outcomes as being so positive that there is a sense that it is unethical to wait for the results of IS before expanding product use (e.g., MMS benefits are greater than for IFAS even where the adherence rate of MMS is the same as compared to IFAS).

- The first method used for determining demand is based upon the number of live births (calculated from crude birth rates). Later in this analysis we also present demand based upon an estimate of the number of pregnancies. To illustrate the underestimate of demand when using live births vs. total pregnancies, the authors consulted data available from the Guttmacher Institute<sup>10</sup> which currently estimates that there are 228 million pregnancies (188 million excluding China) in all LMICs annually. The authors used the publicly available data at Guttmacher.org combined with estimates of pregnancies for countries where data are not available at country level, to estimate demand in LMICs based on pregnancies for all countries included in our forecast of future demand as shown in **TABLE 5**.

**TABLE 5. Anticipated demand 2024 through 2030 (based upon total estimated pregnancies)**

YEAR	2024	2025	2026	2027	2028	2029	2030
<b>ESTIMATED NUMBER OF PREGNANCIES SUPPORTED</b>	18.0 m	23.0 m	34.3 m	53.1 m	68.6 m	81.3 m	96.8 m

### 3.2. Forecasting Supply

As shown in **TABLE 3**, demand is anticipated to grow gradually through 2024. This demand is driven primarily from procurement by organizations donating MMS to support country introduction efforts, including early exploration. Available supply supports this demand because procurement of product to be donated gives manufacturers a basis for future forecasting of product needed and future purchase commitments. Firm purchase commitments from Kirk Humanitarian, The Vitamin Angel Alliance, and UNICEF ensure manufacturers acquire necessary raw material reserves to build/maintain manufacturing capacity to fulfill orders.

As shown in **TABLE 4**, starting in 2024 and into 2025, demand begins to significantly increase year-over-year as governments begin to scale MMS nationally. This shift from donated only product (for IS initiatives, including exploratory activities) in 2021 through 2024, to a combination of continued donations alongside government purchases for scaling MMS is anticipated to create a supply shortage by 2025 as shown later in this section.

Future supplies will depend, in part, on some or all the manufacturers shown earlier in **TABLE 2** in **SECTION 2.2**. Additional manufacturers will be required to close the demand-supply gap described in the next section. While landscaping of the manufacturing base and a more complete supply analysis are needed, a preliminary supply forecast for 2024 to 2030 (**TABLE 6**) has been developed based upon the assumptions in **FIGURE 4**.

**FIGURE 4. Supply modeling assumptions**

- Total supplies until 2024 are driven by the demand from donating organizations for use in exploratory and IS introductions.
- At scale, the model assumes a continued level of donation support (from all donative organizations) of up to 20% of pregnant women in country. This assumes that up to 30% of pregnant women in LMICs remain underserved or unserved by government health systems, and implies that donation support will increase, not decrease, as governments scale MMS (NB. today, donative support is less than 20%).
- All supply model assumptions are based on the current recommended dosing regimen of 180 MMS doses per pregnancy. For simplicity the author’s projections are: based on delivery of MMS product, not use of MMS product; and assume distribution of 180-count bottles. As a result, adherence is not considered, and product loss due to low adherence or wastage are not considered. If projections were to be based on usage of MMS product rather than delivery of MMS product, it is assumed that supply and demand projections would be affected by adherence levels, and packaging used (e.g., 30-, 60-, 90-count packaging). Projections would also be altered if ongoing research finds that the optimal, recommended dosing regimen is less than 180 doses per pregnancy.
- The model assumes 3-4 years for a potential manufacturer to develop and produce UNIMMAP MMS for the first time, including registration and approvals in one or more countries. For existing UNIMMAP MMS manufacturers, it is assumed additional capacity could be added within one year of purchase order commitment.
- The five existing manufacturers will make modest increases in production to support demand from firm orders through 2024 (and beyond) but will not build capacity beyond the known purchase forecasts plus a modest year over year increase.
- Limited regional (new) capacity (e.g., one to two new manufacturers) will be realized in 2024 or 2025, driven primarily by supply readiness assessments in two early adopter nations furthest along in the IS introduction efforts. Discussions are underway with one manufacturer as of the writing of this paper. It is expected that new manufacturers will require at least 24 months (probably 36 months) to achieve a commercially viable product. For these manufacturers to be ready by 2025, their product development, testing, and manufacturing capacity plans must begin by late 2022.
- In the absence of more advance purchase agreements beyond those issued by current donor organizations, significant increases in manufacturing capacity from existing global/regional manufacturers will not be seen until 2029 or later.
- The basic model does NOT include demand that may be generated as a result of private sector initiatives to introduce UNIMMAP MMS through non-government channels of distribution, therefore, private sector supply needs are also not considered.

**TABLE 6. Anticipated supply 2024 through 2030 (represents pregnancies supported with 180 doses/ pregnancy)**

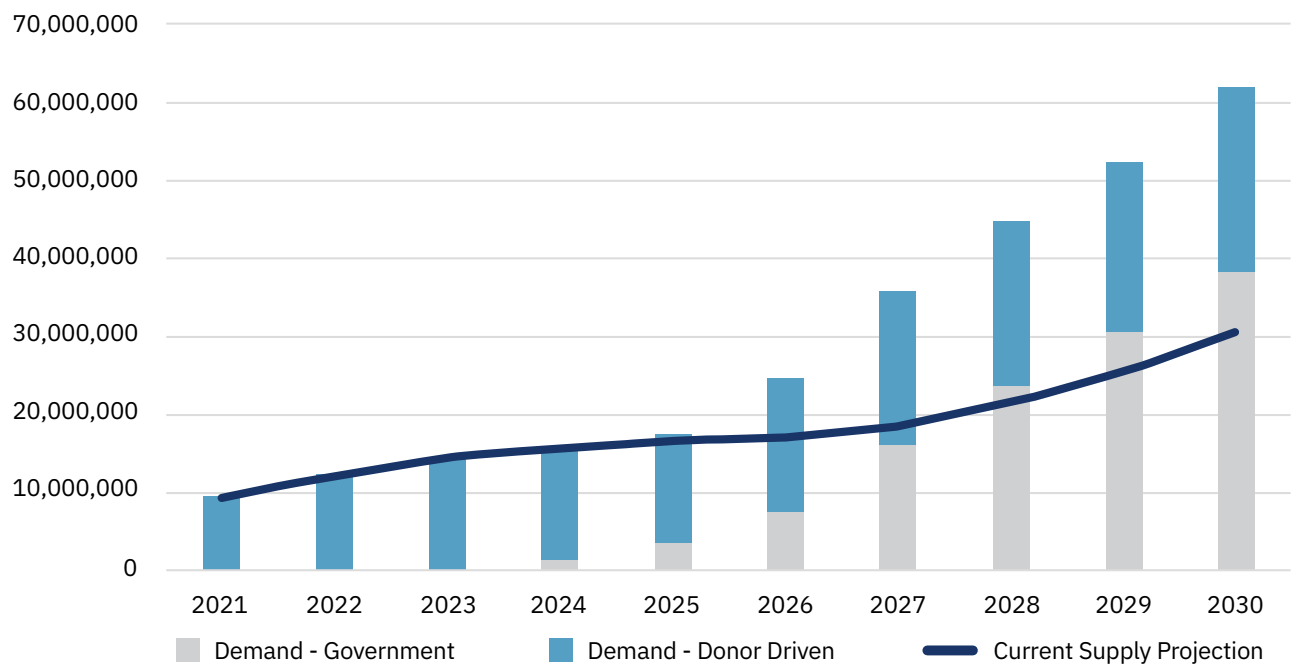
YEAR	2024	2025	2026	2027	2028	2029	2030
UNIMMAP MMS SUPPLY PROJECTION	15.5 m	16.7 m	17.1 m	18.4 m	21.5 m	25.4 m	30.5 m



### 3.3. Supply and Demand Gap Analysis

An initial analysis of supply and demand (see **GRAPH 1**) implies that product supplies to 2024/2025 are sufficient to satisfy the demand generated by the application of IS and very limited scaling in a portion of early adopter nations. Analysis also suggests that projected supplies for IS and limited/full scaling will **not** keep pace with anticipated future demand for MMS starting in 2025. Consequently, overall program implementation progress can be expected to slow in 2025 unless steps are taken to ensure an increasing and sustainable supply of MMS. It is assumed that national health systems will not eliminate IFAS altogether as MMS is being introduced and scaled, so that if MMS supplies lag demand, there is still a supply of IFAS to fill the gap until MMS accessibility is fully scaled. This underscores the importance of applying a systematic IS approach to introduction to synchronize product supplies with program implementation as discussed elsewhere in this paper.

**GRAPH 1. Current demand and supply forecast for UNIMMAP MMS**



Given the assumed importance of manufacturing by producers able to export to supply MMS to other countries in the region and manufacturing by producers who intend to serve only a single domestic market, there is a need for investment to secure long-term access to an expanded supply of MMS product. Such investment will be critical to address the gap between product supply and demand forecast to commence in 2025 when demand is projected to outstrip supply.

The forecast suggests that the 2024-2026 timeframe will be a critical juncture for the community of advocates for deployment of MMS. From now to 2025 there is almost certainly sufficient MMS product to support virtually any country that seeks to use an IS approach to introduction. At that 2025-2026 juncture, without more investment now, demand will almost certainly overwhelm available supplies.

The challenge for ensuring significantly more supplies in 2025-2026 is tied to an understanding of the length of time it takes a manufacturer to develop and produce UNIMMAP MMS for the first time, and availability of financing to support advance purchase agreements. Developing an approved, quality product and necessary manufacturing capacity (an undertaking of three or more years) is described in **SECTION 4.2** in the context of considerations for building manufacturing capacity. It should be noted that existing manufacturers may or may not be able (or not wish) to increase production capacity for reasons related to: i) physical plant limitations; ii) constraints forced by other production commitments; iii) product profitability; iv) reluctance to service governmental contracts; and v) uncertainty of governmental or other purchaser commitments among other reasons. To prepare for the anticipated growth in demand, investment must be made in development of both regional and global capacity by the end of 2022.

Even with this recognition, to achieve the supply needed to meet the projected demand starting in 2026, robust action is needed to incentivize qualified manufacturers to set out on a path of investment to build additional manufacturing capacity. Such actions should include:

- Actively seeking additional, qualified high-volume manufacturers – where a business case can be made – to anticipate the coming demand and begin the product development and manufacturing process for both domestic and export markets.
- Encouraging key stakeholder organizations to issue advance purchase commitments to existing and emerging manufacturers for product that is eventually donated to national initiatives to introduce and scale MMS or transitioned to government procurement. A variation of this action might be to encourage donors to offer governments a blended approach including offers by donors to co-finance advance-purchase agreements.
- Encouraging governments to plan for and initiate agreements with existing or emerging manufacturers for product needed to scale and maintain national programs as driven by the IS approach.
- Communicating to existing manufacturers the need to add production capacity.

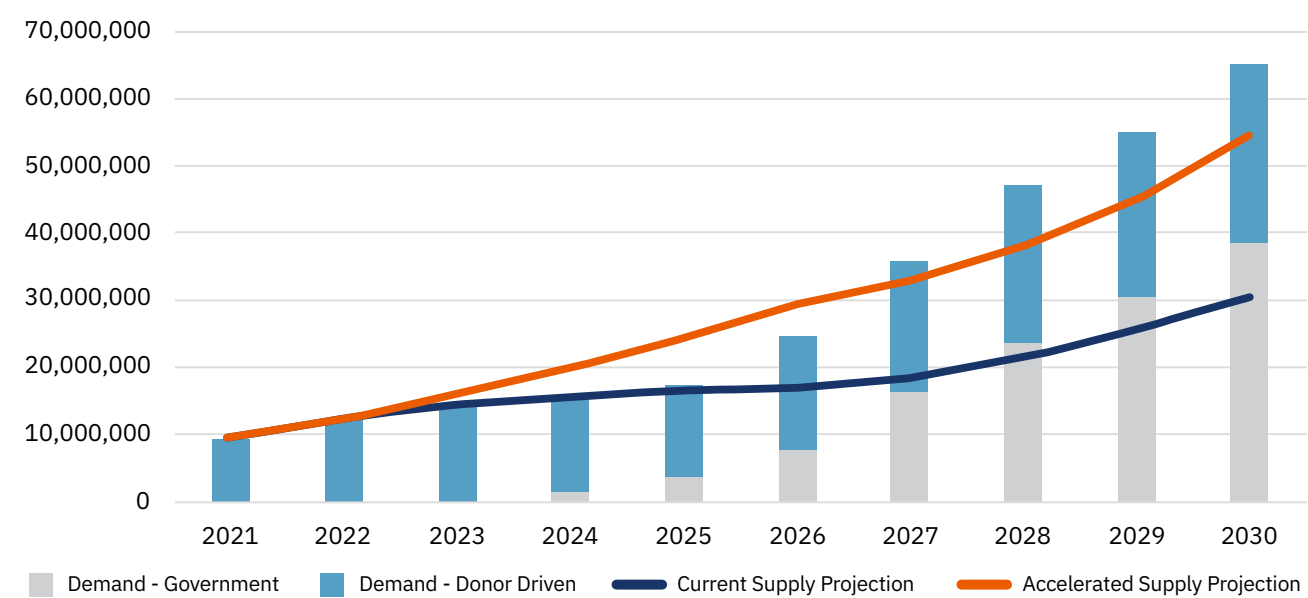
Initiating these actions now can have significant impact on availability of quality UNIMMAP MMS by 2026, and thus, further reassure governments that the product supplies needed long-term for scaling will be available.

