Task Force on Multiple Micronutrient Supplementation in Pregnancy, Meeting 1
Reported by Hallie Kapner

Overview

On November 15, 2017, The New York Academy of Sciences and the Bill & Melinda Gates Foundation convened the first of two meetings of a task force charged with examining and interpreting the guidelines for use of multiple micronutrient supplementation (MMS) in pregnancy as issued by the World Health Organization in 2016. Comprised of international experts in micronutrient deficiencies, public health, nutrition, pediatrics, and statistics, the task force reviewed the research that informed the WHO recommendations, and considered the results of new meta-analyses of individual patient data from multiple micronutrient trials around the globe. Benefits and potential risks of multiple micronutrient supplementation highlighted in the analyses formed the basis for a discussion identifying research gaps, populations that may benefit most from supplementation, and considerations for the development of a roadmap to guide countries considering MMS implementation.

Speakers

Simon Cousens, Dip Math Stat, London School of Hygiene & Tropical Medicine
Alison Gernand, PhD, MPH, RD, Pennsylvania State University
Roland Kupka, PhD, UNICEF
Lynnette Neufeld, PhD, Global Alliance for Improved Nutrition
Saskia Osendarp, PhD, Osendarp Nutrition
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Chris Sudfeld, ScD, Harvard University

Additional Task Force Participants

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WHO Guidelines on Multiple Micronutrient Supplementation in Pregnancy

Lynnette Neufeld described the process by which WHO develops guidelines, and reviewed the current recommendation regarding the use of multiple micronutrient supplementation in pregnancy. Issued in 2016 as part of the WHO Antenatal Care recommendations, the guideline states,

"Multiple micronutrient supplementation is not recommended for pregnant women to improve maternal and perinatal outcomes.

There is some evidence of additional benefit of multiple micronutrient supplements containing 13 to 15 different micronutrients over iron and folic acid, but also some evidence of risk, and some important gaps in the evidence. Although the WHO guideline development group that developed this recommendation agreed that overall there was insufficient evidence to warrant a recommendation, the group agreed that policymakers in populations with a high prevalence of nutritional deficiencies 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."

Neufeld reviewed the WHO process, including the evidence review and guideline development group, noting that a guideline (or recommendation) is a mandatory outcome of this process. The guideline development groups are composed of experts from a variety of backgrounds, including clinicians, policy makers, and program implementers. The MMS guideline specifically was released as part of the antenatal care guidelines, coveraging many issues beyong nutrition. The actual guideline was the product of the formal WHO process including the evidence review and guideline development group deliberation and voting. In 2015 prior to intiation of that formal process, WHO in collaboration with UNICEF and the Micronutrient Initiative had convened a technical consultation to discuss the evidence related to MMS as a potential replacement for iron and folic acid (IFA) supplementation for pregnant women in lower and middle income countries (LMICs). Neufeld noted that while important as part of the dialogue on the issue, this technical consultation was not the decision making body for the WHO guideline.

She emphasized that WHO guidelines are meant to inform decision-making, not serve as a one-size-fits-all mandate, although policymakers often view such guidelines as prescriptive. "A guideline that states 'not recommended' may mean there is evidence of harm or lack of benefit, but may also mean that evidence is insufficient to support a modification from current practice," Neufeld explained, a distinction that she deemed particularly relevant to the WHO decision on MMS.

The guideline text directly acknowledges circumstances in which policymakers may wish to consider implementing MMS. Neufeld commented that "while intending to create choice, the guideline leaves ambiguity for countries." Specifically, the guideline references a "high prevalence" of micronutrient deficiencies, yet there are no well-defined criteria for what constitutes high prevalence of deficiency, and data on nutritional status among pregnant women in LMICs are scarce. The guideline makes reference to benefits of the intervention and the need for policy makers to reflect whether those benefits may "outweigh the disadvantages," yet no formal risk/benefit analysis of MMS in pregnancy has been conducted. The lack of specific recommendations related to MMN formulation also leaves ambiguity on options for alternatives to IFA. Additionally, limited data exist to assist either policymakers or WHO in evaluating factors such as acceptability of MMS versus IFA, cost-effectiveness of the two supplementation regimens, and feasibility of implementation. "All told, this leaves big gaps for countries," Neufeld concluded.

Overview of UNIMMAP: History and Formulation

Roland Kupka reviewed the history of the United Nations International Multiple Micronutrient Preparation, or UNIMMAP—the supplement most commonly used in trials of multiple micronutrient supplementation in pregnant and lactating women. Support for utilizing multiple micronutrient supplements to address well-documented deficiencies in pregnant women coalesced in 1999, when the United Nations Sub-Committee on Nutrition convened a meeting to determine the formulation of a multiple micronutrient supplement that could be used in effectiveness trials in pregnant women in LMICs.

Comparison of UNIMMAP composition with selected dietary reference values

Different from UNIMMAP

Nutrient	UNIMMAP Amount	U.S. RDA 1989/1997/1998	U.S. DRIs 1997/1998/2000/2001/2005/2011	WHO/WFP/ UNICEF 2007
Vitamin A (RE)	800	800	770	800
Vitamin B1 (mg)	1.4	1.4	1.4	1.4
Vitamin B2 (mg)	1.4	1.4	1.4	1.4
Niacin (mg)	18	18	18	18
Vitamin B6 (mg)	1.9	1.9	1.9	1.9
Vitamin B12 (µg)	2.6	2.6	2.6	2.6
Folic Acid (µg)	400	600	600 µg DFE	600
Vitamin C (mg)	70	70	85	55
Vitamin D (IU)	200	200 (AI)	600	200
Vitamin E (mg)	10	10	15	15
Iron (mg)	30	30	27	27
Zinc (mg)	15	15	11	10
Copper (mg)	2	1.5-3.0 (ESADI)	1	1.15
Selenium (µg)	65	65	70	30
Iodine(µg)	150	175	220	250

Fifteen vitamins and minerals—including iron and folic acid— were selected based on likelihood of widespread deficiency in LMICs, tolerability, and availability of pre-mixes. Some minerals, such as calcium, potassium, and magnesium were not included due to their bulky size or a lack of evidence for their inclusion. The composition of UNIMMAP largely reflects 1999 DRIs and RDAs for each vitamin and mineral, with some exceptions for folic acid and iodine, both of which are included at slightly lower dosages than the RDAs at that time. Kupka noted that while the composition of UNIMMAP has remained the same since its original formulation, nutrient intake recommendations have evolved. As a result, some discrepancies exist between the UNIMMAP composition and current dietary reference values. For example, vitamins D and E are present at lower amounts in the UNIMMAP formulation than the DRIs, while iron and zinc are present in slightly higher amounts than the DRIs.

