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Cost-Effectiveness Analysis and Priority Setting in the Transition from Iron-Folic Acid (IFA) to Multiple Micronutrient Supplementation (MMS) for Pregnant Women in Indonesia

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Introduction: The World Health Organization (WHO) has advocated for multiple micronutrient supplementation (MMS) for pregnant women since 2016 to mitigate the risk of various complications. As a country considering investment in MMS, Indonesia requires an assessment of the cost-effectiveness analysis and priority setting in the transition from IFA to MMS, which is essential in the decision-making process.

Methods: An open-access online modelling tool was used to estimate the cost-effectiveness of MMS (ICERs per DALY averted) at national and sub-national levels (38 provinces) in Indonesia. The results were then prioritized via a cost-effectiveness league table, with a deterministic sensitivity analysis testing the robustness of the results.

Results: Implementing MMS under 44% and 100% coverage scenarios has the potential to avert 54,897 and 124,766 DALYs in Indonesia, respectively, and produced an equivalent incremental cost-effectiveness ratio (ICER) value of USD 10 per DALY averted, which is regarded as highly cost-effective. Since costs and benefits scale linearly with coverage, ICER per DALY averted stays unchanged. The MMS program is recommended to be prioritized in 18 provinces having favorable ICERs, which are Southwest Papua, Highlands Papua, Bali, West Java, South Kalimantan, North Maluku, West Papua, Aceh, North Sumatra, Central Java, Central Kalimantan, West Sulawesi, Maluku, Yogyakarta, East Java, North Kalimantan, South Sulawesi, and South Papua. Related to the sensitivity analysis, the cost of MMS and IFA are the most significant variables influencing the ICER value.

Conclusion: The findings show that the implementation of MMS, in comparison to IFA, produces a highly cost-effective outcome in 44% and 100% scenarios. The MMS implementation strategy may initiate with a 44% coverage scenario across 18 prioritized provinces, subsequently expanding to achieve 100% coverage for all pregnant women in Indonesia.

Keywords: cost-effectiveness, economic evaluation, iron-folic acid, multiple micronutrient supplementation, pregnant woman

Introduction

During pregnancy, adequate maternal nutrition is required to provide the increased nutritional requirements necessary for metabolic maintenance and fetal growth.[1–4] In 2020, the Indonesian Ministry of Health documented 4627 maternal deaths, indicating an increase relative to 2019.[5] The increase is attributed to the poor nutritional status of pregnant women.[6,7] Insufficient multiple micronutrients during pregnancy can increase the risk of complications, including anemia, which affects about 40% of pregnant women globally and peaks at 49% in Southeast Asia.[8,9] Multiple micronutrient insufficiency could negatively impact pregnancy outcomes, leading to fetal loss, low birth weight

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(LBW), preterm birth, preeclampsia, small for gestational age, postpartum depression, elevated risk of neural tube defects, and increased mortality risk.[1,10,11] These have been related to immunological development and inadequate neurodevelopmental outcomes in children.[12,13] Inadequate development during childhood can extend into adolescence and adulthood, resulting in poor academic performance, reduced income, and reduced human capital.[12]

To reduce the risk of various complications, the World Health Organization (WHO) has promoted the supplementation of pregnant women with multiple micronutrient supplementation (MMS) since 2016.[14] The administration of MMS is recommended at a dosage of 180 tablets during the first six months of pregnancy.[15] MMS is crucial for cellular metabolism, development, and maintaining normal physiological functioning in the human body. MMS is a micronutrient containing 15 vitamins and minerals that fulfill the body's nutritional requirements. Micronutrient composition as specified by the United Nations International Multiple Micronutrient Antenatal Preparation – multiple micronutrient supplements (UNIMMAP – MMS) consists of vitamin A (800µg), vitamin D (5µg), vitamin E (10mg), vitamin C (70mg), vitamin B1 (1,4mg), vitamin B2 (1,4mg), vitamin B6 (1,6mg), vitamin B12 (2,6 µg), folic acid (400µg), iron (30mg), zinc (15mg), iodine (150µg), selenium (65µg), niacin 18mg, and copper (2mg).[16–18] MMS plays essential roles for human reproduction from early pregnancy, facilitating gametogenesis, fertilization, embryogenesis, and the development of placental function, redox balance, and vascularization.[2,19–21] MMS contributes a significant role in metabolic processes essential for cell proliferation, growth, and protein synthesis in early pregnancy, and it is crucial for the establishment of the fetal genome throughout gestation. Furthermore, MMS plays an essential role in organogenesis, the development of the fetal central nervous system, and early brain development. MMS is also critical in regulating hemoglobin metabolism and optimizing mitochondrial function during pregnancy.[2,11] MMS was shown to reduce oxidative stress and improve mitochondrial function in a study conducted in Lombok, Indonesia.[11] As a result, the risk of fetal loss or miscarriage was reduced by 10%, the risk of infant death was reduced by 18%, and the risk of LBW and premature birth was reduced by 14%. This was compared to using iron and folic acid (IFA) alone. Research conducted on a group of pregnant women who suffered from anemia revealed more substantial findings, including a reduction of the risk of fetal loss and neonatal mortality by 29%, a reduction of the risk of newborn death by 38%, and a reduction of the risk of low birth weight by 25%.[2]