**FIGURE 5** shows the assumptions used to create an “accelerated” manufacturing scenario. **GRAPH 2** below illustrates the potential impact of early investment by key stakeholders on new production capacity, and thus on the supply and demand picture.

#### **FIGURE 5. Accelerated supply modeling assumptions**

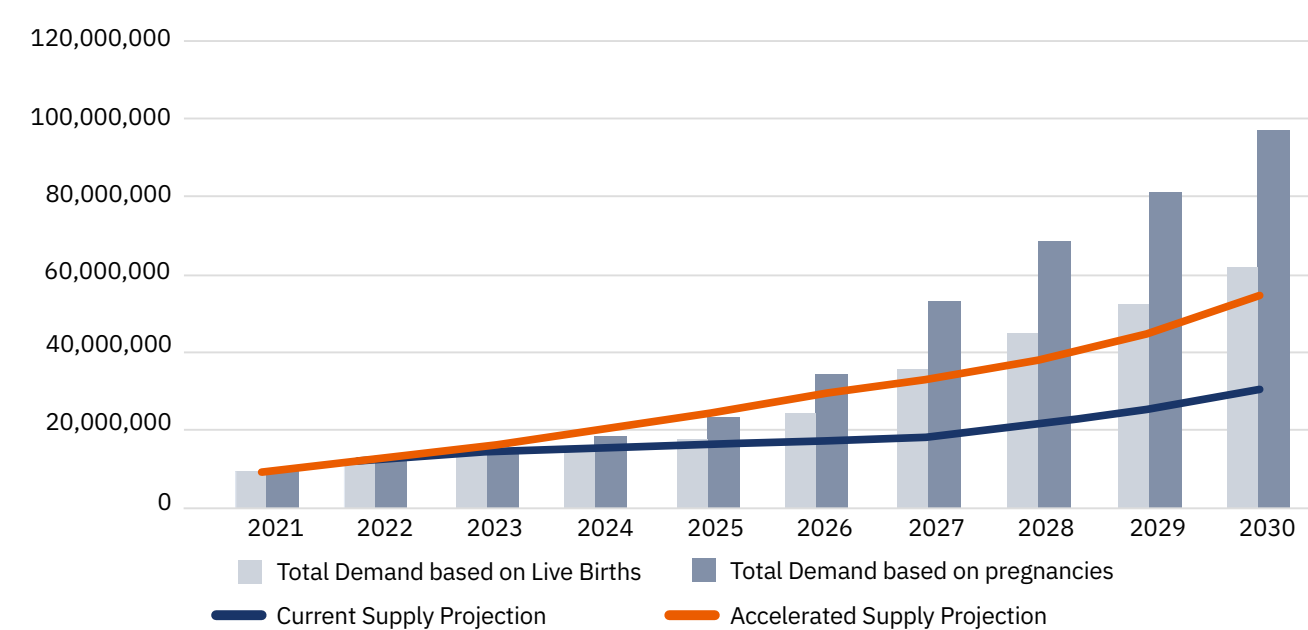
- Growth in manufacturing capacity requires a willingness for donor and/or government buyers to engage in advance purchase commitments to meet the levels of product supply shown in the model.
- Emerging regional manufacturers will be identified in 2022 and will begin fulfilling orders by late 2024. Between 2022 and 2028, no more than four new regional manufacturers will emerge, and no one manufacturer will be able to produce product able to serve more than one million pregnancies for the first two years of production.
- Existing global manufacturers will anticipate the increasing demand in 2024 and will begin making capacity investments in 2022 and 2023.
- Beyond 2024, existing global and emerging regional manufacturers will continue building capacity to fulfill growing demand; by 2028 additional regional manufacturers will be online to help meet regional requirements.

**GRAPH 2. Demand and current vs. accelerated supply forecast for UNIMMAP MMS**



Finally, **GRAPH 3**, similar to **GRAPH 2** insofar as estimated current and accelerated supply forecasts, shows total demand illustrated two ways: demand based on live births vs. estimated pregnancies. This comparison illustrates the increased magnitude of the potential gap in demand when the total number of pregnancies is used. This reinforces the case that there is an urgent need to catalyze MMS manufacturing to avoid demand outstripping supply in coming years. The limitation of this approach (i.e., using total number of pregnancies) is that a meaningful number of countries do not report the total number of pregnancies per year. For these nations, our forecast shown in **GRAPH 3** estimates the total number of pregnancies by multiplying the number of live births by a factor of 1.35.

**GRAPH 3. Demand (live births vs. pregnancies) vs. supply (current vs. accelerated supply forecast)**



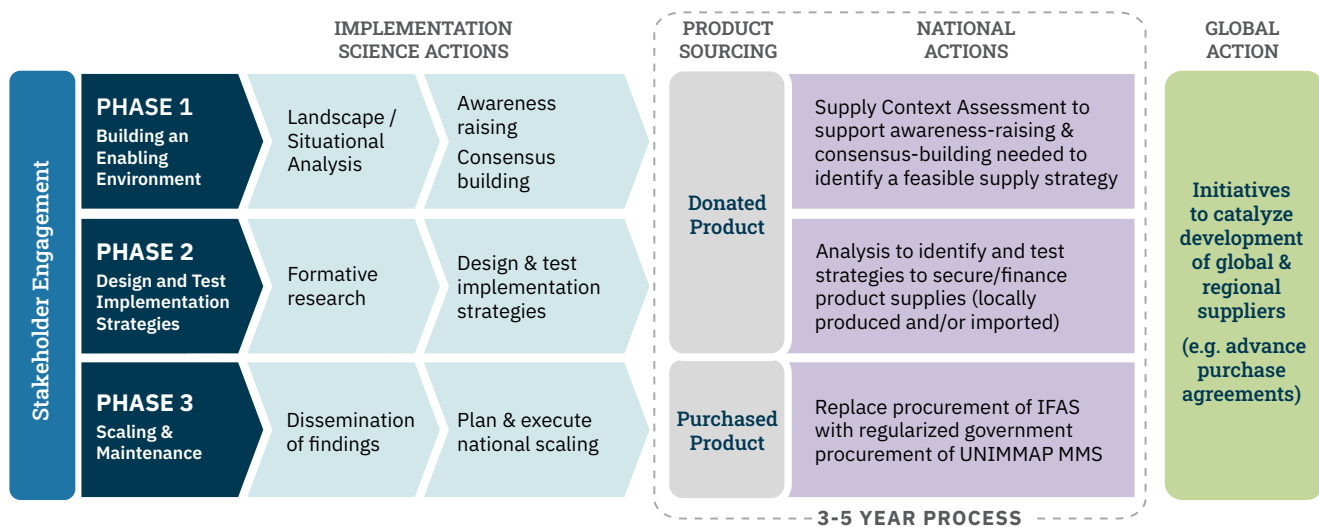
## 4. Considerations for Creating an MMS Supply Strategy

### 4.1. The Need to Synchronize Product Supply with Program Implementation

To better understand the pathway and actions to synchronize product availability/access with program implementation, **FIGURE 6** below presents an initial model – based on country experiences – to synchronize product supplies throughout introduction, scaling, and program maintenance in the context of an IS approach. This approach illustrates how national stakeholders can achieve two key objectives:

1. Identify key issues, in the form of enablers and barriers, that influence the ability of a health system to secure access to a sustainable supply of MMS product. This objective is accomplished largely through activities undertaken to create an enabling environment (Phase 1 of the IS model) as described below.
2. Synchronize MMS product supplies with both program introduction and subsequent national scaling and program maintenance. This objective is accomplished by using the information gathered in Phase 1 to inform actions and activities in Phases 2 and 3 of the IS model (Identifying and Testing Sourcing Options, and Scaling, respectively).

**FIGURE 6. Model for synchronizing product supply with different phases of program implementation**



A full description of this model and the implementation activities and actions for identifying an effective strategy for securing MMS product are described in **ATTACHMENT II**. The following sub-sections outline a few of the key considerations for an MMS supply strategy associated with the 3-5 year process for product sourcing and national actions. These considerations focus on building manufacturing capacity (nationally, regionally, and globally), the importance of product standardization, the need to develop effective procurement systems, and product pricing.

### 4.2. Building Manufacturing Capacity

#### 4.2.1. Timeline to commercial availability

A manufacturer generally will not invest in development of a new product like MMS until: i) national health service stakeholders agree that MMS is an intervention worthy of adopting; ii) national authorities describe the regulatory framework for its manufacture and use; and iii) a committed buyer shows readiness to purchase MMS, typically in the form of a purchase agreement.

Experience shows it can take months to years to gain consensus on adopting the intervention, months to assess the manufacturing environment into which MMS is being introduced, 1-2 years to expand manufacturing capacity at existing manufacturers, and 3-5 years for a manufacturer to fully develop a UNIMMAP MMS product for commercial sale for the first time. These timelines can overlap, but stakeholders should expect this process to take from 3-5 years from initiation of the IS process to a commercially viable product from a manufacturer producing MMS for the first time.

While there are ways to minimize the length of time to a commercially available product, the timeline to a product by a manufacturer producing it for the first time is years, not weeks or months.

A variety of factors drive the length of time to bring the MMS product to commercial availability for use within national health services. This includes the time needed to:

- Assess or examine (and usually adjust) existing policies and the regulatory environment into which MMS is being introduced;
- Identify and resolve procurement and distribution system issues (for both locally manufactured and imported product);
- Examine cost-benefit and budgetary implications;
- Identify/assess prospective manufacturing options, requirements, and capacity;
- Clarify marketplace information that can help identify the effective strategies for ensuring adherence and uptake; and
- Undertake product development, complete product testing, and achieve registration.

For manufacturers producing MMS for the first time, commercial availability requires time for development, test-manufacture, and registration of a product that conforms to the regulatory requirements of the country in which the product is manufactured or to be used commercially – whether for use within a national health service, the private sector, or for export markets. These steps are not trivial for UNIMMAP MMS, which has a formulation of 15 ingredients, a range of excipients, and requires significant manufacturing expertise to develop, produce, and register.

**TIP:** It should not be assumed that manufacturers that produce IFAS (with two ingredients) have the knowledge, skill, and expertise needed to produce a complex product like MMS (with 10 or more ingredients).

The most time-consuming aspect for manufacturers to meet local regulatory requirements for a new product is conducting product stability testing. This is generally achieved by exposing the finished product to some combination of real time and accelerated testing under relevant conditions of temperature and humidity. Stability testing alone generally requires 18-24 months to complete – before documentation can be submitted to a regulatory authority for product approval and registration.

The next most time-consuming aspect of bringing a product to commercial availability is pre-qualifying which manufacturers have the technical and financial capacities needed to manufacture MMS. Subsequently, selecting one or more pre-qualified manufacturers through competitive bidding can also be time consuming. Both pre-qualification and selection of a specific new supplier of MMS by major purchasers can take 12-18 months to complete. In some countries, national drug procurement systems complicate the individual medicine procurement process (especially where governments use intermediary brokers to supply a new drug), and do not easily accommodate new medicines not already on the national essential medicines list.

Competitive bidding for the manufacture of UNIMMAP MMS was undertaken in Indonesia in 2021. The entire process of designing a pre-qualification process, issuing an invitation to respond to a RFP, allowing time for submissions to be made and evaluated, and selecting a company to be invited to negotiate a final contract

consumed just under 12 months. Tools in the form of a pre-qualification questionnaire for prospective manufacturers, a sample RFP, and a model contract for use by those purchasing MMS will soon be made available.<sup>11</sup> A reduction of this timeline (along with optimizing manufacturing costs) is already being achieved in Indonesia by encouraging both purchasers and manufacturers to use the [\*Expert Consensus on an Open-Access Product Specification for MMS for Pregnant Women\*](#) (or an equivalent product specification). Visit [www.kirkhumanitarian.org/resources/consensus](http://www.kirkhumanitarian.org/resources/consensus) to view and download this document. It helps standardize both the product and its manufacture, and comes with many benefits for buyers, manufacturers, and product end-users which are summarized in **SECTION 4.2.2** from a more detailed article prepared for Sight and Life's *Special Report: Focusing on Multiple Micronutrient Supplements in Pregnancy*.<sup>12</sup>

Once the product is available as a registered product in the nation of use, it needs to be procured. Integrating a new product into the procurement system of most countries is difficult and comes with an entirely separate set of needs to landscape and plan for inclusion of MMS into that system, irrespective of the source of the product – imported or locally manufactured.