Following the initial trials of UNIMMAP in pregnant women in Indonesia, Asia, Southeast Asia, and Africa, WHO issued a guideline recommending MMS for pregnant and lactating women in emergency settings. The guideline specifies that MMS should be given *in addition* to iron and folic acid in settings where IFA supplementation exists, and should continue for the duration of the emergency. No additional recommendations on the use of MMS in pregnant women were issued until the 2016 guideline. UNIMMAP has not been widely used outside trials.

Shifts in nutrient intake guidelines and increased awareness of the benefits of nutrients not included in UNIMMAP, such as DHA, choline, lysine, and pantothenic acid, have led experts including Kupka to consider reformulation. “There may be benefits to re-examining and updating the formulation,” he said, while noting that there are potential barriers to such an update. Among them are the costs associated with changing the composition of pre-mixes, the lack of a WHO recommendation for widespread MMS use, and a lack of data to inform potential risks of both deficiency and excess of the micronutrients included in UNIMMAP.

Effects of Micronutrients on Pregnancy Outcomes

Micronutrients have significant influence from the earliest stages of a pregnancy, **Alison Gernand** explained, affecting implantation and vascularization of the placenta, and playing key roles in fetal morphogenesis, organogenesis, and neurological development. While most studies of the specific mechanisms by which micronutrients influence pregnancy outcomes focus on animal models, evidence from limited human trials and observational data indicate that a wide variety of birth defects are tied to micronutrient deficiencies during critical periods of human development. “The critical period for organ development is up until about 8 weeks, while the heart, eyes, arms, and genitalia develop throughout the pregnancy, and we know that the central nervous system can be impacted by maternal nutrient status until birth,” Gernand said.

Impacts on conception and early pregnancy

Maternal preconception nutrient status can impact fetal growth and development. Zinc, folate, vitamins B12 and B6 are considered particularly important, as these micronutrients are involved in one-carbon metabolism, which facilitates cell proliferation, growth, and protein synthesis in the earliest stages of gestation. These micronutrients are also thought to play a role in the rapid demethylation of maternal and paternal genomes immediately following conception, as well as the sustained remethylation of the fetal genome throughout gestation. While folate has long been considered critical micronutrient for the preconception period and early gestation due to the correlation between low folate and neural tube defects, Gernand reported that zinc has emerged as equally important in preventing similar malformations. Studies of zinc-deficient mice not only reveal higher incidence of neural tube defects, but increased risk of pregnancy loss, lower implantation rates, lower placental weights, and reduced ratio of fetal to maternal placental tissue compared to mice with healthy preconception zinc levels.

Zinc, along with vitamin D, is also integral to placental development and functioning. Maternal/fetal circulation, which is not fully established until the end of the first trimester, depends upon significant remodeling of the uterine spiral arteries, including invasion of trophoblasts that widen the arteries and facilitate increased blood flow. Vitamin D is believed to play a key immunomodulatory role in this process. Further, studies show that the biologically active form of vitamin D, 1,25-dihydroxyvitamin D3 increases expression of vascular endothelial growth factor, an angiogenic protein. Establishment of placental circulation is accompanied by high levels of oxidative stress, and antioxidants such as selenium, copper, zinc, and vitamins C and E help protect the fetus from oxidative damage.

Micronutrients also support the necessary maternal physiologic changes of pregnancy. Iron is particularly critical for supporting increases in blood volume throughout gestation.

Impacts on fetal growth and the postnatal period

The fetal central nervous system (CNS) develops throughout gestation, and different micronutrients support this process over time. Gernand described the importance of micronutrients such as iodine in early brain development, and DHA in the late stages of fetal brain growth, while iron, folate, zinc, vitamins B6 and A support CNS development throughout gestation.

Maternal micronutrient status has a direct impact on fetal micronutrient status at birth, especially as it pertains to nutrients typically stored during the third trimester to sustain the baby after birth, including iron—critical due to the low iron content of breastmilk—as well as vitamins D, B12, A, E, B6, and riboflavin. “Our knowledge in this area is incomplete, but we know that mothers transfer these nutrients to their babies in the third trimester, and deficiencies in mothers often result in deficiencies in babies,” Gernand said.

Diet during pregnancy and risk of micronutrient toxicity

Many factors impact women's ability to access a nutrient-rich diet, including socioeconomic factors, agricultural and environmental limitations, and elements of the diet that inhibit or interfere with nutrient absorption.

Micronutrient deficiencies and malnutrition are common among all women in LMICs, but the increased nutrient needs of pregnancy further raise the likelihood that pregnant women in settings with low dietary diversity or food insecurity will experience micronutrient deficiency. In genral, "folate, B12, iron and zinc are the most persistently difficult micronutrients to obtain through diet, and in circumstances where non-pregnant women are unable to meet these nutritional needs, pregnancy makes it much harder, even with increased caloric intake," Gernand said.