In October 2024, the Indonesian government started to implement MMS to improve maternal nutrition nationwide, though it remains in the initial phases.[22–24] However, the transition from IFA to MMS tablets in Indonesia might take several years and require critical resources, including human capital and financial investment.[25] MMS may receive significant government attention and influence healthcare policies. Consequently, the government requires an economic evaluation study as a critical component in the decision-making process. Given Indonesia's extensive territory, high population density, and the unmet nutritional requirements for pregnant women across its provinces, a comprehensive economic evaluation is necessary to facilitate informed decision-making by policymakers in allocating budgets, resources, and areas of coverage for maternal and child health programs.[14,20,26–29] Numerous studies in Bangladesh,[14,26–28] India,[28,29] Pakistan,[28,29] Tanzania,[29] Mali,[29] and Burkina Faso[14] have shown that MMS was a cost-effective intervention compared to IFA in enhancing maternal and child health.[14,26–29] This is the first study aimed at evaluating the cost-effectiveness of transitioning from IFA to MMS in Indonesia for enhancing maternal and child health, and its implications for priority setting in Indonesia based on their incremental cost-effectiveness ratio (ICER).

Methods

Model Setting

We applied an open-access online modeling MMS cost-benefit tool developed by Nutrition International to estimate the cost-effectiveness of MMS compared to IFA in Indonesia at the national and sub-national levels (38 provinces). The MMS Tool incorporates a comprehensive set of background data into its foundational model, which has passed quality assurance by technical specialists to guarantee its accuracy, recentness, and relevance.[30–32] MMS tools supply national and global policymakers with context-specific assessments that evaluate whether antenatal MMS is more cost-effective compared to IFA.[31,32] A 10-year time horizon was applied to assess the cost-effectiveness value, given the substantial effectiveness of MMS in pregnant women. In these scenarios, we applied a coverage scenario at 44% on a national level

(baseline), reflecting the current national adherence level of the IFA program in Indonesia, which stands at 44%,[33] and a 100% coverage scenario, which is a hypothetical highest cost scenario. The assumption of 180 tablets consumed by each pregnant woman was utilized following WHO recommendations.[3,9] The cost-effectiveness analysis of transitioning from IFA to MMS utilized a population of approximately 211,351 pregnant women, as indicated by the 2023 Indonesian Health Survey data.[33] We analyzed the projected economic results of MMS compared to IFA at both the national and provincial levels. Additionally, we calculated the ICER by dividing the incremental costs by the disability-adjusted life years (DALYs). The incremental cost-effectiveness ratio (ICER) was calculated using the standardized Cost-Benefit Tool developed by Nutrition International. This tool, which is publicly available on their website (accessible at: https://www.nutritionintl.org/learning-resources-home/mms-cost-benefit-tool/), generates ICER values automatically. Consequently, the results presented in the manuscript are the direct output from this validated tool. The economic value of DALYs averted, reflecting the total economic benefits of transitioning to MMS, is estimated using a monetised DALY approach based on the Value of Statistical Life (VSL). The VSL quantifies the monetary amount an individual is prepared to pay to prevent injury or illness, with variations observed across different countries. Various methods exist for calculating the VSL for a country. This MMS Tool utilizes country-level VSL estimates in LMICs from Viscusi and Masterman[34] to derive the Value of a Statistical Life Year (VSLY) by dividing the VSL by the expected life expectancy at birth. The economic value of DALYs averted is calculated by taking the product of the estimated discounted DALYs averted in a particular scenario by the corresponding country's VSLY. The calculation of the number of DALYs averted incorporates a discount rate of 3%.[31,35]

Cost Data

Costs are determined from the government's perspective as the health system provider. The MMS cost-benefit modeling tool was designed according to fixed input cost parameters that covered three categories of costs: the cost of IFA, the cost of MMS, and the transition cost (Table 1). These costs are related to a transition from the IFA to the MMS program.[30–32] All costs were converted to USD (2024). The cost of MMS was determined using the United Nations International Children's Emergency Fund (UNICEF) Supply Catalogue.[36] The highest price of MMS was set at USD 4 (IDR 61,600) for 180 tablets. The IFA cost was determined by the decree issued by the Indonesian Ministry of Health regarding drug claim prices. Price differences among regions in Indonesia arise from governmental authorities that adjust drug price claims according to logistics expenses, distribution factors, and geographical characteristics specific to each region.[37] IFA supplementation requires 180 tablets to ensure 6 months of coverage, and it was priced at USD 3.31 (IDR 50,940).

