MEMORANDUM

From:	Director, NFS Director, SRH Director, MCA	**To:**	Team Lead, EML	**Date:**	1 June 2021
Our ref:		**Attention:**			
Your ref:		**Through:**			
Originator:	NFS/AHS	**Subject:**	RESPONSE ON EML REQUEST (EMEMO72387) - MEETING OF THE 23RD EXPERT COMMITTEE ON SELECTION AND USE OF ESSENTIAL MEDICINES, 21 JUNE - 2 JULY 2		

In response to the Essential Medicines List Application for Multiple Micronutrient Supplements During Pregnancy, the Departments of Nutrition and Food Safety (NFS), Sexual and Reproductive Health and Research (SRH), and Maternal, Newborn, Child, Adolescent Health & Ageing (MCA) have discussed the implications of this application. These departments jointly collaborated to develop the most recent recommendation on use of multiple micronutrient supplements (MMS) as part of antenatal care.

The application received is comprehensive. Recommendations on the use of MMS can be found in the three WHO documents, one joint statement and two guidelines. Please note that these guidance or policy documents are context specific (emergencies, tuberculosis, research) and were developed following different processes.

1. WHO, WFP, UNICEF. Preventing and controlling micronutrient deficiencies in populations affected by an emergency Multiple vitamin and mineral supplements for pregnant and lactating women, and for children aged 6 to 59 months. Geneva: World Health Organization; 2007.

- This is a joint statement developed by WHO, WFP and UNICEF. The process by which the recommendations were derived has not been explicitly stated; however, the joint statement was published prior to establishment of the WHO Guidelines Review Committee (GRC) and implementation of the current WHO guideline development process, and is likely based on expert opinion.
- *In populations affected by an emergency*
    - a multiple micronutrient supplement providing one reference nutrient intake (RNI) of micronutrients daily, should be given to pregnant or lactating women whether they received fortified rations or not. It is noted that if women are already receiving iron and folic acid supplements, these should be continued.
    - When fortified rations are NOT being given, children aged 6-59 months should be given a daily multiple micronutrient supplement containing the amounts of

micronutrients specified in Table 1 of the document. For children receiving fortified rations, they should be given 2 supplements per week.

2. Nutritional care and support for patients with tuberculosis. Geneva: World Health Organization; 2013.

These guidelines were developed during three WHO guideline development group meetings of the Nutrition Guidance Advisory Group, held 2009 to 2011, following the *WHO handbook for guideline development*. There are three recommendations on the use of multiple micronutrient supplements within these guidelines for *patients with tuberculosis* – all are *conditional recommendations* based on *very low quality evidence*:

a. A daily multiple micronutrient supplement at 1× RNI should be provided in situations where fortified or supplementary foods should have been provided in accordance with standard management of moderate undernutrition but are unavailable.
b. All pregnant women with active TB should receive multiple micronutrient supplements that contain iron and folic acid and other vitamins and minerals, according to the United Nations Multiple Micronutrient Preparation, to complement their maternal micronutrient needs.
c. All lactating women with active TB should be provided with iron and folic acid and other vitamins and minerals, according to the United Nations Multiple Micronutrient Preparation, to complement their maternal micronutrient needs.

3. WHO antenatal care recommendations for a positive pregnancy experience. Nutritional interventions update: multiple micronutrient supplements during pregnancy. Geneva: World Health Organization; 2020.

- This 2020 recommendation is an update of a 2016 recommendation as part of the *WHO recommendations on antenatal care for a positive pregnancy experience*, both of which followed procedures of the *WHO handbook for guideline development*.
- In 2019, the Executive Guideline Steering Group (GSG) prioritized the update of the 2016 recommendation in response to new evidence on this intervention.
- The 2020 recommendation states: Antenatal multiple micronutrient supplements that include iron and folic acid are recommended in the context of rigorous research. Research in this context includes:
    - Controlled clinical trials in which early pregnancy ultrasound is used to establish gestational age with certainty, with assessment of critical maternal and perinatal outcomes, and follow-up of infants sustained into childhood; and
    - where programmes of MMS are being considered, implementation research to establish the impact of switching from iron and folic acid supplements to MMS,

including evaluation of acceptability, feasibility, sustainability, equity and cost-effectiveness.

- The below table compares the original 2016 recommendation and the recommendation updated in 2020.
- An editorial to describe the rationale of the recommendation and the evidence that informed the updated recommendation was published in BMJ.
- After the publication of this recommendation, as part of living guidelines approach, WHO is closely monitoring new research conducted in this area and the Executive GSG will assess the need for an update as new impactful evidence emerge.

As communicated in our meeting on 25 May 2021, it is highlighted that these recommendations on the use of MMS are all context-specific recommendations, with the recommendation for use of MMS in emergencies being in the form of a joint statement form 2007 developed prior to the institution of the current WHO's guideline development process that is overseen by the GRC, the recommendation on its use for patients with tuberculous being conditional and based on very low quality of evidence, and the recommendation for its use as part of routine antenatal care in the context of rigorous research only. There is concern from the represented departments that inclusion of MMS on the EML at this time would send a mixed message to users of the EML and national governments that MMS is now unconditionally recommended for broader use and will undermine the possibility of addressing research gaps and impede a future WHO guideline updating process and consequent recommendations on this subject.

Thank you

	2016 recommendation	**2020 recommendation**
Multiple micronutrient supplements during pregnancy *(Changed to context-specific – research)*	Multiple micronutrient supplementation is not recommended for pregnant women to improve maternal and perinatal outcomes. *(Not recommended)*	**Antenatal multiple micronutrient supplements that include iron and folic acid are recommended in the context of rigorous research.** *(Context-specific recommendation – research)*

Critical remarks	There is some evidence of additional benefit of MMN supplements containing 13–15 different micronutrients (including iron and folic acid) over iron and folic acid supplements alone, but there is also some evidence of risk, and some important gaps in the evidence. Although the GDG 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 MMN supplements on maternal health to outweigh the disadvantages, and may choose to give MMN supplements that include iron and folic acid.	Research in this context includes: • controlled clinical trials in which early pregnancy ultrasound is used to establish gestational age with certainty, with assessment of critical maternal and perinatal outcomes, and follow-up of infants sustained into childhood; and • where programmes of MMS are being considered, implementation research to establish the impact of switching from iron and folic acid supplements to MMS, including evaluation of acceptability, feasibility, sustainability, equity and cost-effectiveness. Many MMS contain 30 mg or less of elemental iron and WHO recommends antenatal iron (and folic acid) supplements containing 60 mg of elemental iron in populations where anaemia is a severe public health problem (a prevalence of 40% or higher). Therefore, countries should consider their population magnitude and distribution of anaemia, its nutritional determinants (i.e. iron deficiency), as well as the magnitude and distribution of the complex low birthweight and its component parts (i.e. preterm, small for gestational age [SGA] or a combination of these), when undertaking any research in the context of this recommendation.

World Health Organization

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