

Task Force on Multiple Micronutrient Supplementation in Pregnancy, Meeting 2

Reported by Hallie Kapner

Overview

On April 17-18, 2018, The New York Academy of Sciences and the Bill & Melinda Gates Foundation convened the second meeting of a task force comprised of experts in nutrition, public health, economics, and statistics, to begin formulating operational guidance for countries considering replacing iron-folic acid (IFA) supplements for pregnant women with multiple micronutrient supplements (MMS). During the two-day meeting, the group reviewed an updated analysis of evidence used to formulate the 2017 WHO guideline on the use of MMS in pregnant women, considered several cost-benefit analyses comparing iron-folic acid and MMS supplementation, and examined the factors that influence policymakers' decisions on supplementation programs. The task force developed an initial framework for developing a set of guidance materials for countries considering implementing a new MMS supplementation program or switching from IFA to MMS within an existing program.

Task Force Participants

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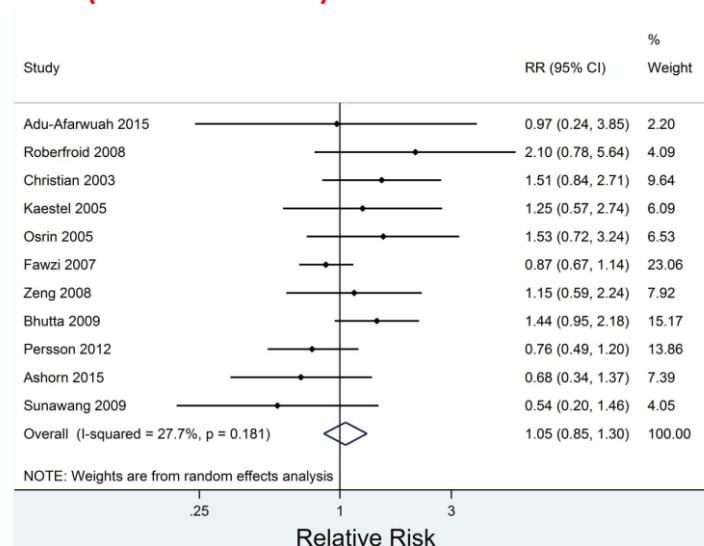
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I. Re-Analysis of WHO Statement on Neonatal Mortality Risk and Review of Adherence (MMS vs IFA)

At the first task force meeting, participants reviewed a new meta-analysis of individual patient data from 17 randomized trials of MMS in pregnant women in LMICs. The analysis, presented by **Chris Sudfeld**, focused on effect modifiers of MMS on mortality and birth outcomes, and found no increased risk of stillbirth or other mortalities associated with MMS compared to IFA. Rather, it revealed significant benefits of MMS, including a 15 percent reduction in mortality during the first year of life for female neonates, and reduced incidence of low birth weight (LBW) and small for gestational age (SGA) in babies born to anemic mothers. Data from these same trials were included in the meta-analysis conducted by WHO as part of the development process for current ANC guidelines, which cites “some evidence of risk” of neonatal mortality associated with MMS among trials which used an iron-folic acid (IFA) comparator consisting of 60 mg iron and 400 µg folic acid.

Re-analysis among all MMS trials with a 60 mg IFA comparator

RR: 1.05 (95% CI: 0.85-1.30) – No evidence of increased risk



In this second meeting, Sudfeld presented the results of that re-analysis, which showed no increased risk of neonatal mortality among all trials using an IFA comparator group of 60 mg of iron. These findings are aligned with the 2017 Cochrane review of multiple micronutrient

supplementation for pregnant women¹, which also determined that MMS poses no increased risk of neonatal mortality.

Sudfeld also presented a brief overview of adherence data from four major trials, which showed no difference in overall compliance between MMS and IFA. Sudfeld commented that these similarities in adherence are evidenced in trial conditions only, and that a “real-world” assessment of compliance will likely yield different results.

II. Cost-Effectiveness and Cost-Benefit Analyses: Comparing MMS and IFA

The task force examined issues related to implementation of MMS programs. Several presenters shared cost-effectiveness and cost-benefit analyses of transitioning from IFA to MMS. While each participant approached the subject differently and analyses were preliminary, a similar theme surfaced in all analyses: MMS appears to be a cost-effective alternative to IFA and offers significant incremental benefits.