Transition costs include a range of expenditures that extend beyond direct interactions between patients and providers. These include logistical expenses and administrative costs at national and provincial levels, as well as investments in training, nutrition education activities, media promotion, and supervision mechanisms.[38,39] In this scenario, the transition

Table 1 Breakdown of Costs (2024 USD/ IDR)

No	Region	Cost of IFA	Cost of MMS	Transition Cost
1	Region 1	2.64 (40,680)	3.34 (51,436)	0.43 (6622)
2	Region 2	2.81 (44,820)	3.48 (53,592)	0.45 (6930)
3	Region 3	3.04 (46,800)	3.73 (57,442)	0.48 (7392)
4	Region 4	3.17 (48,780)	3.86 (59,444)	0.50 (7700)
5	Region 5	3.31 (50,940)	4.00 (61,600)	0.52 (8008)
6	Region 6	3.31 (50,940)	4.00 (61,600)	0.52 (8008)
	INDONESIA	**3.31 (50,940)**	**4.00 (61,600)**	**0.52 (8008)**

Notes: Regional 1: Lampung, Banten, Jakarta, West Java, Central Java, Yogyakarta, East Java, and Bali, Regional 2: North Sumatra, West Sumatra, Riau, Jambi, South Sumatra, Bengkulu, Bangka Belitung Islands, and West Nusa Tenggara, Regional 3: Riau Islands, Aceh, West Kalimantan, South Kalimantan, East Kalimantan, North Sulawesi, Central Sulawesi, and South Sulawesi, Regional 4: Central Kalimantan, North Kalimantan, Southeast Sulawesi, Gorontalo, and West Sulawesi, Regional 5: East Nusa Tenggara, Maluku, North Maluku, West Papua, and Southwest Papua, Regional 6: Papua, South Papua, Central Papua, and Highland Papua.
Abbreviations: MMS, Multiple Micronutrient Supplementation; IFA, Iron-Folic Acid.

cost is set with an additional 13% markup rate applied to the medicine and supply price (ie MMS price) to cover logistics and administrative costs. The costs associated with program transition can constitute an essential component of the total costs.[38,39] Table 1 presents the cost data at both the national and provincial levels.

Maternal Health Parameters

The effect measure is captured as DALY averted. DALY quantifies the overall disease burden by integrating years of life lost due to premature mortality (YLLs) and years lived with disability (YLDs). One DALY lost signifies one year of healthy life lost; consequently, one DALY averted corresponds to the acquisition of one year of healthy life. Assessing the cost per DALY averted allows for the comparison of various health interventions and the evaluation of an intervention's impact.[26]

The approach examines supplements based on their effectiveness in affecting various health outcomes. This study utilized an open-access online MMS cost-benefit modeling tool developed by Nutrition International,[30–32] which was designed according to fixed input maternal health parameters as identified in two published reviews, Keats et al, 2019[40] and Smith et al, 2017.[41] The following maternal health parameters examined in this study, including life expectancy at 73.93 years,[33] maternal anemia at 27.7%,[33] preterm birth at 11.1%,[33] SGA (small for gestational age) at 23.8%, LBW at 6.1%,[33] stillbirth at 10.5 per 1000 births,[42] maternal mortality at 189 per 100,000 live births,[42] neonatal mortality (male and female) at 3.3–3.5 per 1000 live births,[42] and infant mortality at 7.8 per 1000 live births.[42] These numbers are based on national data from the literature. Sources of health outcomes data include the Indonesian Health Survey 2023[33] (ie, for preterm birth, maternal anemia, LBW, and life expectancy), the Indonesian Health Profile 2023[42] (ie, for stillbirth, maternal mortality, neonatal mortality, and infant mortality), and research journals. To determine which provinces should be prioritized in conducting the IFA to MMS transition program, the data collection results were divided into 38 Indonesian provinces (see Table 2).

Priority Setting

We applied a cost-effectiveness league table to evaluate the prioritization of MMS implementation by comparing the ICER in each province to the national ICER. The cost-effectiveness league table can serve as a tool for resource and budget allocation. A cost-effectiveness league table is a commonly utilized tool for quantitatively ranking priorities based on efficacy, safety, and costs. Healthcare resources could be distributed according to the strategies listed in the league table, beginning with the province with the lowest ICERs and subsequently progressing to the provinces with higher ICERs in the ranking.[43] In provincial-level scenarios, we adopted a baseline population coverage of 44%, consistent with the national level.

Sensitivity Analysis

We applied one-way deterministic sensitivity analyses to identify variables that might significantly affect results. We performed a one-way deterministic sensitivity analysis to investigate the effects of different input parameters on ICER. All parameters were adjusted by plus or minus 25% for DALYs lost and associated costs.[44]

Results

Maternal Health Outcomes

Implementing MMS in the 44% and 100% coverage scenarios resulted in 54.897 and 124,766 DALYs averted in Indonesia, respectively. MMS was estimated to have an impact on both scenario (44% and 100% coverage scenarios), resulting in 20,305 and 46,148 DALYs averted in stillbirth, 11,965 and 27,194 DALYs averted in neonatal mortality, 12,879 and 29,271 DALYs averted in preterm birth, 106 and 241 DALYs averted in LBW, 5656 and 12,855 DALYs averted in infant mortality and 9061 and 20,592 DALYs averted in SGA, respectively (Figure S1).

