

STUDY PROTOCOL

04 May 2026

**Early-life thiamine supplementation for infant neurocognitive benefits:
a randomized controlled trial**

Summary of proposed research

Background: Thiamine (vitamin B1) is an essential micronutrient crucial for normal physiological functioning and healthy child development. Thiamine requirements increase with carbohydrate-rich diets (e.g. white rice) and during periods of high metabolism (e.g. perinatal women, infancy). The limited data available show that the prevalence of thiamine deficiency is high in women of childbearing age and their infants in several low- and middle-income settings, notably in South and Southeast Asia, where white rice is the dietary staple, but also in several African countries. Thiamine-deficient pregnant and lactating women produce breastmilk low in thiamine, putting their breastfed infants at risk of deficiency, and potentially fatal beriberi. In addition, recent evidence suggests that sub-clinical thiamine deficiency may be conferred prenatally, **placing millions of infants at risk of neurocognitive deficits, undercutting life-long well-being and productivity.**

Preliminary Data: In coordination with the Cambodian Ministry of Health, we undertook a four-parallel-arm, randomized, controlled trial (NCT03616288) in rural Cambodia to estimate the dose of maternal thiamine required post-partum to optimize breastmilk thiamine concentrations; secondary exploratory outcomes included neurocognitive assessments. Mothers were randomized to consume 0, 1.2, 2.4, or 10 mg daily thiamine from 2 weeks through 6 months postnatal. While milk thiamine concentrations were significantly higher in all thiamine groups compared to placebo, critically, at 6 months postnatal, only infants in the 10 mg/d group showed robust neurocognitive benefits. Additionally, infants whose mothers had higher milk thiamine concentrations at our pre-supplementation baseline (2 weeks postpartum) showed significantly improved neurocognitive outcomes at 6 months postnatal, suggesting that infants' prenatal access to adequate thiamine may have critical benefits for neurocognitive development.

Research Gap: Our prior trial indicated that 10 mg/d maternal thiamine supplementation, higher than current recommendations, was needed to support infant neurocognitive development in several domains. However, we started supplementation at 2 weeks postpartum. Given how much foundational neurodevelopment occurs from conception through infancy, earlier and longer thiamine supplementation -- starting in pregnancy and maintained through 18 months postnatal -- is likely to further support neurocognitive development.

Design: This will be a two parallel-arm, double-blind randomized controlled trial to compare the standard dose of thiamine in multiple micronutrient supplements throughout the perinatal and early childhood periods to a higher thiamine dose. Our primary outcome is infant neurocognitive development (Mullen Scales of Early Learning Early Learning Composite, MSEL-ELC) at 18 months postnatal. Secondary neurocognitive outcomes include the MSEL sub-scales, Global Scales of Early Development (GSED), and Visual Paired-Comparison Task (VPC), at 18 months postnatal.

Sample Size: To detect a mean difference in 3 points in MSEL scores with 90% power ($d=0.16$, two-tailed $\alpha=0.05$), and accounting for 20% losses, we would require $N=1,972$ participants, 986 per group, to detect the main effect on our primary outcome, MSEL-ELC, at 18 months postnatal.

Statistical Analysis for Primary Outcome: Scores on MSEL-ELC at 18 months will be compared between groups using a linear-regression model, with adjustment for health center, gestational age at enrolment, and birth anthropometry, and using generalized estimating equations with an independence working-correlation structure to account for multiple births. The effect of treatment will be described as a mean difference with a 95% CI. In all analyses, missing outcome data will be addressed using multiple imputation, performed separately by randomized group using chained equations. Outcomes will be analyzed on an intention-to-treat basis according to a prespecified Statistical Analysis Plan, which will be published in full alongside the study protocol on clinicaltrials.gov.

Feasibility: Our interdisciplinary team, including Helen Keller International, has a decade-long collaboration with the Ministry of Health and Ministry of Planning to combat thiamine deficiency in Cambodia. This, alongside our well-established, strong working relationships with the Provincial Health Department and Operational District officials, enhance the feasibility of this proposed study.

Study Objectives

Primary Objective

The primary aim is to assess the impact of thiamine dose during the first 1,000 days on infant neurocognitive development. The primary outcome measure will be the *Mullen's Scales of Early Learning "Early Learning Composite"* T-score (MSEL-ELC) at 18 months postnatal.

Secondary Objectives

Secondary objectives will explore other cognitive assessment measures, including the five MSEL sub-scales, the Global Scales of Early Development (GSED), and the Visual Paired-Comparison Task (VPC), as well as biomarker assessments of thiamine status (erythrocyte transketolase activity coefficient, and breast milk thiamine concentrations).

Background

Thiamine

Thiamine (vitamin B₁) is an essential water-soluble vitamin crucial for normal physiological functioning and healthy child development. Thiamine is a key cofactor in energy metabolism pathways for carbohydrates and amino acids, namely the Krebs cycle and pentose phosphate shunt, and is also essential for neurological function, with poor thiamine status impairing neurotransmitter synthesis (Whitfield et al. 2018). As will be discussed at greater length below, suboptimal thiamine intake in infancy can result in long-lasting, irreversible motor and cognitive deficits (Mimouni-Bloch et al. 2014).

Thiamine is found in meat, particularly pork and offal, pulses, soy, yeast, and whole grains (Agriculture Research Service USDA 2020). The recommended nutrient intakes (RNI) for children aged 1-3 years and pregnant and lactating women are just 0.5 mg, 1.1, and 1.4 mg thiamine daily, respectively (WHO & FAO, 2004), but with limited body stores and a short half-life, regular consumption is required to avoid deficiency (Whitfield et al. 2018). Given its roles, thiamine requirements increase with carbohydrate-rich diets (e.g. white rice) and during periods of high metabolism (e.g. pregnancy, lactation, infancy) (Elmadfa et al. 2001).