Luz Maria De-Regil delivered the first of three presentations on these topics. According to De-Regil, many policymakers in LMICs understand that low birth weight and maternal anemia are significant issues, yet they hesitate to transition from IFA to MMS as a means to address them. This reluctance can be attributed to a lack of fully understanding the benefits of MMS by policy makers, such as the 12% reduction in the risk of LBW with MMS over IFA demonstrated by the Cochrane Review. However, policy makers are more aware that MMS is estimated to be two to four times the cost of IFA. In this case, cost-effectiveness and cost-benefit analyses are critical tools to help policymakers re-evaluate the potential gains of switching from IFA to MMS. While these analyses are in the early stages and data gaps exist, the task force considered the preliminary results of three countries to determine cost-effectiveness and cost-benefit data for MMS.

De-Regil’s analysis focuses on Pakistan, Bangladesh, and India— countries with a high burden of low birth weight, stunting, and maternal anemia, with Pakistan and Bangladesh showing a higher degree of policy readiness in considering MMS as an alternative to IFA. For each country, researchers simulated the impact of switching from a supplement with 60mg of iron and 400µg of folic acid to the UNIMMAP supplement of 30mg iron, 400µg of folic acid and 13 other vitamins and minerals. The hypothetical intervention included 270 tablets for six months of

¹ Haider BA, Bhutta ZA. [Multiple-micronutrient supplementation for women during pregnancy](#). *Cochrane Database Syst Rev*. 2017, Issue 4.

pregnancy and 3 months of postpartum supplementation, and assumed a best-case scenario of 95 percent coverage. The team modeled the cost-effectiveness of this intervention on nine birth outcomes included in the 2017 Cochrane review of multiple micronutrient supplementation in pregnant women, in terms of DALYs. A deterministic model was built to estimate the averted DALYs for each health outcome with a probabilistic analysis to determine whether MMS will yield higher health benefits than IFA supplementation.

Results of the preliminary analysis, due to be completed later this year, show that while the costs associated with MMS—which include the supplement itself, along with program and transition costs—are higher than IFA supplements, the incremental benefits are significant in terms of DALYs averted. Preliminary data indicate that MMS has the potential to avert up to 50 percent more DALYs per 100,000 pregnancies per year in some countries studied, compared to IFA. De-Regil emphasized that MMS falls well within WHO parameters for cost-effectiveness, as measured by cost per DALY averted relative to GDP per capita.

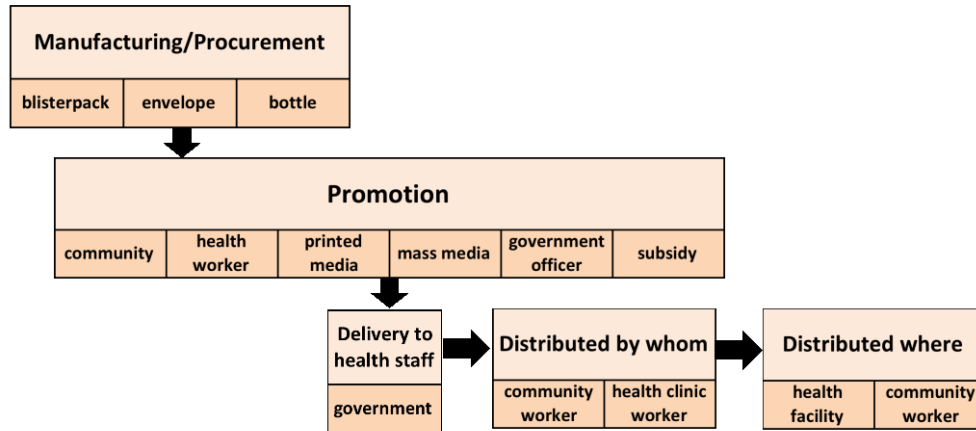
Estimating the Cost-Benefit and Cost of Delivery Channels for IFA and MMS

Anuraj Shankar presented an analysis of the costs associated with transitioning the delivery channels currently used for IFA distribution to MMS, including incremental costs in manufacturing and procurement (including packaging), promotion, distribution to healthcare providers and facilities, and delivery to pregnant women. Delivery channel data from 27 countries were pooled and analyzed to create a series of typologies of service delivery, each representing the various ways countries currently deliver IFA. Countries were clustered by commonalities in the delivery channels used in each country.