WHO Pregnancy recommendation + UNIMMAP

MICRONUTRIENT	RNI*	UNIMMAP	TOTAL	UL*
Vitamin A (µg/day)	800	800	1600	7500
Thiamin (mg/day)	1.4	1.4	2.8	-
Riboflavin (mg/day)	1.4	1.4	2.8	-
Niacin (mg/day)	18	18	36	35
Vitamin B6 (mg/day)	1.9	1.9	3.8	100
Vitamin B12 (µg/day)	2.6	2.6	5.2	-
Folic Acid (µg/day)	600	400	1000	1000
Vitamin C (mg/day)	55	70	125	1000
Vitamin D (µg/day)	5	5	10	50
Vitamin E (mg/day)	7.5	10	17.5	1000*
Copper (mg/day)	-	2	2	-
Selenium (µg/day)	30	65	95	400
Iodine (µg/day)	200	150	350	-
Iron (mg/day)	100*	30	130	-
Zinc (mg/day)	10**	15	25	4000

*supplement; ** based on "moderate bioavailability"

Gernand's analysis revealed that adding UNIMMAP to a diet that meets both WHO recommendations for micronutrient intake during pregnancy as well as Institute of Medicine recommendations (these differ slightly) poses very limited risk for reaching or exceeding upper level (UL). Only three micronutrients—niacin, iron, and folic acid— meet or slightly exceed the UL, and as Gernand explained, many of the potential issues associated with reaching the ULs of these micronutrients are less concerning in the context of UNIMMAP. Intake of folic acid at or above the UL may mask B12 deficiencies, yet UNIMMAP contains B12, thus mitigating that concern. Similarly, while higher doses of iron may cause vomiting and diarrhea, those symptoms are likelier to impact compliance with the supplementation regimen than safety. "There's very little risk of toxicity even for someone with optimal nutrition who takes UNIMMAP," Gernand said.

Prevalence of Micronutrient Deficiencies Among Women of Reproductive Age in LMICs and Prevalence of Adverse Birth Outcomes

Saskia Osendarp reviewed the most recent data on the prevalence of micronutrient deficiencies in pregnant women and women of reproductive age (WRA) worldwide and in LMICs, as well as data on adverse birth outcomes and maternal mortality.

While many countries do monitor some aspects of women's micronutrient status, most countries for which data exists limit their surveillance to 1-3 nutrients— most often iron, iodine, and vitamin A. There are significant gaps in micronutrient status data for these demographics, and many of the 15 micronutrients included in UNIMMAP are not included in national and regional surveys.

Analysis of the existing data from nationally or regionally representative surveys reveals widespread micronutrient deficiencies among pregnant women and WRA, although Osendarp emphasized that most countries do not separate data on pregnant women from WRA, which complicates efforts to assess true prevalence of deficiencies in these groups. Regardless, surveys show high prevalence (>30%) of deficiencies worldwide for all micronutrients surveyed except for vitamin A.

Prevalence of specific micronutrient deficiencies

Surveys indicate that the most prevalent micronutrient deficiencies in LMICs are vitamin D, with more than 60 percent of WRA deficient, iodine and zinc, with about 40 percent of WRA deficient, and anemia, which impacts just over 30 percent of WRA in LMICs. Prevalence of micronutrient deficiencies varies greatly by region and often among countries in the same region.

Surveys of micronutrient status in pregnancy are relatively scarce, but there are data on anemia and iodine deficiencies in pregnant women. According to regional estimates, 48 percent of pregnant women in Africa and 45 percent in Southeast Asia are anemic, and in LMICs overall, anemia affects an estimated 32 percent of pregnant women.

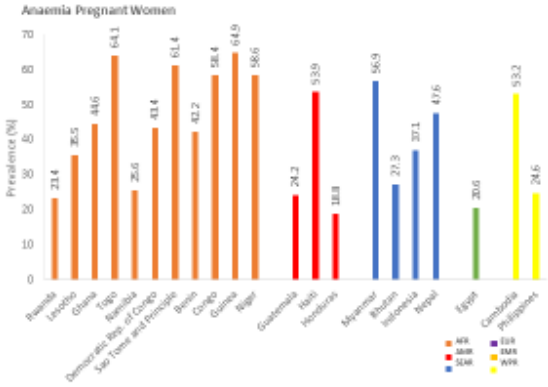
Insufficient iodine intake among pregnant women, as measured by urinary iodine concentration, is surprisingly widespread, and includes the United States and much of Western Europe. Iodine deficiencies are less common in Africa and Latin America due to the success of salt fortification with iodine.

B. Micronutrient Deficiencies: Pregnant Women

Regional and country level estimates of anaemia among pregnant women in Low- and Middle-Income Countries (LMIC) 2011-2015

Region	Prevalence
Africa	48.3
America	27.2
South East Asia	44.8
Europe	N/R
Eastern Mediterranean* (Egypt)	20.6
Western Pacific* (Cambodia & Philippines)	34.3
LMIC	31.6

N/R: Not reported; *Not representative (<3 countries)



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Anemia versus iron-deficiency anemia

Reports of anemia prevalence do not distinguish between anemia and iron-deficiency anemia (IDA), and there is little information on how many of the anemia among pregnant women or WRA in LMICs is caused by iron deficiency. A 2013 *Lancet* analysis estimated that 50 percent of anemia is likely to be caused by iron deficiency, but experts, including Osendarp and many of the participants in this task force, caution against broad application of that estimate due to the high regional variability of micronutrient deficiencies and non-nutritional causes of anemia.

Adverse pregnancy outcomes

Adverse pregnancy outcomes include a wide range of complications impacting both mother and baby, including preterm birth, small-for-gestational age infants (SGA), low birth weight (LBW) infants, maternal mortality, stillbirth and neonatal mortality, perinatal mortality, pre-eclampsia, and premature rupture of membranes (PROM).

Average global rates of preterm birth (11 percent), SGA (19 percent), and LBW (16 percent) are higher in certain regions, particularly Southeast Asia, where SGA and LBW are nearly double the global rate. Sub-Saharan Africa leads the world in maternal mortality, stillbirths, neonatal mortality and perinatal mortality.

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Data on adverse pregnancy outcomes such as preeclampsia, macrosomia, PROM, and insufficient gestational weight gain are often sourced from local—rather than national or regional—studies, and incidence of these outcomes is prone to underreporting.