Thiamine deficiency: a public health issue

Thiamine deficiency has been historically categorized as wet beriberi (cardiac presentation), dry beriberi (neurological symptoms), infantile beriberi, and Wernicke-Korsakoff syndrome (alcoholics); more recently the term 'thiamine deficiency disorders' (TDD) was coined given the broad and overlapping symptoms of deficiency (Whitfield et al. 2018). Deficiency is most common among populations that consume a monotonous, carbohydrate-rich diet, usually polished, white rice; hence, deficiency is common in South and Southeast Asia (Johnson et al. 2019). **In Cambodia, 78% of women of reproductive age and 58% of children 5 years and younger have sub-optimal blood thiamine concentrations** (Whitfield et al. 2017).

Infantile thiamine deficiency

Thiamine deficiency is most concerning among infants as they require comparatively high amounts of thiamine relative to their small body size and low food intakes (Whitfield et al. 2018; Fattal-Valevski 2011). Infantile thiamine deficiency normally presents in the first six months - the exclusive breastfeeding period - when the only source of thiamine for these infants is mother's milk (Luxemburger et al. 2003; Smith et al. 2024). Since there are no body stores of thiamine, mothers must consume thiamine regularly to ensure adequate milk thiamine concentrations (Allen 2012). Infantile beriberi remains a cause of infant mortality in Cambodia, Laos, Myanmar, parts of India, as well as Africa and the South Pacific (Whitfield et al. 2018; Johnson et al. 2019). Here, mothers heavily reliant on rice as a dietary staple produce milk low in thiamine, putting their exclusively breastfed infants at high risk of developing beriberi (Dror and Allen 2018; Whitfield et al. 2017). Infantile beriberi can be fatal within hours of clinical presentation (Luxemburger et al. 2003), with symptoms including tachypnea, tachycardia, dysphonia, edema, cyanosis, colic, and vomiting (Smith et al. 2024). Moreover, sub-clinical thiamine deficiency not serious enough to

trigger potentially fatal beriberi is also concerning, leading to long-lasting cognitive impairment (Mimouni-Bloch et al. 2014).

Sub-clinical thiamine deficiency and infant neurocognitive development

An unfortunate ‘natural experiment’ among Israeli infants resulted from a manufacturing error that erroneously excluded thiamine from infant formula (Fattal-Valevski et al. 2005). These otherwise well-nourished infants had low thiamine intakes in early life. Many of these infants did not develop clinical beriberi symptoms; however, during follow-ups through childhood they displayed persistent language and motor delays compared to their peers (Fattal, et al. 2011; Harel et al. 2017; Mimouni-Bloch et al. 2014). **This recent evidence suggests that sub-clinical thiamine deficiency may put millions of infants at risk of neurocognitive deficits, undercutting life-long well-being and productivity.**

Supportive Preliminary Data

Biologically, thiamine plays a critical role in neurological functioning, with experimental research on non-human species confirming that thiamine deficiency has deleterious effects on neurological function generally, as well as discrete aspects of neurocognitive development more specifically (de Freitas-Silva et al. 2010). Certain neural regions in other species homologous to those known to sub-serve early human cognition are deleteriously affected by thiamine deficiency; in particular, the hippocampus and prefrontal cortex (Langlais and Savage 1995). Presuming analogous neural effects of thiamine in humans, these findings increase concern that thiamine deficiency undercuts critical early cognitive development in human infants (Prado and Dewey 2014).

In humans, accumulating observational evidence from Israeli infants (Fattal-Valevski et al. 2005; 2009) indicates that a diet deficient in thiamine undercuts infants’ neurocognitive development and, in particular, their early language development. Early language development is a foundational neurocognitive capacity that presages children’s rate of advance in other domains of neurocognition, as well as their future overall cognitive functioning (Murray et al. 2007). **A link between thiamine deficiency and possible delays in neurocognitive development is particularly concerning given that millions of children growing up in several global regions, including high population areas such as Southeast Asia, are at risk of thiamine deficiency** (Dias et al. 2013; Johnson et al. 2019; Whitfield et al. 2018).

Until recently, however, experimental evidence of thiamine’s role in human neurocognitive development was lacking. As well, questions remained about what specific neurocognitive abilities thiamine status might affect. As described elsewhere in this application, in coordination with the Cambodian Ministry of Health, **our team conducted the first experimental trial of early-life thiamine supplementation on infant neurocognitive development** (Whitfield et al. 2019). In this four-parallel-arm, randomized controlled trial (RCT), 335 rural Cambodian lactating mothers were randomly assigned to receive capsules containing either 0 (placebo control), 1.2 (estimated average requirement; EAR), 2.4 (2 x EAR), or 10 mg (positive control) of thiamine daily between 2 weeks and 6 months postnatal. The primary objective of the RCT was to assess the dose of thiamine required to optimize human milk thiamine concentrations, vital information required to inform future public health interventions. Thiamine deficiency remains a persistent concern in Cambodia where women with low thiamine intake produce thiamine-poor milk, putting their breastfed infants at risk of morbidity and potentially fatal infantile beriberi. This concern is relevant in most low- and middle-income countries (LMIC) where breastfeeding is common (and strongly encouraged) (Kramer and Kakuma 2012). However, given observational evidence of risks to infant neurocognitive development of deficient thiamine levels, this was also the first study to explore infants’ neurocognitive development with controlled thiamine exposures in the first 6 months postnatal. Clinically meaningful findings in several hypothesized domains in this RCT provide the motivation for our current proposal (Measelle et al. 2021; Baldwin et al. 2025).