Shankar and his collaborators estimated the current costs of each typology for IFA, then derived an estimate for the relative increase of switching to MMS for each typology. Overall, the cost of transitioning to MMS was approximately 1.5-2 times higher than existing costs for IFA, which Shankar explained was driven by multiple factors, such as the type of packaging currently used for IFA.

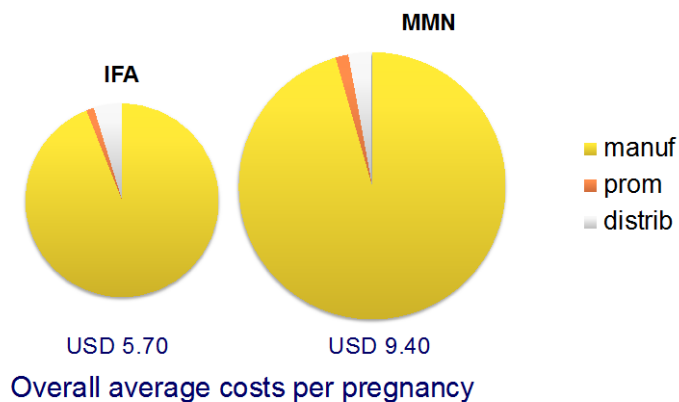
For the 27 countries studied, Shankar estimates the cost of IFA at \$5.70 USD per pregnancy for 270 pills, and MMS at \$9.40. The biggest cost drivers for both supplements is manufacturing, although Shankar noted that in the analysis of individual delivery channel typologies, costs associated with healthcare staff and community workers involved in supplement distribution contributed the highest incremental cost in switching from IFA to MMS.

Conceptual Framework for Delivery Channels



2 | Typologies and costs of delivery channels for MMS | April 17, 2018

IFA vs MMS delivery channels and costs



3 | Typologies and costs of delivery channels for MMS | April 17, 2018

In an effort to develop cost estimates for other countries, the researchers tapped existing data on the economic and developmental characteristics of countries around the world to arrive at five country classifications, or clusters, based on poverty, malnutrition, productivity, and other economic indicators. They mapped the costs associated with the various delivery channel typologies for each category of countries to arrive at cost averages for IFA and MMS for each

developmental cluster. Costs for delivering IFA and MMS were higher in the more developed countries, mainly due to the complexity of delivery channels, Shankar explained.

The research team estimated productivity gains based on the reductions in stillbirth and low birth weight associated with MMS as reported in the 2015 Cochrane review². Gains ranged from 7.5-25 percent, with the benefit to cost ratio of the former at 1.66, and the latter at 5.29. Shankar explained that even with attractive benefit-cost numbers, many countries remain hesitant to switch from IFA to MMS due to low adherence. “When policymakers consider an IFA program a failure, MMS is seen as a more expensive failure,” he said. Yet further modeling by Shankar and his team show that even at 40, 60, or 80 percent adherence, the benefit to cost ratios for MMS remain acceptable.

Modeling the Marginal Costs and Benefits of Switching from IFA to MMS

Steve Vosti shared preliminary data from an analysis that aimed to estimate the marginal costs, benefits, and cost-effectiveness of shifting from IFA to MMS. Using Bangladesh as a sample country, Vosti’s analysis represents the costs associated with replacing IFA with MMS for all pregnant women for 2018—approximately 3 million pregnancies.

Vosti’s calculations account for raw material and production costs for IFA and MMS, as well as procurement, urban and rural shipping and handling, and storage. It is especially important to note that the cost is enormously dependent on packaging, scale and location of production, which vary significantly from country to country. In line with other analyses, overall costs for MMS are approximately double to four times those for IFA, depending on the amount of iron included in IFA and the formulation of MMS. Vosti applied the estimated cost of delivering 180 tablets of IFA and MMS, respectively, to all pregnant women in Bangladesh for one year, with aim to expand the analysis to include multiple years as part of the complete analysis. Vosti and his team modeled the impact of each intervention on selected natural outcomes including stillbirth, LBW, VLBW, preterm, very preterm and SGA to determine the cost per effect gained.