Prevalence of adverse pregnancy outcomes (2)

	Maternal Mortality (per 100,000)	Still Births (per 1000)	Neonatal mortality (per 1000)	Perinatal mortality (per 1000)
Sub Saharan Africa	546	28.7	28	62
South East Asia	62	12.2	24.3	50
South Asia	182	25.5		
WORLD	216	18.4	19.2	47

From: UNICEF, *Maternal Mortality in 1990-2015*. 2015; World Health Organization, *Neonatal Mortality Rate*. 2016; World Health Organization, *Neonatal and Perinatal Mortality*. 2006; Blencowe et al., The Lancet Global Health, 2016. **4**(2): p. e98-e108

Data on prevalence of other adverse pregnancy outcomes is scarce, often from local sources and prone to under-reporting. Some figures:

	Sources of information	Estimated prevalence
Macrosomia	Regional estimates only	< 5% in Africa and Asia
Premature Rupture of Membrane (PROM)	Kenya (2x), Nigeria (2x), India, Pakistan, World (INTERGROWTH-21)	Range: 0.9 – 9.6%
Insufficient Gestational Weight Gain (GWG; defined as < IOM, 2011):	Sub-Saharan Africa, Cameroon, India (3x), Vietnam	Range: 26.6 – 52.7%
Congenital anomalies	Kenya, Nigeria (2x), India (3x)	Range: 6.3 – 23.1%
Pre-eclampsia	Kenya, Cameroon, India (3x)	Range: 0.2 – 11%

Adolescent Nutrition Project: An Individual Patient Data Meta-Analysis Comparing MMS vs IFA

Nearly 90 percent of the 1.2 billion adolescents in the world live in LMICs, and studies suggest that this demographic, defined as those ages 10-19, as well as young mothers (some of whom fall within the adolescent age group) have poorer nutritional status compared to older women of reproductive age. **Simon Cousens** shared the results of an individual patient data (IPD) meta-analysis comparing the effects of MMS and IFA in adolescents as they pertain to four outcomes of interest to this task force: low birth weight, stillbirth, neonatal death, and perinatal death.

Cousens' analysis includes data from 10 published studies comparing the effect of multiple micronutrient supplementation to IFA in 50,000 participants, approximately 25 percent of whom were adolescents. The inquiry attempted to determine a) the effect of the intervention (MMS) on adolescents, b) whether that effect varied based on different characteristics of those adolescents, and c) whether the intervention has a different effect on adolescents versus older women of reproductive age.

Cousens reported the results of two types of analysis—one-stage, and two-stage. The one-stage approach analyses all individual patient data from all trials in a single meta-analysis. The two-stage approach analyzes patient data from each trial individually, then combines the summary data in either a fixed or random-effects meta-analysis. A fixed-effects analysis assumes that the effect under consideration is the same in all studies, while a random effects analysis allows for the possibility of variations in effect between studies. A random effects analysis gives relatively less weight to larger studies than a fixed effects analysis

Low birth weight (LBW)
A fixed effects analysis indicated evidence that the incidence of LBW was lower in those receiving MMN ($P<0.001$). However, a random effects analysis provided little evidence of an effect of MMN ($P=0.18$).

Maternal age, BMI, parity, and hemoglobin status do not modify the overall impact of MMS in reducing incidence of LBW.

Stillbirth
There is little overall difference in risk of stillbirth among women taking MMS versus IFA. There was weak evidence ($P=0.07$) of a more beneficial effect of MMN among women aged 20 years + compared to those aged 10-19 years..

An examination of effect modification based on individual characteristics showed no evidence that among adolescents the effect varied with ageof age ($P=0.83$). There was weak evidence ($P=0.11$) that MMS may be more beneficial among adolescents who have previously given birth. Stronger evidence exists ($P=0.006$) that MMS is slightly *less* beneficial in preventing stillbirth in women who are not underweight (BMI >18.5).

Neonatal Mortality

The only observed potential effect of MMS on neonatal mortality appears in an age-stratified analysis, where the data show weak evidence that MMS may be less beneficial for women older than 20. Cousens noted that this finding, which is in contrast to the above-noted finding that MMS may be more beneficial for reducing stillbirth in older women of reproductive age, may be a result of misreporting or misclassification between stillbirth and early neonatal deaths.

Perinatal Mortality

There is no evidence of an effect of MMS compared to IFA on perinatal mortality in adolescent women compared to older women. However, the effect of MMN on perinatal mortality may differ between women who are underweight (BMI <18.5) compared to women with BMI >18.5.

Conclusions

MMS appears to have little effect on incidence of stillbirth in adolescents overall, although there is some indication that MMS may be more beneficial in reducing incidence of stillbirth among women over age 20, and less beneficial for women with BMIs >18.5. MMS does not appear to reduce perinatal mortality in adolescent women as compared to older women, but may have a more beneficial effect on underweight adolescent women.

Modifiers of the Effect of MMS on Stillbirth, Birth Outcomes, and Neonatal Mortality

Chris Sudfeld summarized the results of a recently published meta-analysis of individual patient data from randomized trials of MMS in pregnant women in LMICs. The analysis focused not on the overall effects, but on effect modifiers—individual level factors that alter the effect of MMS on mortality and birth outcomes. As Sudfeld described the objective, the study aimed to determine whether "some subgroups of mothers and infants experience stronger or weaker effects of multiple micronutrient supplementation on mortality and birth outcomes."

The two-stage IPD analysis included 17 randomized trials in 14 LMICs, totaling 112,953 pregnancies. All studies used a multiple micronutrient supplement with at least three micronutrients *in addition* to iron and folic acid, and all featured an IFA control group. Outcomes of interest were stillbirth, early neonatal mortality, neonatal mortality, 6-month mortality, infant mortality, low birth weight, preterm delivery, small for gestational age (SGA) and large for gestational age (LGA).

Effect modifiers reviewed during discussion include infant sex, maternal anemia, gestational age at randomization, rate of adherence to the supplementation regimen, and maternal BMI.

Sudfeld presented the results of several analyses of trial data: overall analysis of the impact of MMS compared to IFA on mortality and birth outcomes; analysis of the various effect modifiers on mortality and birth outcomes, and analyses to determine whether birth outcomes and effect modifiers differ in trials where the dose of iron is the same in the MMS and IFA groups versus trials where the iron dose differs between groups.