#### 4.2.2. National Considerations Informed by Country Experiences

National stakeholders may consider four models, or some combination of these, to secure access to MMS product.<sup>13</sup> Each model comes with different advantages, challenges, and cost implications for the finished product; different investment requirements by the local manufacturer; varying levels of expertise required by the local manufacturer; and a potential need for national governments to adjust regulatory requirements to permit each of the options.

- **Importation of finished product in consumer packaging** by contracting with a regional or global supplier of MMS manufacturing to internationally recognized product specifications and quality standards.
- **Full manufacturing** conformant with defined quality (both cGMP and pharmacopeial) standards, that includes procurement of ingredients (accessed locally or imported), blending ingredients, pressing and coating tablets (or creating a capsule), and packaging the tablets as a finished product for the consumer.
- **Using a pre-mix produced by another manufacturer and imported** to manufacture a finished product that meets internationally recognized quality standards.
- **Repackaging** product locally that has been fabricated by another manufacturer, meets internationally recognized quality standards, and is received (imported) in bulk.

Among these options, national stakeholders will, justifiably, seek to understand if MMS can be produced locally. Limited experience suggests no single criterion by which to answer the question whether to import MMS or manufacture it locally, but there is widespread agreement that manufacturing in any national environment is more likely to succeed if it is supported by:

- The presence of an existing pharmaceutical/supplement manufacturing base in the country with prospective manufacturers that have: i) experience producing/registering supplement products with at least 10 ingredients; ii) an ability to produce to the *Expert Consensus on an Open-Access Product Specification for MMS for Pregnant Women* or an equivalent specification; and iii) there is an effective national regulatory apparatus to ensure consistency of manufacturers' product quality.
- A sound business case for manufacturing in the target country of interest, achieved at an acceptable price point that satisfies purchaser expectations.
- National government willingness to adopt policies that incentivize adoption of the MMS formulation and supports a business case for qualified manufacturers to produce MMS. Such policies will incentivize cost-effective manufacturing for national government programs, product export to other national authorities, and encourage manufacturers and retailers to place the same product into the private sector retail market without pricing constraint.

- Local manufacturers able to demonstrate that they can generate a sufficient product volume that meets recognized quality (both cGMP and pharmacopeial) standards to satisfy at least local/national demand; and preferentially, local manufacturers with excess production capacity (that meets internationally recognized quality and cGMP standards) to allow product to be marketed and delivered into the export market.
- The existence of at least two qualified manufacturers in the domestic market to be served (to accommodate tendering rules that require at least two bidders), and a domestic market that supports annual product purchasing sufficient to support at least one million pregnancies (i.e., to assure reasonable level of manufacturing efficiency).
- Access to a product specification that helps standardize both the product and its manufacture (Note: A product specification comes with many benefits for buyers, manufacturers, and product end-users which are summarized in *Sight and Life's Special Report: Focusing on Multiple Micronutrient Supplements in Pregnancy*.<sup>14</sup>).
- Willingness of a party with a purchase order ready to commit to a procurement action. This is a critical requirement for a successful marketplace at this particular juncture in the introduction of MMS. Limited market-making and market-shaping forces are likely to persist, reinforcing a current dilemma. Governments are reluctant to switch to MMS because the product is not available, and suppliers are reluctant to invest in MMS manufacturing when the market demand is unclear or ambiguous. The current donors of MMS product will need to exert greater and more aggressive procurement coordination and collaboration to create sufficient market momentum (e.g., in the form of government procurement) before UNIMMAP MMS is available at an optimal cost and before a long-term, market-sustaining level of supply and demand exists.

Experience is beginning to show how national stakeholders can use the IS framework shown in **FIGURE 6**, and further explained in **ATTACHMENT II**, to determine the feasibility of local manufacturing vs. importation vs. a combination of options to secure MMS product supplies. The IS approach includes methods and tools to assess the feasibility of manufacturing models, including pursuit of a strategy for local manufacturing or import of MMS from regional or global suppliers. Application of this IS approach in a coordinated manner could be foundational to advancing efforts to create an overall MMS supply strategy.

### 4.2.3. Regional Considerations

Based on current manufacturers with capacity to produce MMS (identified in **TABLE 2**), progress is being made toward regional, high-volume MMS manufacturing hubs. For discussion purposes, a regional manufacturer is one that has a capacity to produce for export. If a model of using high-volume manufacturers is spread across the major markets servicing LMICs, then investments in Africa and South America could be viewed as future areas of focus (while investment continues in Asia).

Global stakeholders should consider the balance of investment between national and regional manufacturing. The donor community will likely be most attracted to investment in efforts to build capacity among 10-20 globally situated, high-volume manufacturers who can deliver on the needs for MMS product locally in the country of manufacture, and who can deliver excess product that meets internationally recognized quality (both cGMP and pharmacopeial) standards into the export market.

**TIP: Engage and encourage private sector participants to market a generic MMS tailored to private sector retail (generally, pharmacy chain) sales.** There is evidence from Bangladesh that there may be a market for private sector sales of MMS. Any strategy and investment must be directed at linking MMS manufacturers with interested companies that retail a MMS product for the private sector. An initiative to insert the MMS product into the private sector as a branded or generic product could be an important avenue to diversify the deployment of an important public health nutrition intervention while also catalyzing more manufacturing capacity.



This should not preclude investment in manufacturing for a single national market. Rather, it means that the international community's limited resources should be prioritized for the most efficient investment – generally manufacturers that can supply global/regional market needs for those countries that do not have the capacity for local manufacturing. Investment in manufacturing by local investors for a single domestic market (which requires development of a business case as is done for investment in regional manufacturing capacity) may be, under certain circumstances, a viable option.

#### 4.2.4. Global Considerations and Learnings

Extensive experience by global donors with procurement of MMS in the global marketplace yields several considerations/learnings with implications for the creation of an MMS supply strategy in both the short- and long-term. Some of the key considerations/learnings include:

- **Magnitude of the Opportunity.** There is a significant manufacturing gap to be filled to achieve full scaling of MMS and ongoing program maintenance. The annual volume of product required to meet needs of pregnant women just in LMICs eligible to use MMS is a daunting challenge – one that very few pharmaceutical products present. Even if the most capable high-volume manufacturers could be found to produce MMS, each with an ability to produce sufficient MMS product for 10 million pregnancies per year *with potential to scale*, it would still take roughly 10 manufacturers to fill the needs of all 115.2 million live births in LMICs (ex. China) that represent only about two-thirds of all pregnancies in these nations. While it is unlikely that the global market dynamics would lead to just 10 manufacturers producing MMS for all LMICs, the magnitude of the manufacturing challenge provides a basis for thinking about investment by the global (and national) community in MMS manufacturing where it will do the most good.
- **The Global Manufacturing Capacity Landscape.** There is no comprehensive landscaping of manufacturers globally completed that ascertains the full capacity and interest of manufacturers to produce MMS for the global/regional marketplace. For global stakeholders, if the objective is to stimulate availability of a larger volume of product, annually, within 3-5 years, then there is a need to assess the global/regional landscape of manufacturers. This landscaping would focus on identifying larger, experienced contract manufacturers, and comparing their capabilities to industry leaders by benchmarking, at least, their:
  - Available production capacity relative to MMS product need, recognizing that all contract manufacturers produce multiple products at any given time;
  - Ability to meet internationally recognized quality (both cGMP and pharmacopeial) standards, including an ability to demonstrate their ability to appropriately authenticate that they can meet these standards; and
  - Price/volume discount tiers – how much product must be purchased to achieve the maximum discounted price per dose.

The very limited landscaping of high-volume contract manufacturers conducted to date along with existing contracting experience implies the following:

- Few contract manufacturers have capacity to produce MMS for export in high volume. Few manufacturers contacted across 15 countries are able to produce sufficient product to support at least one million pregnancies per year (i.e., at least 180 million doses per year), and the capacity to continue to scale from one million. Manufacturing industry leaders estimate that there are at least 15-20 high-volume contract manufacturers across all major world regions that are already exporting pharmaceutical/nutraceutical products – including manufacturers from LMICs (see **TABLE 2** for current location of manufacturers) that could deliver high volumes of MMS.



- High-volume manufacturers are more likely to be able to produce to internationally recognized quality (both cGMP and pharmacopeial) standards.
- Manufacturers in LMICs respond to requests to optimize pricing in exchange for increased volume purchases, but they have not yet been able to match benchmark pricing available from manufacturers in the United States and Europe. It is anticipated that in time with ongoing purchase commitments at higher volumes, many can approach benchmark level pricing established by U.S. and European-based manufacturers.
- The open-access consensus specification gives manufacturers options to meet the technical specifications, but manufacturers entering the market may need assistance developing a product which meets the specification or in fulfilling the testing requirements associated with authenticating their compliance to the specification. Experience is beginning to show that the moment at which transfer of technical knowledge is most required is during the review/negotiations of the terms and conditions of the technical specification for the product being purchased – not during actual manufacturing. Recognized verification programs (e.g., USP Verification) are also proving valuable by providing an additional layer of technical support to first time manufacturers of MMS while assuring conformance with specifications.
- **Identification and Selection of Manufacturing Partners.** Because UNIMMAP MMS is a new product, buyers need to be particularly alert to ensure a contract is awarded to a qualified manufacturer – one that can demonstrate they have a capacity to produce the new product consistent with defined technical specifications acceptable to the purchaser. Initial experience among donors making purchases and early adopter nations embarking on purchasing is that identification of a qualified manufacturer often requires:
  - Engaging with national or regional manufacturers' associations or national regulatory agencies to identify a pool of potentially qualified manufacturers;
  - Engaging in a formal pre-qualification process; and
  - Using a competitive contracting process often in the form of a request for proposal (RFP) in which pre-qualified manufacturers are invited to bid on a specific contract.

**TIP: Pre-qualified** contract manufacturers have a high level of expertise to respond to an RFP and appear more likely to have a capacity to meet the open-access consensus specification.

Combined, these actions help purchasers to identify manufacturers that are likely to produce a product that meets defined product specifications. National governments (and donors) should not enter a contract with a producer manufacturing MMS for the first time without fully vetting the capabilities of a producer.

- **Need for Limited Technology Transfer.** Each of the manufacturing options identified in **SECTION 4.2.2** requires technical expertise/know-how; and manufacturers in LMICs may solicit a transfer of technology to achieve successful production of MMS. Full technology transfer to contract manufacturers in LMICs may not be feasible due to the cost and reluctance of established manufacturers to part with proprietary knowledge and skill that could be used beyond the manufacture of MMS.

Nevertheless, partial technology transfer is working and feasible for those using a full manufacturing approach, and in the partnership model adopted between selected MMS pre-mix suppliers and contract manufacturers with whom they partner.

Experience suggests there is need for only specific, limited knowledge transfer to experienced manufacturers to ensure a finished product meets the desired product specification. Contract manufacturers capable of high-volume production are generally a reliable, efficient, cost-effective option for sourcing incremental supplies of MMS over the short- and long-term and require the least amount of technical assistance.

Modest technical assistance enables a local manufacturer in LMICs to meet internationally recognized cGMP and pharmacopeial standards. During contract negotiations or during independent product verification, some level of technology transfer offered to manufacturers is essential to properly authenticate their ability to meet these standards, and is typically less than 1% of the purchase price of the product.

#### 4.2.5. Product Standardization and Management of Supply Quality

Product standardization is a significant requirement needed to propel uptake of MMS. Unlike IFAS which is simpler to make and able to be produced in many countries (often by many manufacturers) to local standards acceptable to national authorities, MMS is more complicated to manufacture and will likely be procured from a more limited number of manufacturers that export MMS. Governments are already seeking out product (that is interchangeable irrespective of the manufacturer) from suppliers that market/export MMS into global and regional markets. Buyers seek assurance on the quality of product purchased. Open-access product specifications and recognized verification programs can provide assurance of quality and interchangeability of MMS from different suppliers, although stakeholders need to consider ways to strengthen, manage, and monitor the quality of supplies on an ongoing basis.