Vosti explained that this exercise was merely the first step in creating a spreadsheet-based model that would allow developing countries to project the transition costs of switching to MMS over an eleven-year timeframe. Further refinements to the model are needed, but future iterations of such tools will be critical for giving policymakers a customized snapshot of the cost implications and benefits of switching to MMS in their own country. The model will have a wide

² Haider BA, Bhutta ZA. [Multiple-micronutrient supplementation for women during pregnancy](#). *Cochrane Database Syst Rev*. 2015 Nov 1;(11):CD004905.

range of practical uses from being able to replicate similar scenarios in the context of other developing countries, for urban or rural settings, with the ability to address effect modification within strata, to examining the effect of various marketing strategies on production costs.

Moving forward, Vosti and his collaborators plan to increase the robustness of the model, incorporating morbidity and mortality data, transition costs, and projections of which costs are likely to remain static and may decrease as distribution and promotional channels become established. Some challenges to resolve include, identifying a target dose for women, coverage and adherence assumptions, and how best to deal with heterogeneous effects, such as maternal anemia. The model used for this demonstration assumed 100 percent adherence, but future models will allow users to capture the impact of varying levels of adherence on the cost per effect gained.

Limitations to Current Cost Analyses

The analyses presented all reinforce that MMS is cost-effective compared to IFA in terms of DALYs, productivity, and birth outcomes avoided. However, presenters and task force participants acknowledged significant limitations to these analyses. Further research may resolve some limitations, while others are likely to persist. **John Hoddinott** led a discussion to identify the challenges and refine a path forward.

Supplement costs

While all data suggest that MMS is roughly twice the cost of IFA, the actual numbers (many unpublished, thus not included in this report) vary widely. Packaging (blister pack, bottle) and the format of the supplement (tablets, capsules) impact this cost, along with the composition of supplement itself. Participants noted that some ingredients in the UNIMMAP formulation contribute significant expense— notably vitamins C and E—yet it is not known whether or to what degree reducing the dosage of these ingredients may impact cost or benefit. The duration of supplementation also impacts programmatic costs. The hypothetical interventions presented used either 270 or 180 pills, but little is known about the minimum duration or adherence level required to achieve the benefits reported in trials. The discussions noted that key production factors are not included in the current cost estimates for MMS – specifically that only small volumes of MMS are currently being purchased (i.e., to date, mainly for research studies), and that substantial cost savings in MMS per tablet unit costs can be expected when volume purchasing is undertaken. UNICEF and Vitamin Angels are the only organization currently purchasing the UNIMMAP formula MMS. UNICEF’s MMS product is about twice the cost of IFA tablets on a per tablet basis – but a large portion of that “price,” which they quote to donors or

those purchasing from UNICEF for national programs is higher than the cost of manufacturing. Vitamin Angels purchases of the same product that UNICEF purchases, and its actual purchase price has been at about the same cost as what is cited in this document for IFA tablets. All cost studies and cost-effectiveness/cost-benefit studies need to reflect upon how to incorporate pricing derived from volume purchasing, not just estimates of costs or costs to research studies. Nevertheless, even without such analysis, as noted in the De-Regil presentation: *“incremental benefits are significant in terms of DALYs averted. Preliminary data indicate that MMS has the potential to avert up to 50 percent more DALYs per 100,000 pregnancies per year in some countries studied, compared to IFA – showing that MMS falls well within WHO parameters for cost-effectiveness, as measured by cost per DALY averted relative to GDP per capita”*. Thus, as volume pricing is achieved, the cost-effectiveness and cost benefit ratios will only improve.

Adherence

The impact of adherence on both cost and benefit is an area that requires further research. Adherence in trial environments is likely higher than real-world adherence, and the upper and lower boundaries of the relationship between adherence and benefit are not known. As one participant noted, if benefits can be realized with lower dosages of some micronutrients, a shorter course of supplementation (90 or 180 pills), or adherence well below the high levels reported in studies, the impact on program cost would be significant.

Programmatic costs

These analyses also considered the costs associated with promotion and healthcare provider and consumer education, which would contribute significantly to the process of switching from IFA to MMS. However, these costs have not been quantified, nor is it known whether education and promotional costs would remain static or decrease as MMS programs become well-established.

Reduction in mortality and cognitive benefits

No existing cost-benefit analysis accounts for the longer-term cognitive benefits of MMS, as this is an evolving area of research. The reductions in 6-month mortality among babies born to anemic women and the significant reductions in first-year mortality for female infants are also not currently factored into cost analyses; the UCD team will address these shortcomings in the near future. These benefits may have a significant impact on the cost-benefit ratio of MMS compared to IFA.