Cost-Effectiveness Analysis

According to the perspective of the Indonesian government as the health system provider, the implementation of MMS yielded ICER values of USD 10 per DALY averted in the 44% coverage scenario. Implementing MMS under 100% coverage scenarios yielded an identical ICER value of USD 10 per DALY averted. Variations in coverage will affect the

Table 2 Maternal Health Parameters

No	Province	Population	LE (at Birth) (y.o)	Maternal Anemia (%)	Preterm Birth (%)	SGA (%)	LBW (%)	Maternal Mortality (Per 100K Live Births)	Stillbirth (Per 1000 Live Births)	Infant Mortality (Per 1000 Live Births)	Neonatal Female Mortality (Per 1000 Live Births)
1	Aceh	3881	73.06	3.6	29.5	8.77	4.4	134	7.90	12.4	5.3
2	North Sumatera	10,891	73.67	3.3	36.9	23.81	3.1	202	3.49	4.4	2.0
3	West Sumatera	3993	74.14	4.6	8.4	8.61	5.9	118	8.03	10.0	3.6
4	Riau	4976	74.18	4.2	10.1	11.66	5	136	6.39	7.2	3.2
5	Jambi	2789	73.84	4.3	7.2	5.99	2.7	50	5.90	6.3	2.8
6	South Sumatera	6524	74.04	2.6	18.3	15.91	5.4	106	4.23	4.4	1.8
7	Bengkulu	1594	73.11	6.2	8.1	3.25	5	38	5.41	10.9	4.4
8	Lampung	7306	74.17	1.5	6.4	13.50	4	110	3.90	6.0	2.6
9	Bangka Belitung Islands	1126	73.90	4.2	12	2.38	6.6	39	13.33	10.3	4.1
10	Riau Islands	1667	74.90	4.9	8.7	4.99	4.9	49	3.93	5.8	2.3
11	Jakarta	7654	75.81	10.1	7.9	16.92	6.7	115	10.54	6.0	2.5
12	West Java	39,608	74.91	3	10.5	86.01	6.2	792	10.01	6.3	2.7
13	Central Java	28,907	74.69	4.9	5.6	48.04	6.1	466	17.91	9.9	3.8
14	Yogyakarta	2619	75.18	7	4.9	3.66	7.2	26	21.52	10.1	3.8
15	East Java	32,020	74.87	3.7	6.9	53.22	6.8	499	10.14	7.7	3.2
16	Banten	9580	74.77	3.3	6.7	24.02	5.1	209	4.30	6.5	2.8
17	Bali	3293	74.88	5.9	3.7	6.53	4.7	40	45.99	9.7	3.6
18	West Nusa Tenggara	4441	72.02	6	5	9.25	5.3	97	8.76	9.1	4.0
19	East Nusa Tenggara	3779	71.57	6.9	7.8	7.65	7.7	135	13.27	13.5	5.5
20	West Kalimantan	2201	73.71	4.9	5.6	8.53	7	136	8.84	10.0	4.4
21	Central Kalimantan	3121	73.54	4.4	6.2	4.24	5.6	77	5.13	12.5	5.4
22	South Kalimantan	2953	73.97	8.3	5.4	6.53	7.8	102	24.59	12.5	5.2
23	East Kalimantan	551	74.72	5.3	6.4	6.28	7.3	83	11.00	10.1	4.2
24	North Kalimantan	1956	73.54	5.4	3.1	1.32	7.7	20	19.16	11.9	5.0
25	North Sulawesi	2320	73.85	3.8	17.1	2.72	5.7	42	2.41	7.0	2.8
26	Central Sulawesi	6762	70.66	4.7	15.4	3.78	7.9	67	7.28	9.1	3.9
27	South Sulawesi	1979	73.63	7.2	14.2	14.37	7	184	12.66	10.4	4.5
28	Southeast Sulawesi	925	71.79	3.2	13.6	4.52	5.3	74	4.10	8.9	3.8
29	Gorontalo	1100	70.50	5.6	6.6	1.95	7.8	23	11.60	7.3	2.9
30	West Sulawesi	1375	70.76	5.7	6.6	2.51	6.6	48	19.22	14.9	5.7
31	Maluku	957	70.45	4.6	27.9	2.85	4.9	77	9.39	9.7	3.8
32	North Maluku	429	70.76	1.9	20.3	2.16	3.8	50	20.71	14.0	5.2
33	West Papua	481	68.51	23.6	14.2	0.61	4.9	31	11.56	22.8	10.2
34	Southwest Papua	686	68.51	5.6	34.3	0.09	6.5	11	81.21	134.6	55.4
35	Papua	358	68.17	18.9	10.7	1.54	5.3	29	10.24	11.9	5.2
36	South Papua	1174	68.17	11.5	6.9	1.00	6	23	19.03	14.9	5.1
37	Central Papua	1062	68.17	3	8.3	0.95	8	13	6.47	15.1	6.5
38	Highland Papua	3881	68.17	5.5	21.2	0.04	6.1	9	25.00	52.5	15.8
	INDONESIA	211,351	73.93	27.7	11.1	23.8	6.1	189	10.5	7.8	3.3