Product standardization can be viewed at two levels. At a higher level, there is growing convergence by the nutrition community on:

- Default use of UNIMMAP formulation of MMS;
- Product that is in conformance with internationally recognized quality (cGMP and pharmacopeial) standards to assure product quality and interchangeability irrespective of manufacturer across regions of the world;
- Halal certification of MMS product for Muslim populations;
- Default recommendation of 180 doses for a pregnancy irrespective of how doses (e.g., tablets or capsules) are packaged (until definitive IS provides insights into specific recommended packaging);
- At least a 30-month shelf-life for product produced for export; and
- Commitment to pricing that is justifiable in relation to the known benchmark pricing for the finished product of USD 0.01-0.02 per dose, subject to inflation and other factors known to affect manufacturers' ability to meet benchmark pricing.

At a second, more granular level, there is urgent need for global agreement on a standardized product specification for UNIMMAP MMS. A product specification is a technical document for purchasers and manufacturers that provides a detailed description of the product to be manufactured. It defines the formula, including the amount and chemical form of each ingredient; the dosage format (e.g., tablet); the packaging container closure system; the tests, testing methods, reference standards, and acceptance criteria to be applied to verify quantitative label claims; stability study requirements; and any third-party certifications expected of the manufacture.

The primary function of the product specification is to support a procurement action. It serves as a basis for a quality agreement between the purchaser and the manufacturer, providing both parties with a common and transparent technical understanding of the requirements for a product to be manufactured and the means and methods by which both parties can verify that the product delivered is, in fact, the product that was ordered. For new products, the product specification is either developed by the manufacturer for the buyer or it is provided by the buyer – but in either case, it is usually considered a proprietary document unless made an “open-access” document.

Current experience suggests there is merit to promoting an open-access product specification such as the *Expert Consensus on an Open-Access Product Specification for MMS for Pregnant Women*<sup>15</sup> – to optimize benefits

for manufacturers, purchasers, and consumers of the product (and to harmonize the consensus and UNICEF product specifications). The key benefits of an open-access specification include that it:

- Provides the purchasers/donors and national authorities with a level of transparent reassurance on quality when giving or accepting product. The open-access product specification includes a provision for independent verification of product quality; however, as noted, stakeholders need to consider ways to strengthen, manage, and monitor the quality of supplies on an ongoing basis;
- Facilitates expansion of the number of manufacturers with capacity to produce MMS by levelling the playing field for entry into manufacturing for a large potential market;
- Promotes price competition from any manufacturer for the same product;
- Helps to avoid manufacturers developing different products at different price points and quality that could lead to introduction of a MMS product supply of uncertain quality into health systems;
- Increases transparency around product quality including with respect to cGMP and pharmacopeial standards; and
- For consumers, the open-access consensus specification means availability of a MMS product that is of clinically-proven effectiveness and of a consistent dependable quality because it is manufactured to an internationally accepted quality standard.

An expanded discussion of the rationale for the creation of the open-access consensus specification was published by the New York Academy of Sciences (NYAS) in 2020.<sup>16</sup> Additionally, a white paper has been developed (and is available for download<sup>17</sup>) to help interested parties understand, generally, the quality (cGMP and pharmacopeial) standards for MMS – with a focus on quality standards used in manufacturing most of the MMS product in the global marketplace today.

### **4.3. Building Effective Procurement Systems**

As key stakeholders build processes and systems to ensure sufficient MMS manufacturing capacity and standardized product development, time should be taken to ensure both government and donated product stakeholders are utilizing effective procurement systems through which to access MMS product. The following issues should be considered within procurement system development as MMS is being introduced:

- Government policies and taxes on importation of raw materials used in product manufacture or finished product for distribution may create unnecessary complexity in flow of materials/finished products and may increase the price of finished MMS goods.
- The experience for product imported for the exploration and introduction of MMS may fall under different guidelines than the registration and importation requirements for product used in full national scale-up. Government policies, rules, and regulations for both in-country manufacture and import should be reviewed during the IS process and selectively modified to ensure that delays are not incurred at the point that scaling begins.
- Government systems are generally set up to purchase established medicines (i.e., included on the national essential medicine list and readily available in the marketplace.) However, when government procurement systems need to procure a new product from a manufacturer making the product for the first time (including products requiring product development and test manufacturing that adds to the production/delivery timeline, or products that must be imported), traditional government procurement templates do not easily accommodate such transactions. This is especially so if the product is just being included in health policy, and is still in the process of being added to the essential medicines list. Undertaking procurement of these types of products likely requires identification of special procurement mechanisms or processes.

- Decision-makers and national stakeholders should recognize that a manufacturer of MMS for a single domestic market is unlikely to achieve the benchmark price at the initiation of manufacturing a new product especially where demand for MMS is to support less than one million pregnancies per year. Nevertheless, the benchmark price helps buyers and sellers understand what price can be achieved with maximum efficiency. To achieve benchmark price, manufacturers typically need to have sufficient production requirements to meet optimum batch size and efficiency. New manufacturers may be able to achieve the benchmark price for MMS as production volumes increase and manufacturing efficiency is gained. Larger, high-volume manufacturers may also have a built-in advantage in that they can achieve better pricing as a result of existing ingredient vendor relationships, and synergies that derive from capacities available because they are used in conjunction with other existing products (e.g., lab capacity).

#### 4.4. Pricing Experience for UNIMMAP MMS

**FIGURE 7** below shows the current benchmark price for the MMS product which is defined as the lowest price for MMS of fixed quality (quality consistent with internationally recognized quality standards) at a volume beyond which there is no further price reduction (using a 180-count bottle as an illustrative format only since packaging format will affect benchmark pricing). Kirk Humanitarian, which currently procures approximately 80% of the global supply of MMS, has worked for several years to establish benchmark pricing through high-volume purchases. Its purchases, consistent with the Open-Access Consensus Specification, are for a halal certified MMS that adheres to internationally recognized quality (cGMP and pharmacopeial) standards, and is verified by the United States Pharmacopoeia (packaged for shipping) at the price of USD 0.0116 per tablet when purchased in volumes of 10 million bottles or more and packaged in a 180-count bottle<sup>18</sup> – a price that is on par with IFAS on a tablet-to-tablet basis manufactured to similar, internationally recognized quality standards. This is consistent with a recent UNICEF publication that noted the range of benchmark prices for MMS as being between USD .01 to .02 per dose.<sup>19</sup>

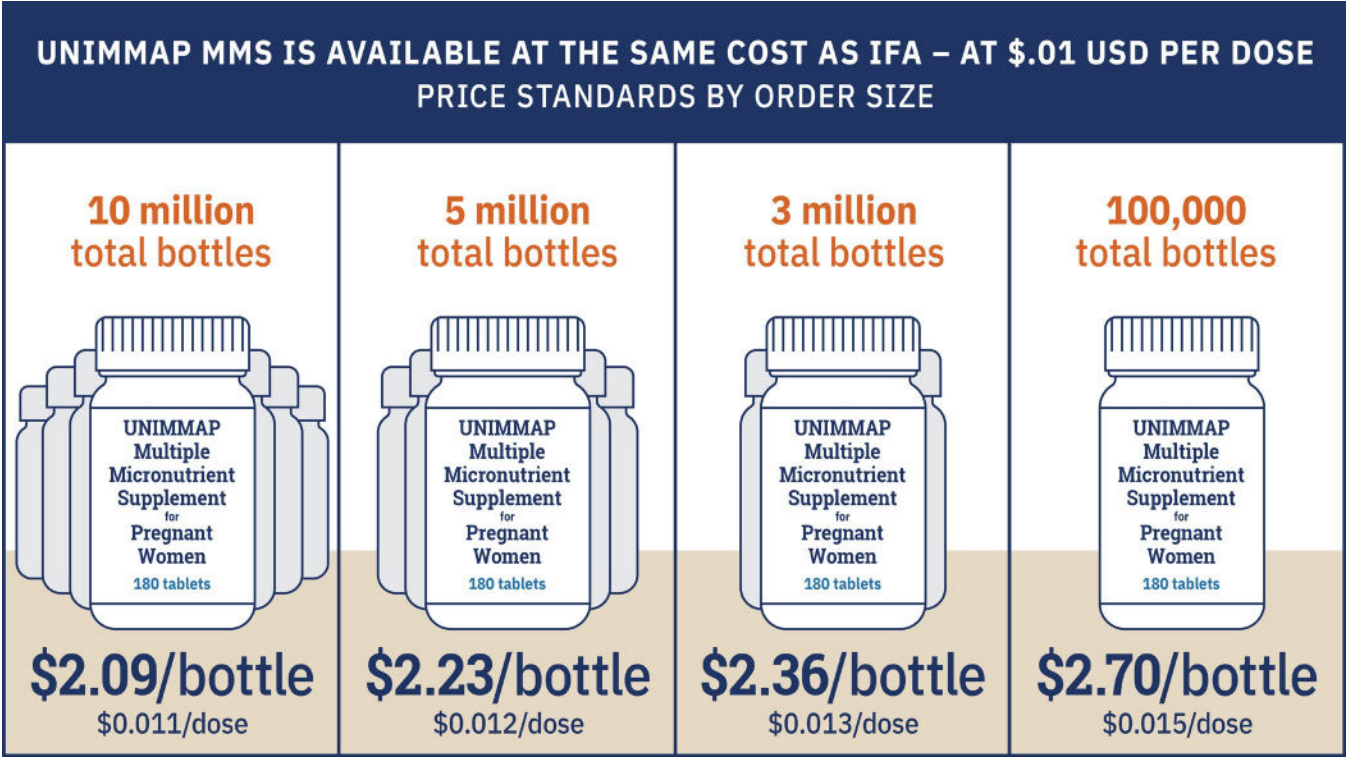
With high-volume manufacturers, Kirk Humanitarian has obtained pricing for MMS at various tiered volumes of product.<sup>20</sup> These range from USD .011 to .015 per dose, depending upon volume purchased (assuming packaged in 180-count bottles), excluding freight/taxes.

By comparison, pricing of IFAS varies widely but on average is roughly USD .010 per dose. UNICEF prices IFAS at USD 0.0078 per dose when packaged in a 100-count bottle. It is important to note, however, that IFA is not a complex product and can be and is manufactured in numerous countries. In Indonesia, for example, IFAS is manufactured locally and purchased by district health authorities in Yogyakarta at a pre-COVID cost of USD .051 per dose.<sup>21</sup>

Readers should be cautioned, however, that global experience also shows, despite the establishment of benchmark pricing for MMS, such pricing is unlikely to be achieved by **local companies producing MMS for a single domestic market** for three reasons:

- Most local manufacturers have **limits on production capacity (e.g., production slot times, or limited physical plant)** that precludes or restrains the ability to offer price discounts based on volume production;
- Most nations have **too few pregnancies per year** (less than one million) that make it very difficult to achieve manufacturing efficiency; and
- **Import taxes** on product ingredient and bulk finished product, unless waived by the government (or reduced or waived under regional trade tariff conventions), represent a significant cost factor. Put another way, import taxes unnecessarily push the cost of MMS for a government program above an optimized price (e.g., the benchmark price) regardless of whether a government is importing ingredients or finished products.

FIGURE 7. Current benchmark pricing for UNIMMAP MMS at tiered volumes





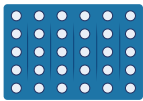
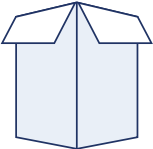


Nonetheless, it is important for stakeholders to be aware of benchmark pricing (when available, preferably for large volume purchases for the product in specific packaging format desired) when negotiating their own purchases. These challenges along with certain technical factors suggest that it may be difficult to create a viable business case for local manufacturing in many LMICs at an acceptable price point for national health systems in the absence of established, very high-volume manufacturers that compete in the global/regional marketplace. Consequently, there is a growing sense that unlike IFAS, MMS supplies will require some level of dependence upon experienced global or regional manufacturers with high-volume manufacturing capacity. This scenario, if borne out, has additional implications for both suppliers and those trying to secure product supplies.

Kirk Humanitarian and The Vitamin Angel Alliance offer their MMS product to national stakeholders for use in conjunction with introduction of MMS informed by IS. Product is provided in a 180-count bottle size with at least 30 months shelf-life; optional bottle sizes are also offered for IS that aims to identify effective implementation strategies that test different packaging configurations.

UNICEF offers their MMS product for regular health services use or in conjunction with IS, packaged primarily in 30- and 100-count bottles at the prices noted in the table below. UNICEF also provides MMS product in blister packaging in limited volume for IS studies.<sup>22</sup> Current pricing from UNICEF’s Supply Division for MMS in 30-count blister packs is listed as USD 0.037 per tablet.