III. Implementation Considerations, Supply Issues, and Demand Generation

Implementation Questions and Issues for Decision-Makers

Clayton Ajello shared a collection of key questions facing policymakers and stakeholders considering implementing or expanding MMS programs based upon 6 years of MMS deployment by Vitamin Angels, which now reaches about 500,000 pregnant women each year and is to reach 2.5m in 2019. Vitamin Angels, which partners directly with governments and NGOs that supply and deliver MMS supplements to pregnant women in more than 70 countries through 1300 partner organizations, suggested that the task force create a document answering some of these frequently-asked questions based on the evidence of MMS benefits and the experiences of countries with MMS programs already in place.

Policymakers' questions and areas of concern include:

- **WHO Recommendation and Evidence Base:** Decision-makers often turn first to WHO guidelines when considering health interventions, and the lack of a WHO recommendation for MMS can be a considerable hurdle to adoption of MMS. Absent a WHO recommendation, policymakers seek country-specific, non-technical, practical summaries of evidence supporting MMS use in place of IFA, an understanding of expected MMS costs and expected benefits (both initial start-up costs and operating costs). An explanation of what is the meaning of the WHO non-recommendation, and what are the gaps in information that lead WHO to a “no” recommendation are important.
- **Technical Assistance and Training:** The availability of technical assistance, including access to technical resources and training, is a common concern among decision-makers. This includes accessing pragmatic advice on how to decide or what criteria to use to decide if MMS should be considered for deployment absent a WHO recommendation, designing an MMS demonstration program to examine operational issues that can inform large scale implementation, scaling an existing program, and developing or localizing monitoring & evaluation, learning, and performance support materials for healthcare staff and community workers.
- **Supply and Procurement:** Policymakers often do not know how to source UNIMMAP or other MMS from global suppliers or how to evaluate feasibility of local manufacturing and procurement. Among the few countries that have capacity to produce their own MMS, quality control and maintaining supply are ongoing issues. Even countries that procure IFA or MMS from a global supplier experience quality issues, supply shortages and delivery delays, which can in turn, impact demand, adherence, and benefits of supplementation. Supply chain issues prompt policymakers to seek technical assistance

on best practice. For example, policymakers want to know the optimal packaging format (e.g., bottle, strip, etc.), packaging volume (i.e., number of MMS tablets to deploy at one time to individuals), information on whether packaging has an effect on return antenatal care visit compliance, what is the optimal number of MMS tablets to take or maximize impact on birth outcomes, and on a range of other supply and procurement-related issues.

- **Delivery and Adherence:** Ajello noted that in many countries, IFA delivery is inconsistent and widely considered ineffective; yet as reinforced during many of the presentations, the impact of MMS, if adopted, will likely hinge on MMS acceptance and adherence. Particularly in light of the *perceived* incremental cost associated with MMS, policymakers are interested accessing technical assistance for the purpose of improving the performance of existing delivery platforms and strategies for boosting adherence.

Ajello added as a matter of information, Vitamin Angels currently sources MMS tablets from two suppliers, one of whom is also used by UNICEF. Both of VA's suppliers meet pharmaceutical-grade production standards and produce supplements that comply with the USP *Oil-and Water Soluble Vitamins with Minerals* monograph. VA's MMS tablets are based on the UNIMMAP formulation; and about 90% of VA's supply will be USP verified by January 2019. VA's MMS product has a 36-month shelf life, and is currently supplied in bottles of 180 tablets (with desiccant). VA is prepared to provide MMS supplies to qualifying government programs and NGO partners, free of charge for the product and negotiated terms for shipment.

Demand Generation: Lessons from IFA Programs

Rolf Klemm led a discussion of the barriers and enablers of individual/household demand generation, which he suggests should inform the guidance documents the task force is developing for countries considering MMS. "There's no end to demand generation as long as there are pregnant women with micronutrient deficiencies that aren't being resolved," said Klemm, noting that the same lack of demand and inefficient distribution platforms that impair the success of IFA programs will also impact MMS without ongoing efforts to change the paradigm.

Klemm reviewed unpublished data from studies of IFA delivery through ANC platforms in Uganda, where despite the fact that more than 90 percent of women receive one ANC visit and 60 percent receive IFA, less than 10 percent of women take 30 or more tablets. Similar studies in India yielded slightly better but still suboptimal coverage, with just 12 percent of women taking 90 or more IFA tablets.