Overall Analysis Results

Stillbirth and Mortality

The overall analysis showed a statistically significant 8 percent reduction in the risk of stillbirth in the MMS group compared to IFA. MMS had no overall impact on neonatal, 6-month or 1 year mortality overall. .

Birth Outcomes

Overall analysis revealed statistically significant risk reductions in three outcomes among the MMS cohort—a 12 percent reduction in low birth weight, an 8 percent reduction in preterm birth, and a 3 percent reduction in SGA. There was also a slight but not statistically significant increase in risk for LGA among the MMS group.

Effect Modifier Analysis Results

Infant sex

Incidence of stillbirth was similar among male and female infants in the MMS group. However, female babies born to mothers receiving MMS had *significant 15% reductions in all mortality outcomes through the first year of lifewhile male infants saw no reduction in mortality*.

Infant Sex, Stillbirth and Mortality

	Stillbirth RR (95% CI)	Early Neonatal Mortality RR (95% CI)	Neonatal Mortality RR (95% CI)	6-month Mortality RR (95% CI)	Infant Mortality RR (95% CI)
Males	0.92 (0.82-1.03)	1.03 (0.92-1.15)*	1.06 (0.95-1.17)*	0.98 (0.89-1.09)	1.05 (0.98-1.18)*
Females	0.91 (0.80-1.03)	0.86 (0.75-0.98)*	0.85 (0.75-0.96)*	0.85 (0.75-0.95)	0.87 (0.77-0.99)*

* p-value for heterogeneity <0.05

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There is no evidence of a difference in risk of LBW, preterm delivery, SGA, or LGA between males and females in the MMS and IFA groups. Sudfeld commented that the sex-specific effect of MMS on mortality outcomes indicate that the differences in effect between males and females are not operating through differences in birth outcomes, but through a different

benefit that may be due to cause-specific mortality by sex, immunological ,placental or other reasons.

Sudfeld emphasized that the sex-specific benefits reported in the overall analysis are in part due to the largest individual studies included in the analysis, JiVitA-3 and SUMMIT, which both found benefits among females but not males.

Maternal Hemoglobin, Anemia at Randomization

Among women categorized as anemic at randomization, those who received MMS had a 30 percent reduction in 6-month mortality.Anemic women who receive MMS had a slight but not statistically significant reduction in risk of stillbirth compared to non-anemic women receiving MMS.

Anemic women who received MMS also appear to show greater benefits in birth outcomes than non-anemic women. While both anemic and non-anemic women given MMS had reduced risk of LBW, anemic women had a 19 percent risk reduction, versus 9 percent in non-anemic women. Similarly, anemic women in the MMS group had an 8 percent risk reduction of SGA compared to non-anemic women, who saw no change in risk of SGA.

Adherence to supplementation

For this adherence analysis, women were divided into two groups: those who complied with the MMS regimen >95 percent or <95 percent of the time.

Those with higher adherence to MMS saw greater benefits, including a 13 percent risk reduction in early neonatal death and 15 percent reduction in infant mortality compared to mothers who were less adherent.

Gestational age at randomization

Gestational age at the start of supplementation affected birth outcomes only when MMS supplementation began prior to 20 weeks gestation.. That cohort saw an
11 percent reduction in risk of preterm delivery, while pregnant women who began MMS supplementation later than 20 weeks had no risk reduction in preterm delivery.

Pregnant women who started MMS prior to 20 weeks' gestation had no reduced risk of SGA, but there was a slight—but statistically insignificant—reduction in risk of SGA for those who started MMS later than 20 weeks of pregnancy.

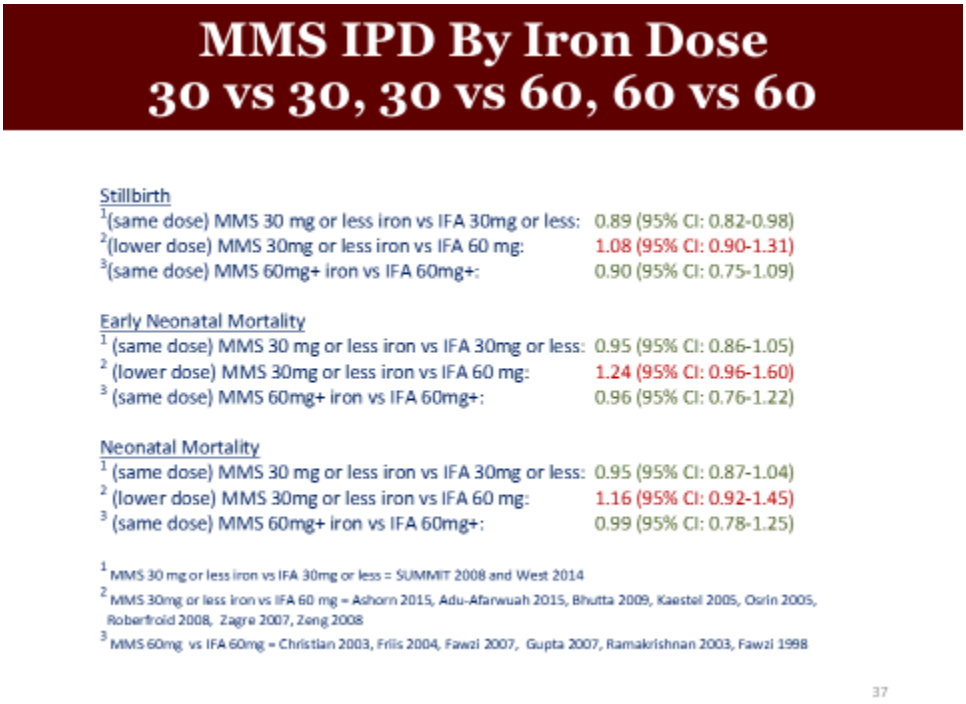
Maternal BMI at randomization

Supplementation with MMS appears to have greater positive effects on birth outcomes in women with BMIs <18.5. Underweight women had a 16 percent reduced risk of preterm delivery, while women with BMIs ≥18.5 had a risk reduction of 6 percent. Women with BMIs ≥18.5 had a statistically significant increase in risk of LGA when taking MMS compared to underweight women.