The level of thiamine that infants’ lactating mothers received in a daily supplement beginning at 2 weeks postnatal displayed a dose–response relationship to infants’ receptive and expressive language development at 6 months as measured by the Mullen Scales of Early Learning (MSEL) (Measelle et al. 2021). See **Figure 1**. Notably, **infants whose mothers received a 10 mg daily thiamine supplement displayed significantly enhanced performance on both MSEL language measures at 6 months relative to all other supplementation levels (and, in particular, the 0 mg daily**

group). These findings indicate that thiamine supplementation at 10 mg daily confers a significant degree of protection for breastfed infants' language development during this early period of life. Importantly, while mothers achieved sufficient human milk thiamine concentrations at lower levels of supplementation (1.2 mg/day) (Gallant et al. 2021), only the dose of 10 mg/day produced robust benefit to infants' linguistic functioning (Measelle et al. 2021; Baldwin et al. 2025), which brought Cambodian infants close to language development norms on the MSEL for 6-month-olds in more advantaged countries (Measelle et al. 2021).

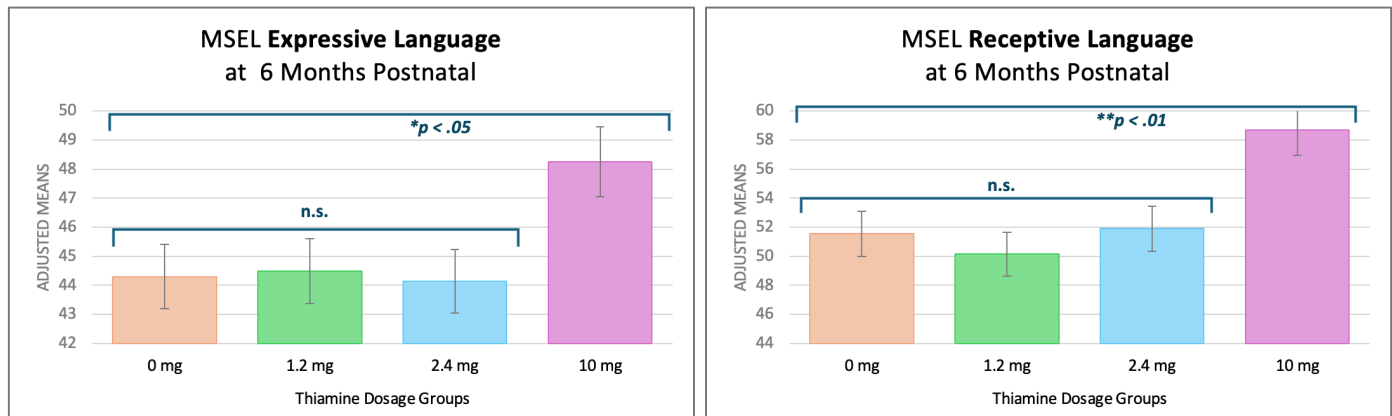


Figure 1: MSEL Expressive and Receptive Language domain scores from previous RCT (Measelle et al, 2021)

These findings in MSEL's language domains were further validated in our study using the **Infant-Directed Speech (IDS) Task**, which measures infants' well-documented enhanced attention to infant-directed versus adult-directed speech (Baldwin et al. 2025; ManyBabies Consortium, 2020). Among other things, infants' enhanced attention to infant- versus adult-directed speech appears to facilitate their ability to a) extract relevant messages from speech before they comprehend the linguistic content of that speech (e.g., Fernald 1995), b) detect when speech is directed to them (e.g., Csibra 2010), c) analyze linguistic patterns inherent within speech (e.g., Thiessen, Hill, & Saffran 2005; Werker et al. 2007), and d) link words to meanings (Graf Estes & Hurley 2013).

In short, infants' enhanced attention in response to infant- versus adult-directed speech serves as a powerful index of the integrity of their early, pre-verbal language-processing skills. In our previous RCT, maternal thiamine supplementation displayed a statistically significant dose-response relationship to the magnitude of infants' IDS-elicited attentional-enhancement; see **Figure 2**. Moreover, only infants whose mothers received a daily thiamine supplement of 10 mg showed fully robust IDS-related attentional enhancement.

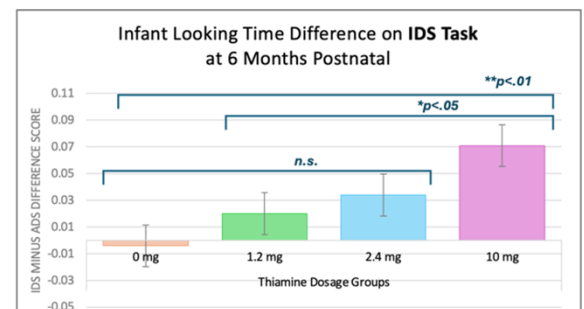


Figure 2: IDS looking time differences from previous RCT (Baldwin et al. *In Press*)

An additional, secondary, aim of our previous RCT was to explore effects of maternal thiamine supplementation on other foundational – yet non-linguistic – neurocognitive capacities. To this end, we used the **Visual Paired Comparison (VPC) task** to measure infants' visual encoding and discrimination skills. The VPC task tests the integrity of these foundational information-processing skills, which have broad and cascading effects on subsequent learning across many domains (Rose et al. 2008). Recent work utilizing a closely related visual working memory task in an LMIC setting (rural India) documented the feasibility of measuring these key neurocognitive processes in the field, as well as the sensitivity of these processes to variability in infant rearing circumstances (Wijeakumar et al. 2019). The VPC task we utilized involves a familiarization phase in which infants have the opportunity to encode a new visual pattern for just 15 seconds. Then they enter a test phase in which that new pattern is paired with a similar, yet distinct, novel pattern for two trials with counterbalanced