A review³ of the primary motivations among pregnant women for seeking antenatal services reveal that ANC clinics are often a less than ideal platform for distribution of either IFA or MMS. Women typically visit an ANC clinic to address pregnancy concerns or to confirm a pregnancy, not to obtain vitamin supplements. A study of time allocation by healthcare practitioners in Tanzania⁴ shows that the *least* amount of time during ANC visits is spent on “health education and counseling,” which is widely viewed as a critical component of teaching women the benefits of IFA or MMS and encouraging adherence.

“We have to think very carefully about the kind of priority MMS would get if it is embedded in this delivery platform,” Klemm said. “Whether it’s improving delivery or demand, or substituting IFA for MMS, just doing what we’ve been doing hasn’t led to a lot of change in most countries.”

Qualitative research among pregnant women in seven LMICs⁵ highlight additional barriers to both individual/household demand generation and adherence, notably a low perceived risk of anemia, a reluctance to disclose pregnancy in the first trimester, inconsistent availability of a local practitioner to prescribe IFA (or MMS), and a lack of credibility among community volunteers who distribute IFA.

Supply considerations

Supply issues impact coverage and adherence to IFA, and as there are fewer manufacturers of MMS tablets, product access at both the country and local level is a significant concern among decision-makers and pregnant women. **Alison Fleet** of UNICEF briefed the task force on the organization’s supply strategies for MMS.

UNICEF sources multiple micronutrient supplement tablets from two long-term suppliers, both of whom meet stringent pharmaceutical-grade production standards and produce supplements that comply with the USP *Oil-and Water Soluble Vitamins with Minerals* monograph. Fleet

³ [Overcoming Barriers to Effective Maternal Anemia Interventions during Antenatal Services in Uganda](#). USAID Micronutrient Program (MOST), 2002.

⁴ von Both C, Flessa S, Makuwani A, et al. [How much time do health services spend on antenatal care? Implications for the introduction of the focused antenatal care model in Tanzania](#). *BMC Pregnancy Childbirth*. 2006 Jun 23;6:22.

⁵ [Siekman K, Roche M, Kung'u JK, et al. Barriers and enablers for iron folic acid \(IFA\) supplementation in pregnant women](#). *Matern Child Nutr*. 2017 Dec 22.

noted that MMS tablets supplied by UNICEF are based on the UNIMMAP formulation, which is unique among multiple micronutrient supplements. Despite previously stated concerns about the comparatively shorter shelf life of MMS tablets, Fleet confirmed that the product supplied by UNICEF has a 36-month shelf life, identical to that of IFA tablets. It is currently available in bottles of 100 or 1000 tablets.

Supply of MMS tablets can be erratic, mostly due to relatively low public-sector demand and fluctuations in healthcare funding, which can cause production delays and shortages. Fleet explained that higher, steady demand would likely remedy these challenges and perhaps prompt an expansion in the number of MMS producers. In line with previous estimates, the cost of UNICEF's MMS product is twice the price of IFA, driven by higher raw material, manufacturing, and packaging costs.

Fleet and other task force participants noted that MMS are not included in the WHO Model List of Essential Medicines (EML), which may be considered both an inhibitor as well as an enabler to MMS adoption and adherence. Absent a WHO recommendation for MMS, its inclusion in the EML could add credibility and help attract funding and support for countries wishing to switch from IFA to MMS. Local markets are seen as essential in ensuring MMS supply, and the task force agreed that local production may be encouraged under certain circumstances (of which assuring a minimum local demand volume is critical ensure reasonable cost since volume determines cost per unit), although quality control is likely to be an ongoing challenge. Providing a range of acceptable micronutrient amounts may allow countries some leeway in providing the amount desired for their population, but creating tailor-made MMS formulations may delay the distribution process by years.

Implementation Discussion

Regardless of existing supplementation programs for pregnant women, LMICs considering a switch from IFA to MMS face a similar set of concerns and challenges: the lack of a WHO recommendation, low coverage and adherence to IFA outside of trial environments, limited insights about the drivers of individual/household demand, and a lack of technical assistance to begin an MMS program or facilitate a transition from IFA to MMS.

Ajello and Klemm stressed the need for a marketing-inspired approach to demand generation, with efforts to develop an evidence-based “hook” for pregnant women synchronized with efforts to reinforce the supply chain and expand training services for health personnel. “You can

create demand, but without coordinated efforts the services won't be there to support it," said Klemm. "If you create demand, you need to simultaneously improve supply."