Trial analysis stratified by iron dose

Among the 17 trials included in this meta-analysis, 8 trials, including the largest ones, SUMMIT and JiVitA-3, employed the same dose of iron for both the MMS and IFA groups. Eight trials used a reduced iron dose in the MMS cohort compared to the IFA cohort, and one trial, MINIMat, used a combination of the same and different-dose iron among groups.

Sudfeld and his collaborators conducted additional sensitivity analyses to determine if mortality and birth outcomes and effect modifiers varied between the same-dose trials and different-dose trials.



Different-dose iron trials and mortality

Mortality outcomes in same-dose iron trials, regardless of whether the iron dose was 30mg or 60mg in both the MMS and IFA groups, mirror the effects seen in the primary analysis—specifically, there is evidence for reduced risk of stillbirth and neonatal mortality among some groups of women and infants. However, analyses of *different-dose* iron trials where the dosage of iron was *lower in the MMS group compared to the IFA group* show *increased* risk of stillbirth and neonatal mortality among some subgroups of women.

Maternal hemoglobin

Anemic women in different-dose trials where the MMS group received 30mg or less of iron versus 60mg in the IFA group had higher incidence of all mortality outcomes compared to anemic women in same-dose trials, who had significantly *reduced* mortality outcomes.

Maternal Hemoglobin at Randomization, Stillbirth and Mortality

Lower Dose Iron Trials

	Stillbirth RR (95% CI)	Early Neonatal Mortality RR (95% CI)	Neonatal Mortality RR (95% CI)	6-month Mortality RR (95% CI)	Infant Mortality RR (95% CI)
Anaemic (Hb <110)	0.99 (0.69-1.42)	1.15 (0.76-1.72)	1.20 (0.85-1.71)	1.25 (0.74-2.10)	1.19 (0.78-1.82)
Non Anaemic (Hb ≥110)	0.94 (0.79-1.12)	0.96 (0.79-1.17)	1.09 (0.77-1.55)	1.03 (0.65-1.62)	1.19 (0.78-1.82)

Same Dose Iron Trials

	Stillbirth RR (95% CI)	Early Neonatal Mortality RR (95% CI)	Neonatal Mortality RR (95% CI)	6-month Mortality RR (95% CI)	Infant Mortality RR (95% CI)
Anaemic (Hb <110)	0.72 (0.59-0.89)	0.85 (0.68-1.06)	0.78 (0.64-0.96)	0.67 (0.55-0.82)*	0.99 (0.56-1.75)
Non Anaemic (Hb ≥110)	0.93 (0.75-1.16)	0.92 (0.72-1.18)	0.88 (0.71-1.10)	0.91 (0.74-1.13)*	1.08 (0.68-1.70)

* p-value for heterogeneity <0.05

Adherence, Stillbirth and Mortality

Lower Dose Iron Trials

	Stillbirth RR (95% CI)	Early Neonatal Mortality RR (95% CI)	Neonatal Mortality RR (95% CI)	6-month Mortality RR (95% CI)	Infant Mortality RR (95% CI)
<95% adherence	1.06 (0.83-1.34)	1.44 (1.03-2.01)	1.34 (1.00-1.79)	0.94 (0.55-1.62)	1.08 (0.66-1.77)
≥95% adherence	1.03 (0.75-1.27)	1.17 (0.68-2.01)	1.04 (0.66-1.66)	1.20 (0.74-1.92)	1.06 (0.67-1.69)

Same Dose Iron Trials

	Stillbirth RR (95% CI)	Early Neonatal Mortality RR (95% CI)	Neonatal Mortality RR (95% CI)	6-month Mortality RR (95% CI)	Infant Mortality RR (95% CI)
<95% adherence	0.89 (0.80-0.99)	1.02 (0.90-1.16)	1.01 (0.90-1.14)	0.98 (0.88-1.09)	1.06 (0.93-1.21)*
≥95% adherence	0.91 (0.80-1.03)	0.85 (0.73-0.99)	0.87 (0.76-1.00)	0.82 (0.72-0.95)	0.83 (0.72-0.96)*

* p-value for heterogeneity <0.05

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Adherence to supplementation

Women in different-dose iron trials who received MMS (30mg iron or less) and were <95 percent adherent to the supplementation regimen had higher incidence of early neonatal and neonatal mortality compared to women who were more adherent.

In same-dose trials, women who were >95 percent adherent had significant reductions in mortality outcomes, yet those gains disappear *even among adherent women* in different-dose trials.

Conclusions from different-dose iron trial analyses

Sudfeld concluded that while significant questions remain, the analyses appear to indicate that MMS containing 30mg iron or less may perform worse than iron-folic acid supplements containing 60mg of iron on some birth outcomes. In these trials the additional benefits provided by multiple micronutrients may be balanced out or outweighed by negative impact of reducing the iron dose. A lower dose of **iron** in multiple micronutrient supplements may be associated with higher observed neonatal mortality in anemic mothers, women who begin supplementation prior to 20 weeks' gestation, and women who are less adherent to the supplementation regimen.

Sudfeld noted that the WHO Antenatal Care recommendations include a different-dose iron trial analysis among the evidence base supporting the decision to not recommend MMS for pregnant women. This analysis is the only evidence of potential increases in stillbirth or mortality among pregnant women taking MMS. However, in trials using the same dose of iron in both MMS and IFA supplements there were no increases in mortality.

Conclusions from the primary and same-dose iron trial analyses

There was no indication for increased risk of stillbirth or other mortalities associated with MMS among any subgroup in the same-dose and primary trial analyses. MMS is associated with a 15 percent reduction in mortality during the first year of life for female babies, and provides greater benefit to anemic women, women with BMIs <18.5, and women with greater adherence to supplementation. Overall, the benefits of MMS appear to outweigh the risks.