FIGURE 8. UNIMMAP MMS packaging options, costs, and environmental impact

<b>UNIMMAP MULTIPLE MICRONUTRIENT SUPPLEMENTS (MMS) FOR PREGNANT WOMEN</b> <b>PACKAGING OPTIONS, COSTS, AND ENVIRONMENTAL IMPACT</b>						
						
	180 Count	100 Count	90 Count	30 Count	30 Count	Bulk <sup>1</sup>
PACKAGING FEATURES	Child-resistant cap and tamper-evident seal. HDPE bottle.	No child-resistant cap. Unknown tamper-proof features.	Child-resistant cap and tamper-evident seal. HDPE bottle.	Child-resistant cap and tamper-evident seal. HDPE bottle.	Unknown child-resistant features. Polyvinyl film with foil.	No child-resistant or tamper-proof features.
COST PER TABLET <sup>2,3</sup>	.0116 USD	.0162 USD	.0139 USD	.0217 USD	.0370 USD	.0109 USD
FINANCIAL IMPLICATIONS Per million women (per 180 doses) <sup>4</sup>	\$2,090,000	\$2,916,000	\$2,502,000	\$3,906,000	\$6,660,000 <sup>5</sup>	\$1,962,000 <sup>6</sup>
ENVIRONMENTAL IMPLICATIONS Per million women (per 180 doses) <sup>4</sup>	Total waste: 24,500 kg	Total waste: 39,120 kg <sup>7</sup>	Total waste: 39,120 kg	Total waste: 94,560 kg	Total waste <sup>8</sup> : 81,060 kg	Total waste <sup>9</sup> : 4,073 kg
ORDER INFORMATION	Visit <a href="https://cpc.com">CPC.com</a> to order.	Visit <a href="https://supply.unicef.org">supply.unicef.org</a> to order.	For implementation research purposes, visit <a href="https://KirkHumanitarian.org">KirkHumanitarian.org</a> to order. For all others, visit <a href="https://CPC.com">CPC.com</a> to order.		Visit <a href="https://supply.unicef.org">supply.unicef.org</a> to order.	Visit <a href="https://CPC.com">CPC.com</a> to order.

<sup>1</sup> Bulk amount = 40,000 tablets. MMS shipped in bulk requires repackaging for consumer use before dissemination (business-to-business (B2B) option).

<sup>2</sup> 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.

<sup>3</sup> The current recommendation for MMS dosing is 180 tablets per pregnancy beginning as early as possible.

<sup>4</sup> Data provided by Contract Pharmaceutical Corp. (CPC), 2022.

<sup>5</sup> 6 blister packs x 30 tablets per pack = 180 tablets

<sup>6</sup> Additional repackaging costs for consumer use (required before dissemination) are not included in this amount.

<sup>7</sup> 100 count bottle waste assumption based off of 90 count bottle waste amount.

<sup>8</sup> It is more difficult and costly to recycle polyvinyl film and foil when compared to HDPE bottles.

<sup>9</sup> Waste amounts are variable, contingent on both bulk configuration and required repackaging.

Data current as of September 2022



## 4.5. Other Factors Affecting Cost of MMS

Decisions about methods to administer and dispense product to pregnant women have an impact on manufacture, distribution, pricing, and the environment. **FIGURE 8** compares various packaging configurations and features, cost per tablet, environmental impact, and availability in the global marketplace.<sup>23</sup>

The packaging configuration of donated product supplies varies by donor. Experience suggests that the current range of packaging options may lead to confusion at the program level. Kirk Humanitarian and The Vitamin Angel Alliance offer their product donations in 180-count bottles primarily for national programs embarking on an evidence-based approach to introduction and scaling. This configuration was chosen to optimize cost for a high-quality product; avoid confusion on the full recommended dosing regimen for MMS; and recognize that among the hardest to reach populations, women may not be able to participate in all recommended ANC visits when re-supply with IFAS (or MMS) is often designed to occur. Kirk Humanitarian and The Vitamin Angel Alliance also provide MMS supplies in 30- and 90-count bottles if a government seeks to make direct comparisons in well-designed IS to examine other factors influencing adherence.

By comparison, UNICEF offers MMS in 30- and 100-count bottles for regular program use and a 30-count blister pack format for IS programs. Achieving an understanding among donor agencies on each agency's product packaging rationale could serve to clarify messaging that helps national stakeholders considering MMS introduction informed by IS to better understand how different product packaging configurations might fit into packaging strategies being assessed. Stakeholders need to undertake further study to determine the most effective packaging option that facilitates adherence and uptake by pregnant women, balanced against considerations of the overall program cost and environmental impact.

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## 5. Conclusion

The emerging market-shaping challenge for creating manufacturing capacity commensurate with anticipated product demand is aligning the interests of investors in manufacturing capacity with those purchasing or influencing purchasing decisions in both the near- and long-term. In this case, suppliers are reluctant to invest in MMS manufacturing when the market demand is unclear or ambiguous, and governments are reluctant to switch to MMS because the product is not available. Until investors' and purchasers' interests are coordinated, this dilemma will impede growth in product availability. The current donors of MMS product need to exert greater and more aggressive procurement coordination and collaboration to create sufficient market momentum (e.g., in the form of government procurement) before UNIMMAP MMS becomes available for sale at an optimal cost and before a long-term, market-sustaining level of supply and demand exists.

Through 2024, there is sufficient manufacturing capacity worldwide to meet product demand associated with the exploration, introduction, and scale-up of MMS. The demand is generally driven by purchases by donor entities (e.g., by Kirk Humanitarian, The Vitamin Angel Alliance, and UNICEF) that typically purchase MMS from fewer, larger-scale manufacturers able to serve both national and regional markets.

Starting in 2025, it is expected that early adopter governments will begin scaling MMS alongside ongoing and new introduction activities (including early exploration) in existing and new country settings. At this point, current manufacturing capacity will be insufficient to meet forecasted demand. The manufacturing cycle to bring a new manufacturer online is 3-5 years. New manufacturers generally will not begin product development without purchase commitments. In order to meet demand in 2025, key stakeholders should invest in advance purchase commitments now with regional manufacturers (able to serve both the domestic market in the country in which they are manufacturing and the export market) to ensure adequate capacity is available when governments are forecast to begin scaling. This model is unfolding in Indonesia and Pakistan.

Alongside the need to invest in building manufacturing capacity in preparation for 2025 demand, key stakeholders – global, regional, and national – should invest time and resources on the following:

- **Gain consensus on an overall approach for positioning, building, and allocating resources to expand manufacturing capacity that will meet short- and long-term needs.** Most LMICs do not have a capacity (i.e., either technical and/or manufacturer volume) for local manufacture of MMS, and/or a sufficient local MMS demand needed to optimize manufacturing cost-efficiency resulting in an affordable price point for governments. Using donor supplied product appears to be the most efficient way to manage and assure short-term supply needed to accommodate an IS approach to introduction – during the application of which national (and global/regional) stakeholders identify and execute a strategy to secure product to meet long-term demand. In the long-term, more manufacturers are needed to close the supply/demand gap over the next 3-5 years.
- **Build a product supply strategy to manufacture and deploy MMS commensurate with demand in 2025 and beyond.** Meeting future demand will require a combination of global/regional suppliers that can serve both domestic and export markets. Any future MMS supply strategy developed by key donors (and other stakeholders directly involved in) purchasing product or growing manufacturing capacity should be informed by a systematic landscaping of global manufacturing capability, viewed from a regional perspective. This will lead to enhanced supply/demand forecasting models.
- **Coordinate procurement and deployment of donated product supplies.** Improved coordination among groups donating available product will accelerate opportunities to activate exploratory initiatives and plan and activate MMS introduction while making more efficient use of available product supplies.
- **Identify and activate strategies to finance both incremental advance purchases by existing donors to expand product availability and anticipated regular purchases by governments scaling their transition from IFAS to MMS.** Financing of product manufacturing is emerging as an issue given existing donors are not expected to significantly scale their purchases in the next 2-3 years. After 2025, incremental financing is projected to be needed to grow the supplies of donated product. Additionally, as governments begin to scale their transition from IFAS to MMS, individual nations importing product will need financing or access to foreign exchange to make their initial purchases until their procurement systems transition to purchase MMS.
- **Acknowledge the importance of achieving a common approach to producing MMS that regularly meets quality standards.** Effort is needed, starting with the current donor agencies that procure MMS, to align on product specifications for the MMS tablet, regional standardization that benefits trade among regional partners, a common approach to building quality into product development and manufacturing, developing an approach to ongoing supply management, and technical engagement with key high-volume manufacturers. Such actions could speed product availability and lower costs while optimizing benefits for manufacturers, purchasers, and consumers.

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## 6. Recommended Next Steps

The authors recommend one or more meetings of key global stakeholders (e.g., UNICEF, Kirk Humanitarian, and The Vitamin Angel Alliance) to begin discussions and identify more formal action steps that could involve a larger number of stakeholders organized around or focused on specific interest areas (e.g., regional regulatory bodies that harmonize standards, manufacturers, etc.). The initiatives below are provided as a general outline of discussion topics and considerations for future meetings and action.



1. **Fully embrace the implementation science (IS) framework, including Supply Context Assessments as a standard way to inform national strategy to secure MMS product supplies.** Applying IS provides national governments with ample opportunity to introduce MMS in a manner conformant with WHO's current (and evolving) context-specific recommendation (and UNICEF's interim guidance) to use MMS in the context of rigorous research. The MMS – TAG hosted by the New York Academy of Sciences is currently working to create a harmonized and practical IS framework based on the earlier work of multiple agencies to guide such initiatives and is anticipated to be published in 2023.<sup>24</sup> The IS approach can also be applied to address the issues pertaining to securing MMS supplies. Using an evidence-based approach to introduction (including landscaping of existing national supply readiness, and awareness-raising and consensus-building activities) can identify optional strategies for testing to secure long-term MMS supplies while short-term product supplies needed for IS are met through product donations.
2. **Undertake a systematic landscaping of global/regional manufacturing capability.** Any consensus strategy to create sufficient MMS manufacturing capacity will require a systematic landscaping of global manufacturing capacity, including in LMICs, to identify countries where there exists a meaningful pharmaceutical and/or nutritional supplement manufacturing base onto which MMS manufacturing can be built.
3. **Collaborate for consensus for a minimum level of product standardization and a consensus approach for assuring product quality.** This includes availability of a public (open-access) product specification (possibly created by harmonizing the existing consensus product specification for UNIMMAP MMS and the UNICEF product specification); default use of UNIMMAP formulation; conformance with internationally recognized quality (cGMP and pharmacopeial) standards to assure product interchangeability irrespective of manufacturer across regions of the world; halal certified product for Muslim populations; default recommendation of 180 doses per pregnancy with access afforded to alternative packaging count for IS projects; at least a 30-month shelf-life for product intended for export; commitment to pricing that is justifiable in relation to the current benchmark pricing for the finished product of about USD 0.01 per dose, and commitment to use of independent verification services to ensure that product produced conforms to label claims.
4. **Undertake enhanced supply/demand forecasting to create a more robust forecasting model.** To make forecasting more accurate, investment is needed to create a more robust forecasting model and tool that identifies (or estimates) the number/percentage of annual pregnancies, by country, that are served by the public sector vs. the private sector, and more accurate estimation of product required for IS initiatives by country. While there is a good deal of information about supply and demand forecasting from early adopter nations that will assist planning for the next few years, there is a need for a more robust analysis of global MMS supply and demand that takes account of: i) anticipated coverage among each nation's population of pregnant women who will be served by the national health services; ii) potential for a private sector role in deploying MMS; and iii) more exacting analysis of qualified manufacturers and their probable ability to scale manufacturing once established.
5. **Develop a strategy to finance the transition by national governments from IFAS to MMS.** Building a sustainable, global manufacturing supply implies a long-term commitment to financing product purchases. It is a reasonable assumption that some significant portion of the funds spent on IFAS will be transitioned to purchases of MMS. Governments will need time to adjust their policy, regulatory framework, and procurement mechanisms to accommodate MMS purchases that can eventually sustain a global manufacturing base, while still serving their populations with IFAS and a growing scale of MMS. Financing mechanisms need exploration given the ranking associated with MMS as among the most important and impactful nutrition interventions.<sup>25</sup>

6. **Gain consensus on an overarching regional supplier development strategy that secures an available, accessible supply of MMS that synchronizes national needs and capabilities with global/regional resources.** The global donor community can bring value by expressing, discussing, and shaping a more coordinated approach to secure and deploy MMS product supplies in both the near-term and long-term. The most effective way to catalyze manufacturing development is to make firm advance purchase commitments targeting both existing regional suppliers with an ability to expand their manufacturing capacity and new regional suppliers. Development of a supply strategy by key stakeholders willing to invest in advance purchase commitments should include discussion of:
- Product standardization and product verification;
  - Policy interests by national LMIC governments for incentivizing local businesses to grow export markets for MMS;
  - Identification of objective criteria that can predict when local manufacturing can be successful;
  - The role for regionally situated high-volume contract manufacturers in LMICs well-positioned to service the potential target population of pregnant women in their region;
  - The need to provide resources (and avenues for channelling resources) to underwrite the costs of local landscaping and assessments needed by the national government to determine the capability of local manufacturers to play as a national or regional supplier; and
  - Avenues for providing limited technical assistance during the contracting stage to ensure compliance with product standards.
7. **Encourage deployment of branded and/or generic MMS products through private sector channels such as retail pharmacy chains and social marketing schemes.** Such an effort could mitigate the total cost of introduction and maintenance; bolster sustainability, availability, and accessibility; provide opportunities to further address consumer preference and convenience; lead to improved segmentation of the market and thereby better manage limited subsidies; and create increased demand through additional and complementary channel support.