The group agreed that a two-tiered approach to supply is necessary, with both public (including both government and NGO sectors) and private sectors providing supplements sourced from global suppliers initially with the addition of local suppliers based on local assessment of need and supply quality factors. Participants also acknowledged the need to encourage countries to look beyond the ANC clinic setting for distribution of supplements to pregnant women, as the barriers that prevent women from seeking early antenatal care can also prevent them from accessing IFA or MMS. The task force agreed to create a concise, non-technical document for decision-makers to address frequently-asked implementation questions.

Considerations in Bangladesh and Madagascar

Prof. Dr. Habibe Millat, a physician and member of the Parliament in Bangladesh, offered a first-hand perspective of the decision-making process in countries considering MMS implementation. Bangladesh has nationally representative data showing high prevalence of micronutrient deficiencies beyond iron deficiency, along with a high burden of low birth weight, neonatal mortality, and SGA. Millat detailed the country's multi-year plans for addressing malnutrition and improving maternal-child health, which include IFA and calcium supplementation and social behavior change efforts.

Millat emphasized that he and other policymakers give considerable weight to WHO recommendations when reviewing healthcare interventions, and that the cost of interventions is less of a factor amid persuasive evidence of benefit. He acknowledged that despite the evidence base for MMS— which includes data from one of the largest trials comparing IFA and MMS (JiVitA-3), conducted in Bangladesh— the lack of a WHO recommendation may hinder a pilot project in the country, although it was not deemed impossible. Millat also noted that little is known about coverage and adherence to IFA in Bangladesh, and that most women who receive ANC care do not seek it until the second or third trimester. Devising a strategy and materials for raising awareness of the benefits of MMS through public channels including the media; training healthcare providers and community health volunteers to communicate about MMS; and exploring distribution platforms outside of the ANC system were listed as essential tasks for an MMS pilot in Bangladesh.

Jumana Qamruddin and Lisa Saldanha of the World Bank shared perspectives on the factors that could influence the likelihood of an MMS pilot in Madagascar, one of the world's poorest

countries and the focus of a major World Bank investment and initiative package to reduce stunting over ten years. The Malagasy government currently provides IFA for 90 days to pregnant women through primary health centers, but only 8 percent of women receive 90 tablets and the degree of adherence is unknown. Madagascar has recently developed and is scaling up a comprehensive policy to improve maternal and child nutrition. Qamruddin suggested that this environment may be conducive to an MMS pilot, as there are no well-entrenched norms among pregnant women or healthcare providers to displace. “Madagascar is a very low-income country with very little activity in this area,” she said. “But this situation actually presents a big opportunity to help shape policy and introduce innovation.”

IV. Framework for Decision-Making in Countries

Operationalizing the WHO Guideline

One of the most important outcomes from the two task force meetings is the consensus to create a framework to describe the considerations and guide the decision-making process for countries contemplating an MMS program. Participants agreed that despite the lack of a recommendation for MMS, the WHO guideline must be the starting place for guidance. Rather than circumventing or countermanding the guideline, the group embraced the notion of guiding countries in their efforts to operationalize it.

According to the guideline, “policymakers in populations with *a high prevalence of nutritional deficiencies* (emphasis added) might consider the benefits of multiple micronutrient supplements on maternal health to outweigh the disadvantages, and may choose to give multiple micronutrient supplements that include iron and folic acid.” The task force agreed that the general term “nutritional deficiencies” and the explicitly stated permission to consider MMS in the presence of such deficiencies represents an “open door” for countries.

The Framework

Task force participants reached consensus on the following blueprint of a decision-making framework for countries to consider multiple micronutrient supplementation for pregnant women. The group agreed to flesh out the framework in a concise document to be drafted in the coming months.

A. **Background.** The framework will reiterate the WHO guideline on MMS and explain the intent of WHO recommendations—to guide rather than prescribe. Countries considering MMS may benefit from clarification on the language used in WHO guidelines—specifically, that “not recommended” is not synonymous with “harmful,” and often indicates that inadequate

evidence exists upon which to recommend an intervention. In the case of MMS, the WHO explicitly states that MMS may be considered within a context of “high prevalence of nutritional deficiencies.”