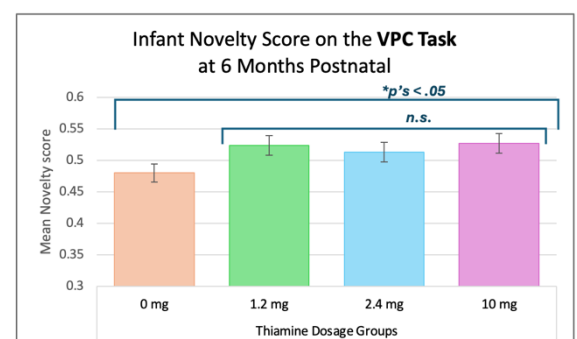


Figure 3: VPC novelty scores from previous RCT (Baldwin et al, 2023)

right/left positioning, each lasting 10 seconds. The degree to which infants look at the novel pattern during the two trials of the test phase is a measure of their encoding and discrimination skill. As predicted, in our past RCT at 6 months postnatal, infants whose mothers consumed supplemental thiamine displayed significantly better VPC performance relative to those whose mothers received a placebo (see **Figure 3**). As well, curve-estimation regression more clearly revealed that **maternal thiamine supplementation dose was significantly positively associated with infants' VPC Novelty Score** (Baldwin et al. 2023). These findings indicate that infants' thiamine status in the early postnatal period has implications for developing neurocognitive systems beyond the language domain.

Finally, data from our past trial shed light on the importance of access to sufficient thiamine during the prenatal (as well as postnatal) period. Mothers' total milk thiamine concentrations measured at the 2-week postnatal time point (i.e., pre-intervention in this supplementation RCT) provided another important source of evidence regarding the importance of adequate thiamine for infants' neurocognitive development. Specifically, **infants whose mothers showed higher milk thiamine concentrations at 2 weeks postnatal (our estimate of infants' access to thiamine prenatally and during the immediate postnatal period) displayed significantly improved cognitive outcomes at 6 months** (Measelle et al. 2021). This pattern of positive association emerged for infants' MSEL scores (receptive language, expressive language, and fine motor scores) as well as maternally reported scores on an early version of the *Global Scales of Early Development (GSED)*. Importantly, our data show that maternal milk thiamine levels at 2-weeks postnatal and our supplementation treatment group variable were each significant, independent predictors of infants' MSEL scores at 6-months postnatal. **Combined, these findings suggest that infants' access to adequate thiamine during both the prenatal and early postnatal period have relatively critical implications for neurocognitive development early in life. With this, our proposed study explores thiamine supplementation throughout the critical window of neurocognitive development, *in utero* and out to 18 months postnatal.**

Experimental Design and Methodology

STUDY DESIGN

Study design

This will be a two-parallel arm, double-blind randomized controlled trial of thiamine supplementation throughout early life, with the primary outcome of infant neurocognitive development at 18 months postnatal.

Study site: Kampong Thom, Cambodia

This community-based trial will take place in villages throughout Kampong Thom province, Cambodia. Thiamine deficiency has long been common in Southeast Asia, and for the past decade our team has worked closely with the Cambodian Ministry of Health and Ministry of Planning to understand the extent of this issue and conduct applied research to tackle deficiency (Whitfield et al. 2015; 2016; 2017; Gallant et al. 2021). In fact, the national coordination body for multi-sectoral nutrition plan, the *Council for Agricultural and Rural Development of the Office of the Council of Ministers* outlines explicit goals in the *Cambodian National Strategy for Food Security and Nutrition 2024-2030* (draft document) to include thiamine as a key nutrient of interest in the national strategy for food fortification.

Within Cambodia, Kampong Thom is an ideal study site: the latest national data indicate that women aged 16-49 years in this province had well below the average erythrocyte thiamine diphosphate concentrations (mean [95% CI]: Kampong Thom, 122 [112 – 133] vs Cambodian national average, 150 [146 – 153] nmol/L) (Whitfield et al. 2017). Kampong Thom is also an optimal location given the lower potential for attrition due to migration compared with other provinces that are closer to Phnom Penh and the border to Thailand. The driving distance on a major national road allows for blood and human milk sample storage in Phnom Penh. Finally, we conducted our previous trial in Kampong Thom and have established strong working relationships with the Provincial Health Department and Operational District officials, enhancing the feasibility of this proposed study.

Population: eligibility and recruitment

Inclusion criteria:

- women aged 18-45 years
- 12⁺⁰ to 15⁺⁶ weeks pregnant, based on last menstrual period (LMP)
- planning to breastfeed for at least 6 months

Exclusion criteria:

- consumed thiamine-containing supplements in the preceding 3 months
- planning on moving out of province in the next year

Using convenience sampling, pregnant women (either primi- or multi-gravida) will be recruited from antenatal care programs within local health centers in Kampong Thom province. Local midwives and nurses will provide a general overview of the research study and will share names and contact information of interested women with the field research team. The research team will follow up with women, screen for eligibility, obtain consent, and enroll women, with recruitment continuing on a rolling basis until 1,972 women are enrolled and randomized.

Pregnant women will be recruited between 12-16 weeks gestation based on last menstrual period (LMP). While imperfect, LMP is the most common means of dating in most low-resource settings where ultrasounds are not available. (Note: measurement of the symphysis fundal height will not be used, as it does not accurately estimate gestational age until after ~24 weeks).

We are confident that recruitment through health centre antenatal care programs is the best way to ensure recruitment of our target sample size. The most recent Cambodia Demographic and Health Survey (2021-22) reports that 99% of women received antenatal care from a skilled provider in the 2-year period before the survey, with 87% attending their first antenatal care visit in the first trimester (with a median gestational age of 2.2 months). Given our team's experience from a recent prospective cohort trial that recruited n=1,545 pregnant women <14 weeks gestation from select health centres in Kampong Thom province within 5 months (Hoang et al. 2024), we are confident that we can recruit 1,972 pregnant women within 6 months of rolling recruitment.