Abbreviations: LE, Life Expectancy; SGA, Small for Gestational Age; LBW, Low Birth Weight.

overall costs and benefits, both of which change linearly and proportionally. This is, provided that the ICER, defined as the cost per DALY averted, remains unchanged. The MMS implementation is considered highly cost-effective, as the ICERs remained significantly below the Indonesian one GDP per capita (USD 4870.13) in 2024.[45]

Priority Setting

The MMS implementation in each province is considered highly cost-effective. The ICER of each province in Indonesia is presented in a cost-effectiveness league table (supplementary material 2). Nevertheless, determining priority coverage areas is crucial due to budget constraints and significant disparities in monetary value across different provinces.[46] The resource and budget allocation applied to the national ICER as a cost-effectiveness cut-off value. Provinces prioritized for the introduction of MMS in Indonesia are those with ICER values lower than the national ICER value (USD 10 per DALY averted). Therefore, the implementation of the MMS program is recommended to be prioritized in 18 provinces: Southwest Papua, Highlands Papua, Bali, West Java, South Kalimantan, North Maluku, West Papua, Aceh, North Sumatra, Central Java, Central Kalimantan, West Sulawesi, Maluku, Yogyakarta, East Java, North Kalimantan, South Sulawesi, and South Papua as illustrated in Table 3 and Figure 1.

Sensitivity Analysis

Related to the sensitivity analysis, MMS cost and IFA cost seemed to be the most influential variables affecting the cost-effectiveness value in the implementation of MMS. Other variables that importantly influence the cost-effectiveness value are stillbirth, life expectancy (at birth), neonatal mortality (female), preterm birth, and small gestational age as presented in a tornado chart (Figure S2).

Table 3 Cost-Effectiveness League Table

No	Province	GDP/GRDP Per Capita[47] (USD/IDR 2024)	ICER Per DALY Averted (USD/IDR 2024)
1	Southwest Papua	3850.21	1 (15,400)
2	Highland Papua	1111.26	4 (61,600)
3	Bali	4103.35	5 (77,000)
4	North Maluku	4194.52	7 (107,800)
5	South Kalimantan	4201.24	7 (107,800)
6	West Java	3468.22	7 (107,800)
7	West Papua	7120.81	7 (107,800)
8	Aceh	2688.23	8 (123,200)
9	Central Java	2977.34	8 (123,200)
10	Central Kalimantan	4959.75	8 (123,200)
11	Maluku	2006.19	8 (123,200)
12	North Sumatera	4435.45	8 (123,200)
13	West Sulawesi	2604.11	8 (123,200)
14	East Java	4684.94	9 (138,600)
15	North Kalimantan	13,289.57	9 (138,600)
16	South Papua	3865.36	9 (138,600)
17	South Sulawesi	4591.40	9 (138,600)
18	Yogyakarta	3185.43	9 (138,600)
	INDONESIA	**4870.13**	**10 (154,000) highly cost-effective**

Abbreviations: GDP, Gross Domestic Product; GRDP, Gross Regional Domestic Product; ICER, Incremental cost-effectiveness ratio; DALY, the disability-adjusted life year.