B. Safety. The WHO guideline mentions “some evidence of risk” associated with MMS. Further analysis of the evidence base used to formulate the WHO guideline shows no increased risk of any outcome—including neonatal mortality—in any subgroup of pregnant women who receive MMS. This new analysis is critical to share with countries considering implementing or expanding MMS.

C. Defining Context Within Countries. The task force identified a series of general conditions/steps that countries may follow to determine if MMS may be worthy of deeper consideration and assessment. Acknowledging that population-level data on the prevalence of micronutrient deficiencies are often not available, and that data on pregnant women are even more scarce, the group agreed upon several types of data that may be considered, including information on extant services being delivered and cost information.

- a) ***Identifying indicators or risk of population-level nutritional deficiencies, including in women of reproductive age and pregnant women.*** Most countries do not have biomarker data to inform this process, but the group agreed that several other types of data are acceptable proxy indicators of what the WHO guideline broadly terms “nutritional deficiencies.” In order of preference, they are: 1a) Biomarker data, 1b) Anemia prevalence, which is widely measured, 2) Dietary intake data gleaned from DHS surveys, and 3) Dietary diversity. Absent these measures, additional indicators such as low maternal BMI, short stature, and child malnutrition indicators may be considered.

The task force noted that similarly flexible criteria for determining need appear in the WHO guideline on calcium supplementation, and that the suggestion to consider proxy measures is intended to help identify populations at high risk for micronutrient deficiencies and make the case for more in-depth situation analysis in countries.

- b) ***Prevalence of outcomes.*** To the extent that birth outcomes are measured, the task force suggests countries examine prevalence of outcomes for which MMS can provide benefit: LBW, SGA, preterm birth, neonatal mortality, infant mortality, stillbirth.
- c) ***Availability of an existing IFA delivery platform.*** To the extent that a country is already delivering IFA to beneficiaries, the presence of this platform or similar types of

platforms onto which an MMS delivery strategy can be built would give added reason to initiate MMS deployment

- d) **Cost, Supply, and Coverage Considerations.** While this is an evolving area of analysis, countries considering MMS require cost estimates, cost-benefit analyses, and information on both local and global procurement for MMS. The task force agreed to create a frequently asked questions document to address some of these issues, along with implementation questions.

V. Outstanding Questions and Research Needs

Despite data showing powerful benefits of multiple micronutrient supplements over iron-folic acid supplements when consumed per protocol, particularly in anemic and underweight women, significant research gaps and questions remain, especially in the areas of adherence, cost-effectiveness, and long-term benefits. The task force noted that the SDGs and strong interest in improving maternal health around the globe present opportunities for drawing attention to the role of nutritional interventions, including multiple micronutrient supplementation during pregnancy.

Among the outstanding questions and research needs are:

Maternal outcomes: Little is known about the potential for MMS to have a greater impact on maternal health outcomes than IFA. MMS can improve biochemical status and treat anemia, but the task force agreed that any additional information that can be gleaned from current literature about benefits of MMS over IFA in the areas of maternal morbidity and mortality may strengthen the case for countries to consider it.

Long-term benefits: Whether MMS confers long-term cognitive or physiologic benefits to children—including reducing incidence of stunting—is unknown, but this information would significantly influence cost-benefit analyses and is likely to be of interest to policymakers.

Drivers of Adherence: Adherence is a challenging yet important factor to consider, and little is known about the drivers of MMS adherence among pregnant women in real-world circumstances. Some studies show greater adherence to supplementation when women pay even a nominal fee for tablets, and while willingness to pay for IFA has been demonstrated in several countries, the impact on adherence is difficult to generalize. Many countries distribute IFA within the context of ANC visits—a platform that is less than ideal and may even deter

supplementation. The task force agreed that efforts to better understand adherence and demand drivers among pregnant women are critical to creating successful MMS programs.

Target Dose, Adherence, and Cost-Benefit: The ideal dose/formulation of MMS needed to reap the benefits evidenced in trials is unknown. For countries considering MMS, factors such as the minimum duration of supplementation (number of pills per pregnancy) and the timing of supplementation (how late is too late to realize benefits?) all impact the cost-benefit ratio. There are likely “tipping points” of coverage and adherence where the cost-benefit proposition of MMS begins to nullify: those points are important but currently unknown.

Essential Medicines List: Multiple micronutrient supplements are not included on the EML, and the next opportunity for submitting products for consideration is later this year. The task force discussed, but did not decide, whether to pursue a submission.