We have performed several research projects in Kampong Thom province, and we have excellent relationships with the provincial and district health authorities, health center staff, and village elders. Our international interdisciplinary team has a decade-long collaboration with HKI Cambodia and well-established relationships with the Ministry of Health and Ministry of Planning.

Intervention groups

Women will be recruited in early pregnancy, and will be randomized between 12-16 weeks pregnancy to one of the two groups outlined below, and shown in **Figure 4**:

- 1) **"Standard of Care+":** multiple micronutrient supplement formulations containing the RNI for thiamine, 1.4 mg/d for pregnant/lactating women, and 0.5 mg/d for children (6-18 months)
- 2) **High-thiamine MMS:** multiple micronutrient supplement formulations containing a higher dose of daily thiamine, 10 mg/d for pregnant/lactating women, and 5 mg/d for children (6-18 months)

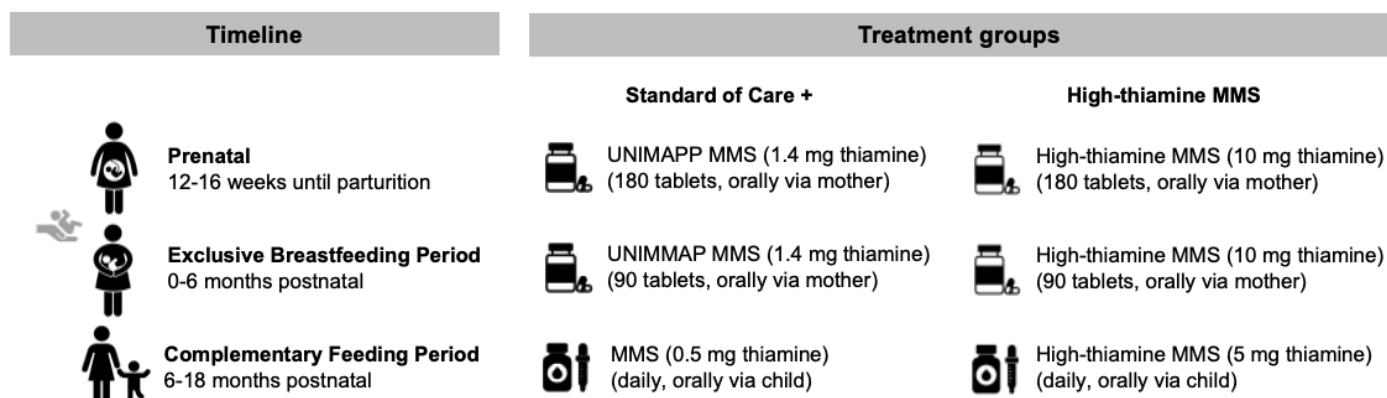


Figure 4: Study intervention

From 12-16 weeks pregnant through to 6 months postnatal, women will consume tablets orally. Starting at 6 months postnatal, supplements will then be administered directly to infants as daily liquid supplement drops. Supplements will be delivered to families by research staff, and pill/volume counts will be used to assess compliance (with individuals who consumed $\geq 75\%$ pills/drops over the study period being seen as compliant).

Details of supplement contents are shown in **Table 1**. These multiple micronutrient supplements will include the standard 15 micronutrients included in the United Nations International Multiple Micronutrient Antenatal Preparation Multiple Micronutrient Supplements (UNIMAPP MMS) formulation (World Health Organization 2023a), which are the same found in standard micronutrient powders designed for children 6-24 months (UNICEF, 2023): thiamine, as well as vitamins A, D, E, K, C, B₂, B₃, B₆, B₁₂, folic acid, iodine, zinc, selenium, and copper. The women's supplements will follow the UNIMAPP MMS dosages, and the children's supplements will contain the same doses required for inclusion in micronutrient powders for children aged 6-23 months, which generally align with the RNIs for children 1-3 years.

Study supplements will be manufactured and packaged in a licensed facility in accordance with the Code of Good Manufacturing Practice for Medicinal Products and have been donated to the trial by *Factors Group of Nutritional Companies Inc*, Burnaby, British Columbia, Canada. The supplements will be packaged in 180- and 90-tablet bottles (women), and 31-dose liquid supplement bottles (children), labelled with the study title, a numeric identification code and the statement 'for clinical trial use only' in English and Khmer, as well as batch number, expiry date, ingredients, research ethics board clearance numbers, and consumption and storage instructions in Khmer.

Table 1: Contents and doses of supplements for the four study treatment groups.

Intervention group	Contents	Dose – Women	Dose – Children
Standard of Care+	thiamine (vitamin B ₁)	1.4 mg	0.5 mg
	vitamin A	800 µg RAE	400 µg RAE
	vitamin C	70 mg	30 mg
	vitamin D	5 µg	5 µg
	vitamin E	10 mg alpha-TE	5 mg alpha-TE
	vitamin B ₂	1.4 mg	0.5 mg
	vitamin B ₃	18 mg NE	6 mg NE
	vitamin B ₆	1.9 mg	0.5 mg
	folic acid	400 µg	90 µg
	vitamin B ₁₂	2.6 µg	0.9 µg
	iron	30 mg	10 mg
	iodine	150 µg	90 µg
	zinc	15 mg	4.1 mg
	selenium	65 µg	17 µg
	copper	2 mg	0.56 mg