# ATTACHMENT I: MMS EVIDENCE

The United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) Multiple Micronutrient Supplement (MMS) for Pregnant Women is a nutritional supplement containing 15 vitamins and minerals formulated as shown in **Figure 1**.<sup>26</sup>

Micronutrient (vitamin and mineral) deficiencies are common among women in low- and middle-income countries (LMICs) due to inadequate dietary intake.<sup>27,28</sup> These deficiencies are magnified during pregnancy due to the increased nutrient requirements to maintain women’s health and fetal development.<sup>29,30</sup>

UNIMMAP MMS is the only MMS product repeatedly demonstrated to be efficacious for improving maternal health and pregnancy outcomes through extensive clinical trials in multiple country settings. Two decades of randomized controlled trial research demonstrates that UNIMMAP MMS is proven efficacious, safe, and cost-effective.<sup>31</sup>

Examination of results of these studies and several secondary analyses of their results,<sup>32,33</sup> shows many benefits accrue to pregnant women (and their infants) who use UNIMMAP MMS during pregnancy in place of IFA alone. Pregnant women using UNIMMAP MMS experience improved health and reduced risk of a range of pregnancy outcomes including stillbirth, mortality in infants at 6-month of age, low birth weight, pre-term birth, and small for gestational age. The reduction in risks for these pregnancy outcomes are even more favorable among pregnant women who are anemic or underweight.

Based upon an examination of these results and secondary analyses, the World Health Organization (WHO) issued an update to its 2016 antenatal care guidelines (ANC) in 2020 entitled: *WHO antenatal care recommendations for a positive pregnancy experience. Nutritional interventions update: Multiple micronutrient supplements during pregnancy*.<sup>34</sup> The updated guidelines provide a context-specific recommendation for the use of UNIMMAP MMS that supersedes the 2016 WHO ANC guidance.<sup>35</sup>

Building on WHO’s updated recommendations, leading implementing and advisory agencies, including UNICEF, the Micronutrient Forum, the MMS – Technical Advisory Group (an advisory group hosted by New York Academy of Sciences), Nutrition International, and The Vitamin Angel Alliance created further interpretive guidance for country-level decision-makers in the form of *Interim Country-level Decision-making Guidance for Introducing Multiple Micronutrient Supplementation for Pregnant Women*.<sup>36</sup> This guidance focuses on country-level decision-making to operationalize introduction of UNIMMAP MMS in the context of ANC services, informed by implementation science (IS).

In October 2021, WHO placed UNIMMAP MMS on the WHO Model Essential Medicines List (EML).<sup>37</sup> Prior to this designation, its formulation was recognized and recommended for “emergency use.”<sup>38</sup>

The updated or new policy guidance from WHO and UNICEF taken together with available supplies of product from key donor agencies as described in this paper; and a wave of advocacy, knowledge-sharing, tools development, collaboration, and emerging lessons from early adopter nations – provide support and information to national governments considering the introduction of UNIMMAP MMS.

**FIGURE 1. UNIMMAP Composition**

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

## Why UNIMMAP MMS is the Default MMS Product Used in National Health Systems

1. **UNIMMAP MMS is purpose-built for use by pregnant women.** At the time that randomized controlled trials were begun to examine the efficacy of MMS as compared to IFAS for improving pregnancy outcomes, there was no single multiple micronutrient supplement formulation recommended for use in clinical trials beyond IFAS. In the absence of a recommended formulation, many of the early clinical studies assessing the benefit of MMS on pregnancy outcomes opted to use supplements that included various configurations of micronutrients to compare to IFAS. Some of the early clinical studies used an MMS with only a few micronutrients; others used an MMS preparation with 10 or more micronutrients.

In 1999, a panel of experts was assembled jointly by UNICEF, WHO, and the United Nations University for the specific purpose of creating a standardized multiple micronutrient supplement for pregnant women that could be used in future clinical trials.<sup>39</sup> The micronutrient formulation devised was the United Nations International Multiple Micronutrient Antenatal Preparation or “UNIMMAP MMS” for short. More than half of all the randomized controlled trials completed used the UNIMMAP MMS formulation to compare with IFAS.

UNIMMAP MMS is the only MMS product repeatedly demonstrated to be efficacious for improving pregnancy outcomes through extensive clinical trials in multiple country settings. Two decades of randomized controlled trial research demonstrates that UNIMMAP MMS is proven efficacious, safe, and cost-effective.<sup>40</sup>

2. **UNIMMAP MMS is different than and superior to most commercially available prenatal multivitamins and minerals.** Because UNIMMAP MMS is often perceived to be unavailable, national stakeholders who are anxious to derive the benefits of UNIMMAP MMS in a national program consider using a locally produced and available product that is “similar” to the UNIMMAP formulation of MMS. The MMS – Taskforce and its successor body, the MMS – Technical Advisory Group (MMS – TAG) have both discussed defining an MMS product that is “similar” to UNIMMAP MMS to give wider latitude to decision-makers in national programs.<sup>41</sup> Yet, both groups concluded that it is not feasible to define what “similar” means – if the goal is to help proponents of “similar” products claim that any MMS can deliver the result that is delivered by UNIMMAP MMS in randomized controlled trials. To date, the default position is that where decision-makers decide to introduce MMS, UNIMMAP MMS should be the selected formulation because it has been repeatedly demonstrated to be efficacious, safe, and cost-effective through numerous well-designed randomized controlled trials. Those MMS formulations that stray from UNIMMAP cannot claim to deliver the same results as UNIMMAP MMS for improving birth outcomes. The UNIMMAP formulation is, by default, the standard MMS formulation to be used in public health nutrition programs for pregnant women in LMIC settings.<sup>42</sup>
3. **UNIMMAP MMS is now listed on the WHO Model Essential Medicines List, and its formulation has been recognized and recommended for “emergency use” for decades.** The UNIMMAP formulation of MMS was added to the WHO Model Essential Medicines List in October 2021 and has been recognized by the WHO and UNICEF since it was established in 1999. WHO and the World Food Programme recommend UNIMMAP MMS for “emergency use,” meaning for nutritionally vulnerable pregnant and lactating women as well as young children who do not have access to sufficient fortified foods needed to avert or prevent micronutrient deficiency.<sup>43</sup> Importantly, the circumstances defined in “emergency use” persist and have only been exacerbated by the COVID-19 pandemic.
4. **UNIMMAP MMS is a preventive intervention that can be used with confidence even while global research continues to improve upon the current formulation.** There is considerable and animated discussion by the research community about adding new ingredients to improve upon UNIMMAP MMS. Some believe that introduction of UNIMMAP MMS might best be delayed until an “improved” or more perfect version of UNIMMAP MMS has been created.

While the current UNIMMAP MMS supplement is not a magic bullet, it is accepted as an additional and highly effective tool in a range of other public health nutrition interventions that can result in better health and well-being for pregnant women and their infants. UNIMMAP MMS is demonstrated to reduce the risk of adverse pregnancy outcomes significantly more than IFAS – especially among pregnant women who are anemic or underweight – including low birth weight, preterm birth, small for gestational age, and infant mortality at six months.

**FIGURE 2** shows the percent risk reduction for key adverse pregnancy outcomes when using MMS versus IFAS during pregnancy (both for the general population of pregnant women and among pregnant women who are anemic or underweight).

#### **REDUCE THE RISK OF STILLBIRTH**

- By 8% in the overall population of pregnant women
- By 21% in the group of anemic pregnant women

#### **REDUCE THE RISK OF MORTALITY AMONG 6-MONTH INFANTS**

- By 29% in the group of anemic pregnant women
- By 15% in female infants

#### **REDUCE THE RISK OF LOW BIRTH WEIGHT (<2500 g)**

- By 12% in the overall population of pregnant women
- By 19% in the group of anemic pregnant women

#### **REDUCE THE RISK OF PRETERM (<37 WEEKS) BIRTH**

- By 8% in the overall population of pregnant women
- By 16% in the group of underweight women

#### **REDUCE THE RISK OF BEING BORN SMALL-FOR-GESTATIONAL AGE**

- By 3% in the overall population of pregnant women
- By 8% in the group of anemic pregnant women

Nevertheless, it is important to recognize the need for ongoing research. One issue that illustrates this need is the question of whether the amount of iron contained in UNIMMAP MMS is adequate. While IFAS with 60 mg of iron has been the standard of care in national settings known to experience severe and possibly even moderate anemia, UNIMMAP MMS has only 30 mg of iron. Over the past year, the MMS – TAG has reviewed this issue. Based upon actual performance of UNIMMAP MMS in randomized clinical trials, it remains that UNIMMAP MMS is a safe and effective preventive intervention that improves pregnancy outcomes; and that pregnant women residing in areas with severe anemia do not experience worse pregnancy outcomes when using UNIMMAP MMS as compared to women using IFAS with either 30 or 60 mg of iron. **Figure 3** presents a more complete description of this issue, including conclusions of the MMS – TAG on the issue of adequacy of the amount of iron in the UNIMMAP MMS formulation.<sup>44</sup>

#### **FIGURE 3.**

An issue that has given some pause to the widespread introduction of the UNIMMAP formulation of MMS is that it contains 30 mg of iron, while IFAS often contains 60 mg of iron. Recognizing that: i) not all anemia is a result of iron deficiency, ii) that there are significant levels of iron deficiency anemia in many LMICs, and iii) many LMIC health systems recommend 60 mg of iron for pregnant women – there is a legitimate question as to whether the UNIMMAP formulation with 30 mg of iron is adequate for universal use in LMICs experiencing severe levels of anemia. The rationale for adopting a UNIMMAP MMS with 30 mg of iron is:

- WHO’s recommendation is that pregnant women should receive, preventively, 30-60 mg of iron, and UNIMMAP MMS complies with that recommendation;
- Clinical trials show that pregnancy outcomes are not adversely affected by the differential amounts of iron in UNIMMAP vs. IFAS;
- If a pregnant woman is found to be experiencing severe anemia (a condition that should be screened for routinely in antenatal care), and it is due to iron deficiency, it should be dealt with through treatment which requires a much larger dose of iron than that contained in either IFAS or UNIMMAP MMS (UNIMMAP MMS and IFAS are recommended as preventive interventions, not treatment interventions);
- Not all anemia is caused by iron deficiency and adding more iron to UNIMMAP MMS will not reduce anemia attributable to conditions unrelated to iron status, and could be associated with other adverse health consequences; and
- Unlike IFAS, UNIMMAP MMS contains other micronutrients (e.g., vitamin C, vitamin A, and riboflavin) that increase absorption and/or utilization of iron, which may explain why the lower amount of iron in UNIMMAP formulation remains adequate for prevention of iron-deficiency anemia.

The MMS – TAG has taken up this issue (and other clinical/technical issues that pertain to UNIMMAP MMS as they are raised). Results from a re-analysis of data from randomized controlled trials undertaken under the guidance of the MMS – TAG’s secretariat suggests that there is no disadvantage to maternal anemia outcomes because of differential iron dosing. A formal paper has been published in the *Annals of the New York Academy of Sciences*.<sup>45</sup> The paper’s authors found that “the overall effect of MMS vs. IFA on third trimester maternal anemia and iron related outcomes does not seem to be modified by baseline levels of anemia. We also found no differences for any of the outcomes when the analysis was limited to the studies that provided MMS with 30 mg of iron vs. IFA with 60 mg of iron”.

A second study published in *Public Health Nutrition* analyzed the effects of MMS vs. IFA on neonatal mortality within subgroups of studies categorized by dose of iron provided by the supplements (varying between daily doses of 20 mg and 60 mg in both formulations.) The authors reanalyzed published data from 13 trials included in the 2020 WHO guidelines, and while doing so, uncovered methodological issues that were corrected. The adjusted analysis found that:

- There were no statistically significant differences in neonatal mortality between MMS and IFA within any of the subgroups. When data from the 2020 WHO analysis was extracted and corrected, there was no increase in risk of neonatal mortality with MMS, regardless of iron dose in either supplement.
- Providing MMS with 30 mg of iron during pregnancy likely results in little or no difference in neonatal mortality, when compared to IFA with 60 mg of iron. A transition from IFA containing 60 mg of iron to MMS containing 30 mg of iron would not adversely affect neonatal mortality.