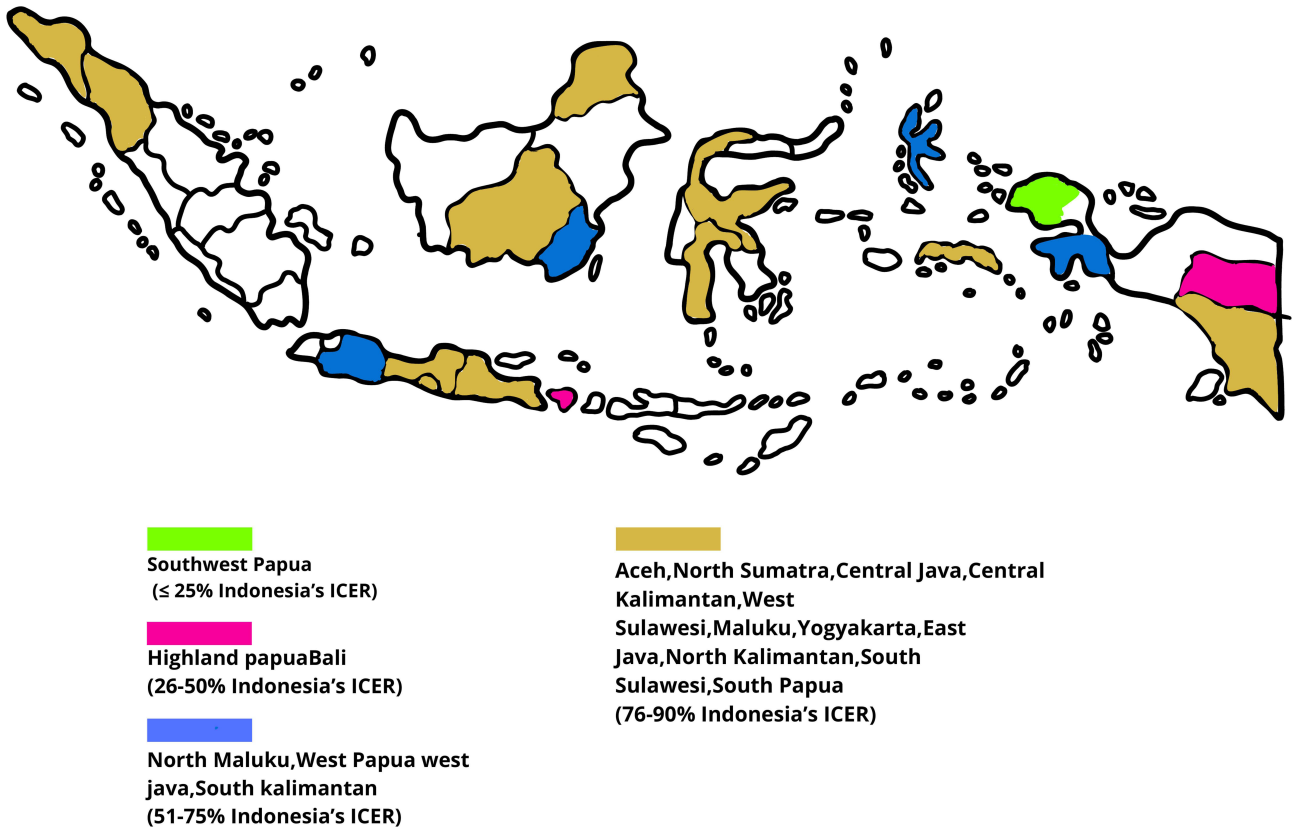

Figure 1 Priority setting for the MMS Program in Indonesia.

Discussion

Insufficient maternal nutritional intake significantly contributes to adverse birth outcomes.[1,8,10,11] The WHO has advocated for the supplementation of pregnant women with MMS since 2016 to decrease the risk of numerous complications.[9] Our findings show that the projected positive impacts of transitioning from IFA to MMS resulted in reduced mortality rates and adverse birth outcomes. The monetary investment necessary to realize these improvements indicates a cost-effective outcome. Additionally, priority setting based on cost-effectiveness was considered a reasonable option to guide decision-makers in resource allocation to maximize health outcomes, serving as a key consideration in strategic planning for achieving universal health coverage.[48,49] Furthermore, the outcomes exhibited stability throughout one-way deterministic sensitivity analyses, indicating that these conclusions were reliable.

Assuming that all pregnant women adhere to a regimen of 180 pills throughout their pregnancies, the transition from IFA to MMS is projected to 54,897 (44% coverage scenario) and 124,766 (100% coverage scenario) DALYs would be averted in Indonesia. The difference in DALYs averted between the 44% and 100% coverage scenarios is attributable to the differing number of women who benefit from the intervention in each case. With 100% coverage, a greater percentage of pregnant women receive MMS, resulting in a more significant overall decrease in negative maternal and neonatal health outcomes, thus yielding higher DALY estimates. Consuming 180 MMS tablets has played an essential role in pregnant women from early pregnancy in human reproduction, facilitating gametogenesis, fertilization, embryogenesis, placental development, function, redox balance, and vascularization.[19–21,50] The growth and function of the placenta are crucial throughout pregnancy to reduce the risk of LBW (14%). MMS demonstrates improved mitochondrial function, which is associated with a reduced risk of premature birth (14%). MMS contributes to hemoglobin metabolism, thus decreasing the risk of anemia in pregnancy. MMS effectively reduces the risk of infant mortality (18%).[1,8,10,11,50,51] It is crucial to highlight that, even at existing coverage levels, significant reductions in maternal and child mortality and morbidity are projected in Indonesia if there is high adherence to the prescribed amount of tablets.[14] Adherence level is

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crucial for maximizing the health advantages of MMS intervention[20] since medication non-adherence has been identified as a major contributor to health issues and economic burden.[52] A report concerning the previous IFA program in Indonesia shows that the adherence rate for the consumption of 90 IFA tablets is merely 44%.[33] Consequently, adherence to MMS consumption will be a potential challenge that must be addressed.

As a country considering investment in MMS, Indonesia requires an assessment of the cost-effectiveness of transitioning from IFA to MMS.[29] The MMS cost-benefit tool was utilized to quickly calculate predictions regarding maternal and child health outcomes, as well as the cost-effectiveness of MMS in comparison to IFA for pregnant women. The MMS cost-benefit tool works as an evidence-based modeling instrument designed to facilitate national and international policymakers' access to data that aids in evaluating the cost-effectiveness of transitioning from IFA to MMS for pregnant women. The MMS cost-benefit tool presents a valuable resource for countries to perform comprehensive, sub-national, and ongoing analyses within the framework of implementation research on MMS.[31]