Intervention group	Contents	Dose – Women	Dose – Children
High-thiamine MMS	thiamine (vitamin B₁)	10 mg	5 mg
	vitamin A	800 µg RAE	400 µg RAE
	vitamin C	70 mg	30 mg
	vitamin D	5 µg	5 µg
	vitamin E	10 mg alpha-TE	5 mg alpha-TE
	vitamin B ₂	1.4 mg	0.5 mg
	vitamin B ₃	18 mg NE	6 mg NE
	vitamin B ₆	1.9 mg	0.5 mg
	folic acid	400 µg	90 µg
	vitamin B ₁₂	2.6 µg	0.9 µg
	iron	30 mg	10 mg
	iodine	150 µg	90 µg
	zinc	15 mg	4.1 mg
	selenium	65 µg	17 µg
	copper	2 mg	0.56 mg

Treatment group rationale

1) Standard of Care+

At present, standard antenatal care provided by the Cambodian health system includes weight, height, and blood pressure measurements as well as provision of deworming medication (500 mg mebendazole) and iron and folic acid supplements (IFA: 60 mg iron, 400 µg folic acid) (Han, Nagpal, and Bauhoff 2022). The World Health Organization recommends 180 IFA tablets during pregnancy, followed by another 42 IFA tablets during the first 3 months postnatal, which the Cambodian Ministry of Health has implemented in their national guidelines.

However, the Cambodian government is currently re-assessing perinatal supplementation recommendations with the intent of replacing IFA with UNIMAPP MMS, which contains 1.4 mg thiamine. It is likely that the Cambodian Ministry of Health will soon recommend 180 tablets of MMS in pregnancy, and 90 tablets of MMS postnatally, as standard of care throughout the country.

Given this trajectory, a placebo control was deemed neither appropriate nor ethical. Instead, the comparator treatment group in this study is termed ‘Standard of Care+’ since it is likely to mimic the upcoming Standard of Care, but is also enhanced in that children (6-18 months) will receive direct supplementation of MMS including the RNI of 0.5 mg/d thiamine.

2) High-thiamine MMS

The intervention group will receive the same supplements as the comparator group, except that they will have a higher thiamine dose of 10 mg/d (pregnant/lactating women) or 5 mg/d (children 6-18 months).

Why 10 mg? Our last RCT assessed four thiamine doses (0, 1.2, 2.4, and 10 mg), starting supplementation from 2 weeks postnatal. As described above in ‘*Supportive Preliminary Data*’, infants of mothers in the 10 mg daily thiamine group displayed significantly enhanced performance on both MSEL language measures at 6 months relative to all other supplementation levels (and, in particular, the 0 mg daily group) (Measelle et al. 2021). This protection for infant language development was further validated in the Infant-Directed Speech (IDS) Task, where we only saw fully robust IDS-related attentional enhancement among infants of 10 mg group mothers. However, these were exploratory secondary outcomes of the RCT (~n=85 per group, powered for breastmilk thiamine assessment as the primary outcome). This proposed trial is designed specifically to assess neurocognitive development, and given that robust benefits to language were previously only seen with 10 mg daily thiamine supplementation, we do not want to provide a dose lower than this. The 10 mg dose also aligns with regional policies, as before the 2021 coup d’état, the government of Myanmar was attempting to roll out a 10 mg daily thiamine supplement for pregnant women.

Some may ask: if there was benefit at 10 mg, why not provide an even higher dose? The RNI for pregnant women is 1.4 mg/d (WHO & FAO, 2004), but given our previous findings, higher levels of thiamine might be needed to compensate for pre-existing thiamine deficiency (which is common among rural Cambodian women of childbearing

age, Whitfield et al 2017). The WHO guidelines for thiamine administration in emergencies reflect this: the WHO recommends 10 mg oral daily for a week followed by 3-5 mg/day for 6 weeks for the treatment of mild thiamine deficiency (before clinical symptoms appear) (World Health Organization 1999). However, since thiamine is a water-soluble vitamin with no storage depots, physiologically, there is little reason to provide very high doses of thiamine: it simply wouldn't be absorbed, or would be quickly eliminated by renal excretion (Bemeur and Butterworth 2014). Although there is limited evidence of adverse health outcomes even at high doses 100x higher than recommended daily intake levels (Institute of Medicine 1998; Johnson et al. 2019), "the absence of evidence of toxicity is not evidence of the absence of toxicity" (Mills 2000), therefore, as is best practice in public health nutrition interventions, we strive to identify the lowest possible dose that yields impact.

It is also for this reason that we have set the high-thiamine dose for children 6-18 months at 5 mg (rather than the same 10 mg/d as their mothers), as this reflects a dose 10x higher than the RNI for 1-3 year olds (WHO & FAO, 2004).

Selection of 18 months as the study endpoint

The primary outcome measure is MSEL-ELC scores at 18 months of age. Based on our previous research, we predict that thiamine supplementation will specifically benefit children's receptive and expressive language capacities on the MSEL. Language acquisition is a vital aspect of developmental progress in early childhood, playing a key and cumulative role in a neurocognitive cascade that underpins domain-general learning, social capacities, and long-term cognitive performance. Infants' emerging receptive and expressive language capacities are influenced by a variety of factors (e.g., health and nutrition, quality of input, sleep, parental well-being, socio-economic status) (Anderson et al. 2011). By 18 months, infants already display considerable linguistic skill, with receptive vocabularies in the hundreds of words, and rapidly increasing expressive vocabularies (Frank, et al, 2016). Many are combining words with gestures to communicate complex ideas (Özcaliskan & Goldin-Meadow, 2009), and using word combinations to predicate one idea of another (e.g., "All gone milk!") (Braine & Bowerman, 1976). At this early age, language skills are already strongly predictive of school achievement eight years later and beyond (Pace, et al, 2019). School achievement at this later age, in turn, predicts tangible outcomes such as subsequent academic performance, employment, and income (Denning, et al, 2023). For these reasons, we focus heavily on assessing language function at 18 months in our proposed study via the well-validated and LMIC-appropriate MSEL. As well, our prior research confirms that MSEL language scores are sensitive to infants' thiamine access.