Results Overview: MINIMat Trial

Launched in 2001 in Bangladesh, the 8-year MINIMat trial differs from other major trials of multiple micronutrient supplementation in pregnant women in several ways. **Lars Åke Persson** provided an overview of the methodology and results of MINIMat.

MINIMat combined both MMS and food supplementation, as the trial population was undernourished and food security was a significant challenge in the region. The food supplement was standardized across all trial participants, however, the timing of entrance into the supplementation program—as well as the vitamin supplement itself—varied between cohorts.

Four thousand women were randomized to two groups with regards to initiation of supplementation—those who began at 9 weeks of gestation (early start), and those who began at 20 weeks' gestation (usual start). Participants received a standard food supplement along with one of three micronutrient supplements—30mg iron +folate, 60mg iron + folate, or MMS containing 30mg iron +folate.

Summary of MINIMat Results

The only cohort of women who showed benefits were those who began the program at 9 weeks of gestation and received food supplementation and MMS. Benefits included a significant reduction in risk of early neonatal and infant mortality compared to all cohorts that received IFA.

No group showed any reduction in incidence of stillbirth.

All women who received iron-folic acid supplements in both the early start and usual start cohorts experienced similar rates of neonatal and infant mortality.

Women who entered the trial at 20 weeks' gestation experienced no benefits at all, regardless of whether they were given MMS or IFA supplements.

Results: post-hoc analyses, within Early invitation food group

Outcome	Groups	RR (95%CI)
Stillbirth	Fe30Fol vs. Fe60Fol	0.77 (0.37-1.60)
	MMS vs. Fe30Fol	1.48 (0.72-3.02)
	MMS vs. Fe60Fol	1.14 (0.59-2.22)
Early neona-	Fe30Fol vs. Fe60Fol	0.84 (0.43-1.67)
tal mortality	MMS vs. Fe30Fol	0.27 (0.09-0.83)
	MMS vs. Fe60Fol	0.23 (0.08-0.68)
Perinatal	Fe30Fol vs. Fe60Fol	0.81 (0.49-1.34)
mortality	MMS vs. Fe30Fol	0.83 (0.47-1.46)
	MMS vs. Fe60Fol	0.67 (0.39-1.15)
Neonatal	Fe30Fol vs. Fe60Fol	0.85 (0.44-1.64)
mortality	MMS vs. Fe30Fol	0.42 (0.17-1.02)
	MMS vs. Fe60Fol	0.36 (0.15-0.85)

Conclusions from MINIMat

MINIMat concluded that optimizing nutrition early in pregnancy, *along with MMS*, offers significant reductions in neonatal mortality with no impact on infant size at birth. These benefits were not observed in women who began food and vitamin supplementation at 20 weeks' gestation, regardless of whether they took IFA with 30mg of iron, IFA with 60mg of iron, or MMS with 30mg of iron.

Multiple Micronutrient Supplementation and Long-Term Health Outcomes

The long-term benefits of MMS during pregnancy are less extensively studied than infant mortality and birth outcomes. **Saskia Osendarp** presented a summary of a 2016 meta-analysis of 17 follow-up reports from multiple micronutrient trials seeking to determine whether MMS during pregnancy provides long-term benefits versus supplementation with IFA. The studies assessed the potential impact of MMS on long-term child mortality, long-term growth, body composition, cardiovascular disease risk factors such as hypertension, and cognitive development and intelligence.

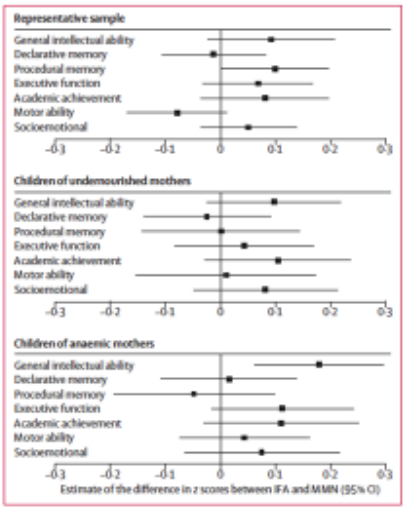
The meta-analysis showed no long-term impact of MMS on any of these health outcomes. Osendarp noted that gains in growth and reduction of CVD risk factors were present in some trials during early childhood follow up, but those advantages universally disappeared by age 8.

A follow-up analysis of the SUMMIT trial, which followed participants past the age of 12, found significant improvements in procedural memory and general intellectual ability at ages 9-12 among children whose mothers received MMS during pregnancy.

Long-term benefits on child cognitive development at 9-12 years of age in SUMMIT trial

- Children of mothers receiving MMN during pregnancy had 0.11 SD (95%CI: 0.01-0.20; p = 0.0319) higher procedural memory at 9-12 years of age

- Children of anemic mothers receiving MMN during pregnancy scored 0.18 SD (0.06-0.31, p = 0.0047) higher in general intellectual ability at 9-12 years of age.



Prado et al. Lancet Glob Health 2017;5:e217-28

Maternal supplementation with MMS, whether started in the preconception period or during pregnancy, has no impact on incidence of maternal depression at six months postpartum.

Osendarp concluded by noting that micronutrient status is just one of many factors that influence long-term growth, health, and developmental outcomes. “Nutrition is important, but as children get older, social and environmental factors become predominant influences on health and cognitive development,” she said. “This may be why the early benefits of MMS reported in some trials disappear over time.”

The Role of Iron and Different-vs Same-Dose Trials

The dramatically different impacts on mortality outcomes seen in the analyses of same-dose and different-dose iron trials provoked extensive discussion. Participants questioned whether iron dose is truly an effect modifier that contributes additional risk or confers additional benefit for certain subgroups of women, or whether meta-analyses that compare results from different-dose trials are simply confounded, which limits their interpretation due to many comparisons and small sample sizes in some subgroups. It was noted that among different-dose trials included in the WHO evidence base, MINIMat— different-dose trial that found no evidence of harm—was excluded.