Our findings prove that transitioning from IFA to MMS is highly cost-effective based on the threshold of one to three times Indonesia's GDP per capita, in the absence of country-specific thresholds.[53] Our analysis shows that the implementation of MMS under both 44% and 100% coverage scenarios produced an equal ICER value of USD 10 per DALY averted at the national level. The ICER is consistent across the two scenarios, as it is defined as the additional cost per DALY averted in relation to IFA supplementation. The proportional scaling of both costs and effects with coverage in the modeling framework ensures that the ratio of incremental costs to health benefits remains constant. This demonstrates the difference in the absolute number of DALYs between the two scenarios, despite the constancy of the ICER. The spending required to achieve these improvements, which is below one GDP per capita (USD 4870.13) in 2024, signifies a favorable cost-benefit ratio. Cost-effectiveness analysis provides a quantitative evaluation of both current and prospective efficiency in a health system.[49] The cost-effectiveness of the IFA-MMS transition in reducing maternal and child mortality and morbidity (eg, neonatal mortality, infant mortality, LBW, preterm births, stillbirth, and SGA) has proven beneficial. Given that most lives saved would occur in the early stages of life, the policy of transitioning from IFA to MMS is worthy of consideration.

Currently, MMS is in the initial phases of implementation in Indonesia. The findings of this study support decision-making on the possibility of MMS being expanded as a key focus within Indonesia's national health program, serving as a primary strategy for lowering the risk of numerous complications in pregnant women.[48,49,54] The findings of this study align with previous studies conducted in Bangladesh,[14,26–28] Burkina Faso,[14] Pakistan,[28,29] India,[28,29] Mali,[29] and Tanzania,[29] which indicated that transitioning from IFA to MMS is considered a cost-effective intervention to enhance maternal and child health. This is the first study conducted in Indonesia addressing this issue.

Related to the sensitivity analyses, the results in this study showed that the cost-effectiveness value was sensitive to changes in MMS cost. Numerous variables can influence MMS costs, including procurement regulations, the volume, and consistency of purchasing bargains with tablet ingredient suppliers, packaging methods, and tablet quantities.[14,18,36,55–57] Consequently, the introduction of MMS at accessible costs is essential, particularly for low- and middle-income countries (LMICs), including Indonesia.[55] Scale economies in tablet production are crucial therefore, the domestic manufacture of MMS in Indonesia should be initiated to provide a consistent, affordable, and high-quality supply of MMS, while supporting the expansion of MMS coverage.[14,58] Domestic manufacture of MMS could be accomplished by following the standards established by the MMS Technical Advisory Group, alongside a comprehensive technical understanding of the manufacturing prerequisites for the UNIMMAP–MMS product, and the methodologies to ensure that the produced product achieves its expected quality.[14,18]

As Islam is the major religion among Indonesia's population, ensuring halal compliance is essential. The UNIMMAP–MMS product can be produced in compliance with Halal standards established by local authorities.[18] Indonesia is home to over 207 million Muslims, representing 87.2% of the population.[59] Halal is an essential concept for Muslim consumers concerning the products they consume, including pharmaceutical ingredients. In contemporary medicine, these ingredients must be completely free of porcine (0%) and contain less than 1% alcohol.[60,61]

In October 2024, the Indonesian Ministry of Health announced the immediate initiation of MMS in Indonesia, a program currently in its early stages.[22–24] Switching from IFA to MMS tablets in Indonesia may require several years and substantial resources, particularly personnel and budgetary expenditure, given the country's expansive territory and

dense population.[25] Due to logistical and budget limitations, determining priority coverage areas is essential to mitigate the disease burden associated with nutritional deficiencies among pregnant women. This involves identifying higher-risk groups and regions where preventive measures are expected to be most effective, thereby maximizing public health returns on investment.[20,46]

Priority settings should focus on optimizing population health, and the availability of further knowledge regarding cost-effectiveness will enhance decision-making and result in improved health outcomes as one consideration in strategic planning.[48,49] Cost-effectiveness evidence in each province enables policy-makers to assess the effective and efficient use of available resources. It also guides optimal investment strategies to meet health targets and achieve universal health coverage within the constraints of limited resources, ensuring the optimal allocation of financial resources in the healthcare sector.[38,49] Universal health coverage signifies that every individual has access to a comprehensive array of quality health services as required, without experiencing financial difficulties.[62] Based on the results of the cost-effectiveness analysis, it's recommended to prioritize introducing the MMS program in 18 provinces where the ICER is below Indonesia's national ICER of USD 10. The analysis commences with the province exhibiting the lowest ICERs, subsequently advancing to those with higher ICERs in the rank order.[43] Public health strategies prioritize introducing MMS programs, especially in provinces with poor maternal health outcomes. Expanding MMS programs in LMICs necessitates advancements in supply chain logistics and improved availability and access to health services.[15,63] The prioritization of MMS implementation allows for the distribution of healthcare resources under the strategies, starting with the province exhibiting the lowest cost-effectiveness and subsequently advancing to those with higher cost-effectiveness in the ranking.