METHODOLOGY

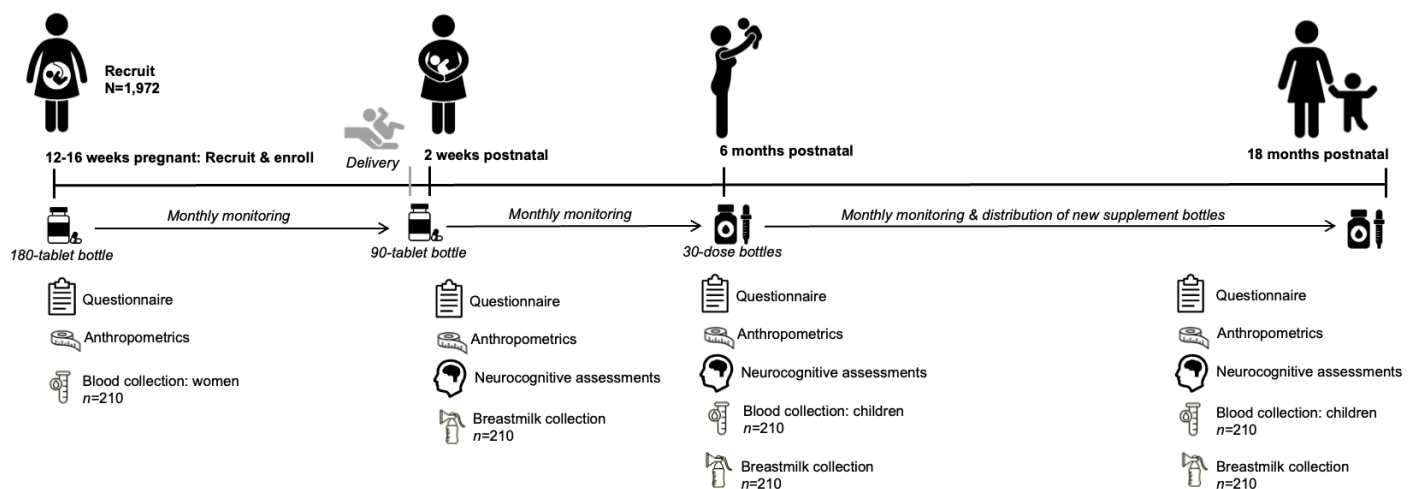


Figure 5: Timeline of main study activities

Data collection and measurements

Data will be collected at baseline (12-16 weeks pregnancy), 2 weeks postnatal, 6 months postnatal, and endline (t=18 months postnatal); we will also conduct monthly monitoring; see **Figure 5**. Each month, a member of the research team will visit families in their homes or phone to ask a small number of questions regarding infant diet and

behaviour. At required timepoints, field staff will collect old supplement bottles and distribute new bottles; participants will be considered compliant if they consume $\geq 75\%$ of supplement doses over the study.

Neurocognitive assessments

PRIMARY OUTCOME MEASURE: Mullen Scales of Early Learning (MSEL)

Our primary outcome is infant neurocognitive development as assessed by the Mullen Scales of Early Learning (MSEL), a field standard researcher-guided instrument that has been extensively validated (Jensen et al. 2019) and used successfully in several LMIC contexts, including in our previous research in Cambodia (see **Figure 6**). We favor the MSEL over another commonly used neurocognitive assessment tool, the Bayley Scales of Infant and Toddler Development (BSID) 3rd edition, in part based on ongoing and recently further-documented concerns about predictive validity of the BSID in LMIC contexts (Rasheed et al. 2023). As well, it is notable in our prior research that infants' MSEL performance is sensitive to their thiamine status (Measelle et al. 2021). The MSEL includes 5 subscales (Gross Motor, Fine Motor, Visual Reception, Receptive Language, and Expressive Language). An Early Learning Composite (MSEL-ELC), which is the primary outcome score, can be derived from four of the five subscales. Based on infants' raw MSEL scores, a T-score can be computed in relation to North American-normed MSEL scores.



Figure 6: MSEL administration with 2 week old infant, Cambodia

We include two additional measures of infant neurocognitive development:

- The **Global Scales of Early Development (GSED)** provides parent-report information about infant development, which prior research validates as a key source of information complementing researcher-guided instruments such as the MSEL. The GSED is currently under development by the World Health Organization (World Health Organization 2023b) and is derived from several previously-validated parent-report instruments, including the Caregiver-Reported Early-Development Index (CREDI) which our team used in the prior RCT in Cambodia.
- The **Visual Paired-Comparison (VPC) Task** (to be employed at 18 months endline only) probes foundational perceptual-cognitive skills that support learning. In our previous RCT, infants' VPC performance displayed a statistically significant dose-response relationship to maternal thiamine supplementation (Baldwin et al. 2023); **Figure 7**. The VPC Task familiarizes infants with a new pattern (such as a geometric shape or a face), and then tests their ability to discriminate that newly learned pattern from a novel pattern. The degree to which infants display a preference for looking to the novel pattern is the measure of their discrimination ability. In previous research, infants' VPC performance at 6-7 months predicts IQ performance as much as 11 years later (Rose et al. 2008).



Figure 7: VPC task with 6 month old infant in Kampong Thom, Cambodia

Questionnaires: Using an interviewer-administered questionnaire, we will collect demographic and socioeconomic information, health information, limited dietary intake data, and infant and young child feeding (IYCF) knowledge and behaviors at all 4 timepoints. At 2 weeks postnatal, we will also ask questions about antenatal care, delivery, and infant anthropometrics at birth.