While the authors conclude that additional research is needed to firm up the conclusions on iron deficiency anemia, they suggest that policymakers proceed with the transition from IFA to MMS “because MMS with 30 mg of iron influenced hemoglobin with clinically comparable results to IFA with 60 mg iron, and because MMS significantly improves fetal growth and survival, especially in anemic women.” There are also additional benefits of MMS when compared to IFA in the risk reduction of stillbirth, infant mortality at 6 months, low birthweight, preterm birth, and being born small-for-gestational age, with greater risk reductions among anemic pregnant women.



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## ATTACHMENT II: IMPLEMENTATION SCIENCE APPROACH AND IDENTIFYING AN EFFECTIVE STRATEGY FOR SECURING MMS SUPPLIES

The 2020 update to WHO ANC guidelines specifically recommends that introduction of UNIMMAP MMS should be informed by “rigorous research.” For national decision-makers seeking to introduce UNIMMAP MMS, “rigorous research” means application of implementation research – as a component of an implementation science (IS) approach<sup>46</sup> or an evidence-based approach to introduction that can include well-designed pilot or demonstration programs – to support effective implementation.

IS serves to identify and understand enablers and barriers to program implementation, and to shape and test possible strategies to achieve successful implementation of an intervention through a systematic, iterative process.<sup>47</sup> Unlike efficacy research which addresses whether a specific intervention works in highly controlled settings, IS helps to identify which implementation strategies can ensure that scaling of a program will be impactful in a particular national setting.

While application of IS provides a general approach to identify and test effective strategies to deliver MMS in any given setting, IS can also help to identify and test effective strategies to secure MMS product supplies for national programs. With regard to securing product supplies, IS provides a roadmap to:

- Examine the key question of whether a government should opt to manufacture UNIMMAP MMS locally, import it, or employ some combination of both approaches,
- Identify, inform, and test alternate strategies to secure product supply, and
- Facilitate initial product supply and demand forecasting.

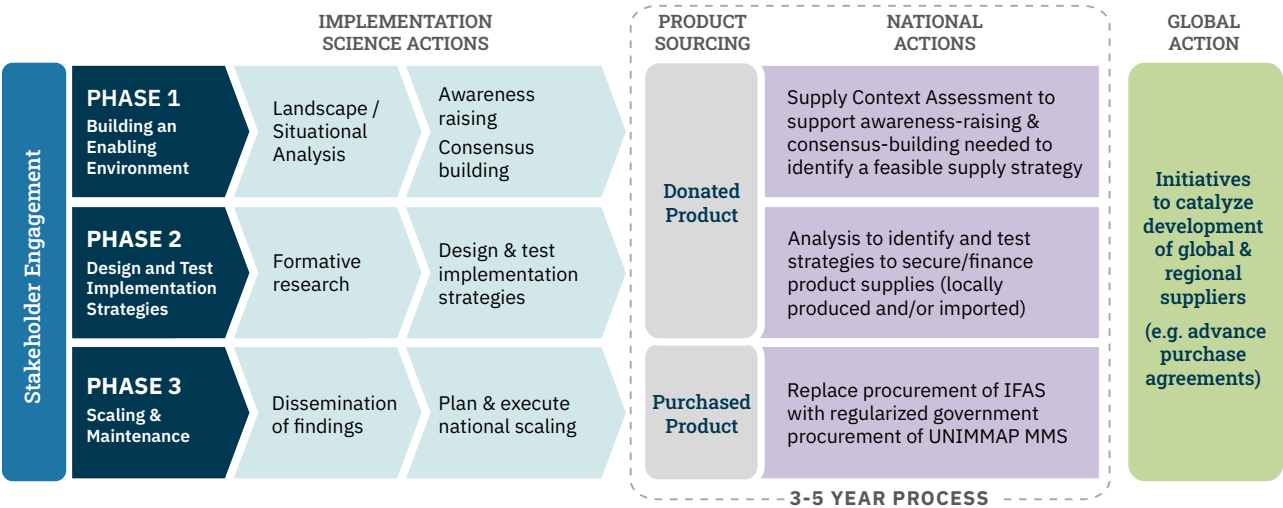
Application of IS to the issue of securing product supplies ultimately assists national stakeholders to achieve two key objectives:

1. Identify key issues, in the form of enablers and barriers, that influence the ability of a health system to secure access to a sustainable supply of MMS product. This objective is accomplished largely through activities undertaken to create an enabling environment (Phase 1 of the IS model) as described below.
2. Synchronize MMS product supplies with both program introduction and subsequent national scaling. This objective is accomplished by using the information gathered in Phase 1 to inform actions and activities in Phases 2 and 3 of the IS model (Identifying and Testing Sourcing Options, and Scaling, respectively).

Consistent with an IS approach, **FIGURE 1** shows a generic IS model illustrated to show key actions and activities needed to secure access to UNIMMAP MMS product supplies in conjunction with each of the model’s three phases, including:

- **Phase 1: Building an enabling environment.** During this phase, national programs are presumed to source donated UNIMMAP product supplies to support short-term product needs for identifying and testing effective strategies to deliver MMS. The actions and activities necessary to secure UNIMMAP MMS product supplies for long-term needs of scaling and maintenance of MMS use in the health system should start with a landscape analysis (i.e., in the form of a supply context assessment – SCA) of the environment into which UNIMMAP MMS product supplies are being introduced. The analysis results will inform subsequent actions and activities designed to raise awareness among key influencers and decision-makers (individuals within academia, government, and the NGO sector) about the supply environment, and to gain consensus on the enablers, barriers, and possible options to secure product availability and access.

**FIGURE 1. Model for synchronizing product supply with different phases of program implementation**



Product availability/accessibility is universally viewed as a rate-limiting factor impeding adoption of an MMS policy and implementing services. A central issue for national stakeholders is determining how product supplies can be secured to sustain services over the long-term; including whether local manufacturing is feasible or if some level of importation will be required. To respond to these questions, phase 1 activities (i.e., national actions in **FIGURE 1** associated with phase 1 IS) include:

- **Conduct a supply context assessment** (SCA) that examines the environment into which UNIMMAP MMS is being introduced – with a focus on identifying enablers and barriers faced by the national health services to secure and deliver product supplies. A key outcome of the SCA is gaining an understanding of the comparative advantages, limitations, and feasibility of local manufacturing vs. importation for securing access to UNIMMAP MMS over the long-term. The SCA toolkit includes modularized questionnaires to guide interviews with key informants to collect this information. Originally developed by *Sight and Life*, it was further adapted (and expanded upon) by Kirk Humanitarian in collaboration with The Vitamin Angel Alliance to focus on achieving **government** access to an available and sustainable supply of UNIMMAP MMS. The SCA focuses on examining four elements relevant to secure and finance product supply, including:
  - » Government Policy and the Regulatory Framework Affecting MMS Use. This module of the SCA focuses on identifying the policy/legal and regulatory challenges that can impede use, local manufacture, and importation of UNIMMAP MMS. For example, what regulatory issues might present if UNIMMAP MMS is to conform to national regulatory standards and be registered locally; understanding the procedures for local approval and registration of a new product; and how UNIMMAP MMS is to be regulated (e.g., as a dietary supplement, as a food, or a therapeutic product).
  - » Manufacturing Sector. This module focuses on providing a high-level understanding of whether to even consider local manufacturing as an option. For example, what is the universe of local manufacturers, are there local manufacturers already producing an MMS product, and which production scenarios might work for existing manufacturers (i.e., manufacturing by purchasing and blending raw ingredients, using a pre-mix, or simply re-packaging product made by another manufacturer).
  - » Government Procurement and Distribution Systems. This module focuses on the capacity of the ministry of health’s procurement system to purchase an entirely new product that is not on the national formulary, what pathways exist for local purchase of a product that may not be produced



locally and may need to be imported by a local agent; how the government procures products not available locally (directly or through a third party); what is the process for integrating a new product into the national formulary (e.g., the national essential medicines list) and into the procurement system; what is the **cost-benefit** of UNIMMAP MMS relative to IFAS for the nation (e.g., by using Nutrition International's cost-benefit calculator); what are the budgetary implications for introducing UNIMMAP MMS in place of IFAS; and understanding how to incorporate the purchase of UNIMMAP MMS into the budget.

- » Current Marketplace Characteristics for MMS Products. This module focuses on understanding the MMS products already available by surveying the local marketplace to ascertain whether and which MMS products are being sold in the private sector; whether any existing MMS products contain 10 or more ingredients (an indication of manufacturer capability); whether these products (assessed by testing of locally produced products) are conformant with locally recognized quality and GMP standards and existing product label claims; and whether existing manufacturers are meeting local and/or internationally recognized quality and GMP standards needed to support product export.
- **Raise awareness** to various supply realities, advantages, and challenges as derived from landscaping activities (including application of the SCA) and their implications for local product manufacturing, product importation, and/or application of some combination of strategies.
- **Build consensus** (based on objective information) around one or more potential strategies for investment that can result in securing long-term product supplies.
- **Phase 2: Design and test implementation strategies.** During this phase, national programs are presumed to continue accessing donated UNIMMAP product supplies needed to support short-term product needs for identifying and testing effective strategies to deliver MMS. Actions and activities in this phase (i.e., national actions in **FIGURE 1** associated with phase 2 IS) aim to help decision-makers to understand which strategies (e.g., a range of local manufacturing options vs. importation) can secure long-term UNIMMAP MMS product supplies for scaling and maintenance of MMS use in national health services. This phase focuses on:
  - **Formative Research on Manufacturing.** Key information is gathered by identifying the universe of local manufacturers, conducting a “**pre-qualification**” process to engage with manufacturers to assess their capabilities, and then comparing the results to sourcing from international vendors. This investigation examines options for local manufacturing (e.g., local repackaging only, use of pre-mixed ingredients that local contract manufacturers can press into finished product, or full manufacturing including blending of ingredients by the manufacturer, tablet pressing and coating, and finished packaging), and assesses whether the technical capacity exists among a segment of the universe of local manufacturers to undertake local manufacturing. It also determines whether local manufacturing capacity alone can realistically suffice to fill national needs or whether a combination of national production plus importation may be required. For purposes of comparison between a local manufacturing options and importation, the investigation should examine in granular detail how the government ordinarily procures product that is not manufactured locally (if not completed during implementation of the SCA) – including any challenges or impediments to sourcing from overseas. During this examination, it is generally possible to understand the level of technical assistance specific manufacturers may need to activate new, local manufacturing.
  - **Identify and Test Supplier Models.** In this activity, investigators develop a comparative business case analysis for local manufacturing vs. importation. As part of the business case development or separately, investigators should examine the feasibility of generating sufficient local investment capital to develop and produce a new product to defined quality standards.

There are two important additional lines of action that are useful during this phase 2:

- » First, if a variation of local manufacturing is deemed feasible, a trial procurement action should be taken to engage (via an **RFP** and **trial contracting**) one or more manufacturers to develop, test, and register a commercial product. Irrespective of the preferred strategy for accessing a product (i.e., local manufacturing or importation), the process of purchasing must result in timely product delivery in Phase 3. It is assumed that Phases 1 and 2 product needs will be met with imported product (donated or in certain circumstances purchased by or for a government from a global manufacturer). Trial procurement is important because most government procurement systems are generally set up to purchase established medicines (i.e., included on the national essential medicine list and readily available in the marketplace.) When government procurement systems need to procure a new product from a manufacturer making the product for the first time (including products requiring development and test manufacturing that add substantially to the production/delivery timeline, or product that must be imported), traditional government procurement templates do not easily accommodate such transactions. This is especially so if the product is just being included in health policy, and is still in the process of being added to the essential medicines list. Undertaking procurement of these types of products likely requires identification of special procurement mechanisms or processes. While a trial procurement can take a substantial amount of time to organize the first time, it can advance the time to product availability substantially and create a template for future procurement actions with one or more established suppliers of MMS. This template for procurement can then be integrated into the government's procurement system during Phase 3 when large quantities of MMS supplies will be needed to support scaling and ongoing maintenance of MMS as a part of regular antenatal care services.
- » Second, it is important to engage in, as appropriate, additional IS activities to identify and test strategies that may affect product manufacturing decisions prior to its purchase. For example, it may be important to understand whether and which consumer preferences (e.g., packaging type or tablets per package, etc.) influence manufacturing decision-making; or whether the ability of the national health services to instruct health care providers in social behavior change communications reduces the need for specialized packaging.
- **Phase 3: Scaling the intervention.** This phase is used to disseminate the findings from earlier phases, plan for national scaling, and activate efforts to scale. Regarding securing product, trial procurement started in Phase 2 is delivered as Phase 3 begins. Phase 3 focuses on regularizing/scaling product purchases using whichever supply strategy (or combination of strategies) is proven effective based on Phase 2 activities by:
  - Issuing routine procurement/purchase orders for UNIMMAP MMS product; and
  - Scaling purchase orders to ensure procurement is synchronized with program expansion and maintenance.