To the best of our knowledge, our study is the first to assess cost-effectiveness analysis regarding the transition from IFA to MMS during pregnancy in Indonesia at the national and sub-national levels (38 provinces). The primary strength of this study is the use of country-specific data, which enables policymakers to make informed decisions regarding finance and resource allocation by prioritizing selected coverage areas in MMS implementation. Specifically, MMS programs have not yet been included in the national healthcare insurance coverage unit, and our study offers valuable insights into the implications of their potential inclusion. With regards to the shifting from IFA to MMS supplementation in Indonesia, our cost-effectiveness study demonstrates that the implementation of MMS is more advantageous than IFA, aligning with the WHO's recommendation to improve the quality of maternal and child health.

Nevertheless, this study has several limitations. The first limitation concerns a proposed transition cost that has been estimated based on population size to assess context-specific expenses associated with initiating a new program. These expenses include developing training components, establishing new policies and regulations, and training healthcare personnel; however, actual costs may differ. In the absence of more reliable data on transition costs, we perform a costing exercise for transition activities informed by a published article on the cost-effectiveness of interventions aimed at improving maternal, newborn, and child health outcomes: a WHO Choosing Interventions that are Cost-Effective (CHOICE) analysis for Eastern Sub-Saharan Africa and South-East Asia.[38] Consequently, we may have underestimated the transition cost. As for the second limitation, this study did not address MMS adherence. The analysis presumes that all "covered" pregnant women receive and take precisely 180 tablets. Achieving all consumption of a precise dosage of tablets by all covered women will be challenging and does not seem to occur systematically. Some pregnant women may take fewer than 180 tablets. Referring to the previous IFA program in Indonesia, a study indicates that the adherence level to the consumption of 90 IFA tablets is only 44%.[33] The costs associated with transitioning from IFA to MMS will rise, while the expected benefits will remain unchanged. Further attempts are required to address these issues. The third limitation is that the modeling tool for cost-benefit analysis, developed by Nutrition International, does not allow the inclusion of additional maternal health parameters that could be significant for assessing the effectiveness of MMS in pregnant women. The model focuses on health outcomes of interest, as identified in two published reviews, Keats et al, 2019[40] and Smith et al, 2017.[41] The fourth limitation is that probabilistic sensitivity analysis (PSA) cannot be performed using the open-access online MMS cost-benefit tool developed by Nutrition International because the tool is designed primarily to provide deterministic estimates based on fixed input parameters rather than full probabilistic modeling. While the tool incorporates rigorous methodologies to estimate health impacts, costs, and cost-effectiveness, it does not support Monte Carlo simulations or the input of probability distributions for parameters that allow quantification of

uncertainty across multiple model inputs simultaneously. However, the deterministic approach can be used to provide clear, interpretable results such as benefit-cost ratios and incremental cost per DALY averted based on fixed assumptions, but without performing full probabilistic uncertainty analysis. More complex PSA requiring simulation of parameter distributions and joint uncertainty are typically conducted offline using statistical software, as seen in some detailed cost-effectiveness studies of MMS interventions. Thus, while the tool does conduct some sensitivity analyses by varying key assumptions, full probabilistic sensitivity analysis is not supported in its open-access online version.

This study provides recommendations for policymakers in Indonesia to decide on following comprehensive policies to improve maternal and child health outcomes. Health enhancements throughout gestation and early childhood might lower the likelihood of poor health and disease, hence supporting life expectancy.[64] The additional budgetary requirement poses significant challenges to implement in a country with constrained healthcare budgets for maternal and child health programs. The MMS implementation strategy could start with a 44% coverage scenario across 18 prioritized provinces and gradually expand to 100% coverage for all pregnant women in Indonesia. This approach is critical for transitioning from the IFA to the MMS program. Transitioning from IFA to MMS represents the ideal approach for enhancing maternal and child health outcomes.[54] We are encouraged that the reviewer acknowledges the policy relevance of our findings and their potential to inform resource allocation and program planning for maternal nutrition interventions. Further study is required to incorporate a concise perspective on the necessity of supplementary qualitative or operational studies, which could highlight the significance of converting economic findings into practical implementation.

Conclusions

This study showed the ICER value of USD 10 per DALY averted for both scenarios (44% and 100% coverage), concluding that the transition from IFA to the MMS program was confirmed to be a highly cost-effective intervention. These results should facilitate decision-making that prioritizes maternal and child health. The MMS implementation strategy could start with a 44% coverage scenario across 18 prioritized provinces and gradually expand to 100% coverage for all pregnant women in Indonesia. This strategy is essential for the transition from the IFA to the MMS program in Indonesia. It is essential to identify several potential barriers to the implementation of the MMS program in Indonesia, including the adequacy of supply chain logistics, the improvement of health service availability and access, and the need for better adherence to MMS consumption.

Ethical Clearance

Data were obtained from publicly accessible documents, and human participants were not involved in this investigation. Consequently, ethical considerations regarding human participants were not necessary. Nevertheless, efforts were made to guarantee that the data were collected and analyzed in a manner that was both ethical and transparent.

Disclosure

The authors report no conflicts of interest in this work.

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