The role of iron dosage in mortality and birth outcomes requires further study. However, the group noted that the effect of iron may be context-specific: in areas of greater food insecurity and malnutrition, where pregnant women are likely to be both macro-and micronutrient deficient, and where factors such as anemia and low maternal BMI are more prevalent, the iron dose may be a greater effect modifier. Task force participants also noted that many of the same-dose iron trials included in the meta-analysis, including the largest trials, SUMMIT and JiVitA-3, were conducted in regions with some diversity of BMI and less food insecurity. Overall, same-dose trials, whether 30mg or 60mg, produced consistent results on the beneficial impacts of MMS on mortality and pregnancy outcomes, and showed no evidence of harm.

Addressing the WHO Guideline

There was consensus among task force participants that while there was no new evidence to inform reconsideration of the WHO decision to "not recommend" MMS for pregnant women, new analyses of existing data warranted, at minimum, a consensus statement or published commentary outlining the considerable positive impact on mortality outcomes and spotlighting the subgroups that appear to potentially benefit most from MMS, namely women in countries with high prevalence of low BMI, food insecurity, and high prevalence of anemia. Some countries, such as South Africa and Mexico, have initiated countrywide implementation of MMS, and a consensus statement and commentary from this task force may serve as a starting point for other countries to consider MMS implementation.

The task force also agreed that while WHO is unlikely to revisit the MMS guideline prior to the 5-year review mark, guidance in the form of a roadmap document or "decision-tree" is likely to be more valuable in the near-term for LMICs considering implementation of MMS.

Designing a Roadmap

Without data on causal relationships between supplementation and outcomes, the task force agreed that a roadmap or guidance document for countries should highlight *predictors of populations that stand to benefit most from MMS*, rather than populations at greatest risk for negative pregnancy outcomes. At present, high prevalence of anemia, low BMI, food insecurity, and lack of dietary diversity appear to be strong predictors of a benefit of MMS versus IFA, and may form the basis of an initial set of criteria for countries to consider when determining if MMS may be preferable to IFA for pregnant women. Such population-level data are also available for many countries, unlike micronutrient status and pregnancy outcomes, which vary among LMICs and are subject to underreporting.

Research Gaps and Recommendations

The task force identified a series of research gaps to be addressed to advance decision-making guidance for countries considering use of MMS for pregnant women. The group prioritized research efforts that could be completed over the course of 6-24 months.

Immediate Research Needs (~6 months)

Revisiting WHO subgroup analysis of iron dose studies to reassess risk of harm: The group recommends reconsideration of the subgroup analysis of different-dose trials included in the WHO ANC evidence base to determine if additional analyses, including the addition of the MINIMat trial, alter the outcome. The WHO guideline references "some evidence of risk," and this task force believes a recalibration of that one analysis may yield less concerning outcomes which are more aligned with same-dose trial outcomes.

Review of evidence on iron dosage: The impact of the iron dose in MMS on outcomes is not clear, nor is it known whether there are certain circumstances where 60mg of iron vs 30 may improve mortality outcomes. The task force suggests a review of the literature comparing the risks and benefits of 30mg vs 60 mg of iron in pregnancy, and particularly in settings of anemia, low BMI, and malnutrition.

Improve understanding of acceptability and adherence of MMS vs IFA: Lack of compliance with IFA is often discussed as a rationale for not introducing MMS, which is more expensive, although cost of MMS has declined considerably in recent years. This group recommends an examination of existing data on adherence and acceptability in MMS trials, not as an effect modifier, but as an outcome. Information on women's willingness to pay for supplementation and whether payment, even if nominal, boosts adherence, may be valuable in this area.

Identify maternal dietary diversity as a predictor of benefit: A lack of maternal dietary diversity is predictive of micronutrient deficiencies, but it is not a known predictor of maternal anemia or other factors shown by the meta-analyses to be powerful indicators of benefit from MMS. Existing country-level data on dietary diversity and maternal anemia may provide additional guidance for identifying countries where MMS may be most beneficial.

Evaluation of UNIMMAP formulation: As the UNIMMAP formulation is not in line with current RDAs, the task force suggests a review of all 15 nutrients using existing data, including an analysis of the risks of deficiency, toxicity, and recommended dose ranges for pregnant women, particularly in light of evidence showing that some malnourished women may require more than one RDA of certain nutrients to compensate for depletion. Nutrients such as calcium, vitamin K, manganese, magnesium, and DHA are not included in UNIMMAP, but the group agreed that consideration of additional nutrients should be included in this review.

Maternal effects of MMS: MMS trials focus largely on birth outcomes and infant health, with little analysis of impact on maternal health, micronutrient status, and micronutrient content of breast milk. The group expressed interest in compiling any existing data—or analyzing remaining maternal blood or breast milk samples from prior studies—to better understand these outcomes in mothers.

Near-Term Research Needs (1-2 years)

Risk-benefit assessment: The task force strongly recommends a risk-benefit analysis of MMS vs IFA as a tool for guiding policy decisions and practice. No such assessment exists currently.

Cost benefit analyses and cost-effectiveness analyses: Neither a cost-benefit nor a cost-assessment analysis of MMS vs IFA outside of an individual trial (MINIMat includes a cost-benefit analysis) has ever been conducted, and the task force agrees that these are critical components of a roadmap or other guidance document for countries considering a switch from IFA to MMS.

Pilot program and evaluations: The group noted that countries such as South Africa, which are expanding MMS programs countrywide, represent potential opportunities to partner and implement evaluation measures to identify successes and challenges in implementation, maternal and infant outcomes, and compliance.

Other research needs mentioned for the medium term:
Effect of zinc supplementation and optimal dose of zinc on maternal outcomes.
Effect of maternal micronutrient status on infant micronutrient status and breastmilk micronutrient content
Formative research on challenges around implementation of programs, other micronutrient supplements (in particular Calcium!) that pregnant women are receiving, and the attitude of clinicians in recommending either MMS or IFA supplements.

Longer term research needs identified:

Look into effects of MNS supplementation before or just after conception.
Look into effects of combined programming interventions, including fortification