While national actions are being undertaken, national stakeholders can take some comfort that simultaneously, global stakeholders are likely to continue taking steps (i.e., Global Actions) to catalyze global and regional suppliers of UNIMMAP MMS to ensure that national governments have suppliers to whom they can turn to purchase UNIMMAP MMS if national manufacturing is not feasible.

All national actions (shown in **FIGURE 1**) required to ensure long-term supplies of UNIMMAP MMS are currently estimated to require a 3–5-year period to achieve.

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- <sup>1</sup> Countries included: Cambodia, Democratic Republic of Congo, Haiti, Indonesia, Mexico, Pakistan, Philippines, and South Africa.
- <sup>2</sup> Source materials include unpublished reports and interviews generated from activities undertaken in the context of an implementation science framework, including:
- National awareness-raising activities including one-on-one meetings, large group meetings, and official national and regional meetings of MMS stakeholders.
  - Landscaping and associated in-country debriefing/consultation meetings for awareness-raising and consensus building conducted in Cambodia, Democratic Republic of Congo, Haiti, Indonesia, Mexico, and Philippines by the respective governments with technical assistance from local teams supported by The Vitamin Angel Alliance, and/or Helen Keller International.
  - Supply Readiness Assessment (SRAs) or Supply Context Assessment (SCAs) conducted in Cambodia, Indonesia, Mexico, Philippines, and South Africa by the respective governments with technical assistance jointly from remote teams supported by Sight and Life, and/or by local teams supported by The Vitamin Angel Alliance and/or Helen Keller International.
  - SRAs or SCAs results considered during meetings conducted (to examine these results) by the respective governments or a government designated MMS Taskforce in Indonesia, Cambodia, and Vietnam with technical assistance from local teams supported by The Vitamin Angel Alliance, and/or Helen Keller International.
  - Manufacturer pre-qualification conducted in Indonesia and the United States by Kirk Humanitarian and/or The Vitamin Angel Alliance.
  - MMS Market Shaping Strategies, Recommendations for Scale-up. The Bill & Melinda Gates Foundation. March 2022.
- <sup>3</sup> World Health Organization, United Nations University & United Nations Children's Fund (UNICEF). (1999). Composition of a multi-micronutrient supplement to be used in pilot programmes among pregnant women in developing countries: report of a United Nations Children's Fund (UNICEF), World Health Organization (WHO) and United Nations University workshop. UNICEF. Available for download at: <https://apps.who.int/iris/handle/10665/75358>
- <sup>4</sup> All relevant clinical efficacy trials comparing IFAS to MMS are identified in: Bourassa, M.W., Osendarp, S.J.M., Adu-Afarwuah, S., Ahmed, S., Ajello, C., Bergeron G., et al. (2019). 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*, 1444(1), 6–21. Available for download at: <https://doi.org/10.1111/nyas.14121>
- <sup>5</sup> Awareness-raising and consensus-building activities in Indonesia have led directly to specific implementation research to examine how social behavior change communications can minimize the need to offset consumer preferences for packaging appeal in an effort to reduce the product cost and environmental impact of packaging.
- <sup>6</sup> Healthy Mothers Healthy Babies. World Map of MMS Activities: <https://hmhbconsortium.org/world-map/>
- <sup>7</sup> Data sources include:
- 2020 Population Data used in certain calculations is derived from UN resources that were accessed from: <https://population.un.org/wpp/Download/Standard/Population/>
  - 2020 Crude Birth Rate Data used to calculate annual numbers of pregnancies in each country is derived from UN resources that were accessed from: <https://population.un.org/wpp/Download/Standard/Fertility/>
  - Income Group and UN Development Group data were accessed from:
    - <https://population.un.org/wpp/Download/SpecialAggregates/EconomicTrading/>
    - <https://datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html>
    - <https://unctad.org/topic/least-developed-countries/list>
- <sup>8</sup> Ibid, note 1.
- <sup>9</sup> In Haiti and Indonesia.
- <sup>10</sup> Guttmacher Institute. (2019). Adding it up: investing in sexual reproductive health 2019. Available for download at: <https://www.guttmacher.org/report/adding-it-up-investing-in-sexual-reproductive-health-2019>
- <sup>11</sup> Communications with Kirk Humanitarian.
- <sup>12</sup> Sight and Life. (April 2020). Expert Consensus on an Open-access Product Specification for Pregnant Women; Special Report: Focusing on Multiple Micronutrient Supplements in Pregnancy, pp 102-108. Available for download at: <https://kirkhumanitarian.org/wp-content/uploads/2020/04/Expert-Consensus-on-an-Open-Access-UNIMMAP-MMS-Product-Specification.pdf>
- <sup>13</sup> Sight and Life. (2020). Procurement and Production of Multiple Micronutrient Supplements for Pregnant Women. Available for download at: [https://kirkhumanitarian.org/wp-content/uploads/2020/04/SightandLife\\_SpecialReport\\_MMS\\_2020-1.pdf](https://kirkhumanitarian.org/wp-content/uploads/2020/04/SightandLife_SpecialReport_MMS_2020-1.pdf)
- <sup>14</sup> Ibid, note 12.

- <sup>15</sup> Sight and Life. (2020). Expert Consensus on an Open-Access UNIMMAP-MMS Product Specification, 2020(3), 102–108. Available for download at: <https://kirkhumanitarian.org/wp-content/uploads/2020/04/Expert-Consensus-on-an-Open-Access-UNIMMAP-MMS-Product-Specification.pdf>
- <sup>16</sup> The Multiple Micronutrient Supplement Technical Advisory Group (MMS-TAG) & The Micronutrient Forum (MNF). (2020). Expert consensus on an open access United Nations International Multiple Micronutrient Antenatal Preparation–multiple micronutrient supplement product specification. *Annals of the New York Academy of Sciences*, 1470(1), 3–13. Available for download at: <https://doi.org/10.1111/nyas.14322>
- <sup>17</sup> Atwater, J. B. (2020). Understanding Product Quality As Applied to UNIMMAP–MMS Product Donated by Kirk Humanitarian. [https://kirkhumanitarian.org/wp-content/uploads/2020/10/KirkHumanitarian\\_ProductQualityWhitePaper\\_9.28.pdf](https://kirkhumanitarian.org/wp-content/uploads/2020/10/KirkHumanitarian_ProductQualityWhitePaper_9.28.pdf)
- <sup>18</sup> Kirk Humanitarian has publicly disclosed that it has engaged in at least 3 contracts since 2018 with Contract Pharmacal Corporation (New York, New York) to deliver a finished, packaged product in 180-count bottles for a contractual price of \$2.09 per bottle or roughly a U.S.\$0.116/tablet.
- <sup>19</sup> UNICEF. (January 2022). UNICEF Programming Guidance. Maternal Nutrition: Prevention of malnutrition in women before and during pregnancy and while breastfeeding. Available for download at: <https://www.unicef.org/media/115361/file/Maternal%20Nutrition%20Programming%20Guidance.pdf>
- <sup>20</sup> These are the current actual contract prices offered by the most efficient contract manufacturers already producing UNIMMAP MMS.
- <sup>21</sup> Pricing quoted throughout this document is as of the time of preparation of this report and is subject to change. For current pricing of UNICEF products cited in this document, see the UNICEF supply catalog with can be found at: <https://supply.unicef.org/>
- <sup>22</sup> UNICEF. (n.d.). UNICEF Supply Catalog. <https://supply.unicef.org>
- <sup>23</sup> Ibid, note 30. Kirk Humanitarian 2021.
- <sup>24</sup> In publication, personal communications with New York Academy of Sciences.
- <sup>25</sup> What works? An update of the evidence for addressing maternal & child undernutrition in: The Lancet Series on Maternal and Child Undernutrition in Progress, 2021.
- <sup>26</sup> Ibid, note 3.
- <sup>27</sup> Black R.E., C.G. Victora, S.P. Walker, et al. (2013). Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* **382**: 427–451. Available for download at: [https://doi.org/10.1016/S0140-6736\(13\)60937-X](https://doi.org/10.1016/S0140-6736(13)60937-X)
- <sup>28</sup> World Health Organization. (2005). Vitamin and mineral requirements in human nutrition, 2nd ed. World Health Organization. Available for download at: <https://apps.who.int/iris/handle/10665/42716>
- <sup>29</sup> King J.C. (2000). Physiology of pregnancy and nutrient metabolism. *Am. J. Clin. Nutr.* **71**: 1218–1225. Available for download at: <https://doi.org/10.1093/ajcn/71.5.1218s>
- <sup>30</sup> Berti C., H.K. Biesalski, R. Gärtner, et al. (2011). Micronutrients in pregnancy: Current knowledge and unresolved questions. *Clin. Nutr.* **30**: 689–701. Available for download at: <https://doi.org/10.1016/j.clnu.2011.08.004>
- <sup>31</sup> Ibid, notes 3, 5, and 9.
- <sup>32</sup> Keats, E. C., Haider, B. A., Tam, E., & Bhutta, Z. A. (2019). Multiple-micronutrient supplementation for women during pregnancy. The Cochrane database of systematic reviews, 3(3), CD004905. <https://doi.org/10.1002/14651858.CD004905.pub6>
- <sup>33</sup> Bourassa, M.W., Osendarp, S.J.M., Adu-Afarwuah, S., Ahmed, S., Ajello, C., Bergeron G., et al. (2019). 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*, 1444(1), 6–21. Available for download at: <https://doi.org/10.1111/nyas.14121>
- <sup>34</sup> World Health Organization (2020). WHO Antenatal Care Recommendations for a Positive Pregnancy Experience. Nutritional Interventions Update: Multiple Micronutrient Supplements during Pregnancy. Available for download at: <https://www.who.int/publications/i/item/9789240007789>
- <sup>35</sup> World Health Organization. (2016). World Health Organization Recommendations on Antenatal Care for a Positive Pregnancy Experience. <https://www.who.int/publications/i/item/9789241549912>
- <sup>36</sup> UNICEF, Johns Hopkins Bloomberg School of Public Health, Micronutrient Forum, Multiple Micronutrient Supplementation in Pregnancy – Technical Advisory Group, Nutrition International, and The Vitamin Angel Alliance (2020). Interim Country-Level Decision-making Guidance for Introducing Multiple Micronutrient Supplementation for Pregnant Women. Available for download at: <https://www.nyas.org/media/23298/012721-mms-guidance-v11.pdf>
- <sup>37</sup> World Health Organization (2021). World Health Organization Model List of Essential Medicines, p. 53. Available for download at: <https://apps.who.int/iris/bitstream/handle/10665/345533/WHO-MHP-HPS-EML-2021.02-eng.pdf>

<sup>38</sup> UNICEF. Recommendation is available for download at: <https://www.who.int/publications/m/item/WHO-WFP-UNICEF-statement-micronutrients-deficiencies-emergency>

<sup>39</sup> Ibid, note 1.

<sup>40</sup> Ibid, notes 3, 5, and 9.

<sup>41</sup> The MMS – Taskforce was funded by The Bill & Melinda Gates Foundation to help address technical issues cited by WHO for which data from clinical trials existed, but analysis was not done. The MMS – Taskforce was hosted by the New York Academy of Sciences (NYAS). The MMS – Technical Advisory Group (MMS – TAG) is the successor body of the MMS – Taskforce, and is also funded by the Gates Foundation and hosted by NYAS. Its role has been to focus on addressing the scientific/technical/clinical issues that arise from implementation experiences by developing and providing consensus information with respect to these issues for implementing agencies, and by identifying for the global research community, areas of inquiry that might yield promising clinical information.

<sup>42</sup> Ibid, note 3.

<sup>43</sup> Joint statement by the World Health Organization, the World Food Programme, and the United Nations Children’s Fund: Preventing and controlling micronutrient deficiencies in populations affected by an emergency.

<sup>44</sup> Bourassa, M.W., Black, R., Christian, P., et al. (2022). Multiple micronutrient supplements versus iron-folic acid supplements and maternal anemia outcomes: an iron dose analysis. *Annals of the New York Academy of Sciences*. Available for download at: <https://doi.org/10.1111/nyas.14756>

<sup>45</sup> Ibid, note 44.

<sup>46</sup> Tumilowicz, A., Ruel, M.T., Gretel, P., Pelletier, D., Monterrosa, E.C., Lapping, K., et al. (2019). Implementation Science in Nutrition: Concepts and Frameworks for an Emerging Field of Science and Practice. *Current Developments in Nutrition*. Volume 3, Issue 3, March 2019. Available for download at <https://academic.oup.com/cdn/article/3/3/nzy080/5129139>

<sup>47</sup> Ibid, note 46.



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