Anthropometrics: Infants: length, weight, and head circumference; mothers: height and weight. Measurement will be collected in participants' homes using calibrated instruments and standard protocols as per Cogill 2003. Z-scores will be calculated for infant anthropometrics (WHO Multicentre Growth Reference Study Group 2006).

Biological samples: We have previously shown that supplementing mothers with 10 mg daily thiamine in the first 6 months postnatal leads to higher infant blood thiamine status compared to placebo (Gallant et al. 2021). To ensure the efficacy of the proposed intervention we will measure blood thiamine status in a random subset of infants ($n=210$, equal across treatment groups) at 6 and 18 months. Trained, Khmer-speaking pediatric phlebotomists on secondment from local health centres will travel to participants' homes to collect venous blood samples. Blood

samples will be collected from the same subset of $n=210$ mothers at baseline only (12-16 weeks gestation), and human milk samples will be collected at 2 weeks, 6 months, and 18 months postnatal.

Human milk samples will be collected with the assistance of field staff, in participants' homes using a battery-powered single breast pump. One full breast expression (single breast) will be collected from the breast women self-identify as being more 'full' (the breast not most recently emptied). Since time of day has little effect on milk thiamine concentrations, samples can be collected at any time of day, however, time of day, time since last meal, and breast side will be recorded.

Blood and milk samples will be collected in the village, placed on ice, and transported to the field lab in Kampong Thom within 5 hours of collection for processing. Blood samples will be centrifuged at 3000 rpm for 15 min at 4°C, plasma and buffy coat aliquoted, and erythrocytes washed three times with phosphate buffered saline before aliquoting and storage. The weight of the full human milk expression will be recorded, the sample mixed, and 2 mL aliquots obtained in amber cryovials. All samples will be stored at -20°C for <2 weeks before being transported to the National Institute of Public Health Laboratory for storage at -80°C. Samples will be batch-shipped on dry ice after the 18-month postnatal data collection is completed. Erythrocyte samples will be assessed for thiamine status via erythrocyte transketolase basal activities (children only) and activity coefficients (ETKac; mothers and children) (Jones et al. 2023). Human milk thiamine concentrations will be measured via HPLC-FLD (Hampel et al. 2012). Any additional sample aliquots will be stored at -80°C in the BioBank in the Department of Applied Human Nutrition at Mount Saint Vincent University in Halifax, Nova Scotia, Canada, for potential assessment of other key micronutrients (i.e. VitMin Lab, BEVITAL Lab; funding beyond the scope of this project).

Considerations for randomized controlled trials

At all four timepoints, participants will receive a modest, study-appropriate gift after data collection (e.g. sarong or laundry soap). This study has received ethical approval from the following ethics boards: Cambodian National Ethics Committee for Health Research (109-NECHR-02March2026), Mount Saint Vincent University Research Ethics Committee (Canada; MSVU REB 2025-234), and University of Oregon Institutional Review Board (USA; ID: STUDY00002346). The trial will also be registered at clinicaltrials.gov.

Written, informed consent will be obtained from all study participants at the beginning of the study. Mothers will provide consent for their infants to participate in data collection. At each data collection timepoint thereafter (2 weeks, 6 months, and 18 months postnatal), participants will be reminded that participation in the trial is completely voluntary and they can withdraw from the study at any time without giving a reason. At these timepoints verbal consent will be re-obtained before data collection proceeds.

We will establish a Serious Adverse Events Committee for this study, made up of local and international expert researchers and clinicians. These groups will provide an arms-length assessment of any serious adverse events in the study. The master ID list will not be unblinded unless in the occurrence of a serious adverse event in the trial deemed to be related to the study intervention. We will note that the likelihood of any adverse events is extremely unlikely, since there is no tolerable upper intake level (UL) for thiamine, and there have been no reports of adverse effects of excess thiamine intake (Institute of Medicine 1998; Gibson 2005), even at clinical doses 100x higher than recommended intakes (Wrenn, Murphy, and Slovis 1989). In addition, if there is a medical emergency and unblinding of a participant is required, our blinding mechanism would allow for the rapid identification of the treatment group in case of an adverse event, while also not allowing for undetectable breaks of the blinding (i.e. other participant's treatment arm will not be unblinded since each supplement bottle is simply coded with ID numbers). We would then document and explain to the funding agency and all ethics committees why any premature unblinding occurred.

While we are confident that there is a very low risk of serious adverse events in this study related to the intervention, we do expect some mortality in our cohort due to other causes. Our sample size calculation includes an estimated 10% rate of pregnancy loss and infant mortality: The latest data (Cambodia National Institute of Statistics 2022) indicate an overall pregnancy loss rate of 21% (overall from conception), and given that the majority of losses occur before our recruitment window of 12-16 weeks, we estimate an overall 10% loss rate including neonatal (birth to 1

month) and infant (birth to 1 year) mortality (8 and 4 deaths per 1,000 live births, respectively; so 6 infants overall). In addition, the maternal mortality ratio in Cambodia is 154 deaths per 100,000 live births (Cambodia National Institute of Statistics 2022), so we would expect 1 maternal death. As with previous trials in Cambodia, mortality will rapidly be investigated by local health authorities, and all ethics boards will immediately be notified of any serious adverse outcomes including mortality.

If either a caregiver or researcher suspects that a child may have severe developmental delay, we will follow internal study protocols to flag concerns with the study's neurocognitive leads. If there is reason to believe the child is at risk of delay, the caregiver will be encouraged to seek assessment by a pediatrician, as research personnel are not licensed clinicians qualified to make such diagnoses. However, since pediatricians with specialty training in the assessment and diagnosis of such delays are not available in Kampong Thom province, we will refer parents to seek assessment and treatment at the Kantha Bopha Children's Hospital in Siem Reap. While healthcare provided at this hospital is completely free of charge, this hospital is located ~190 km from our study area, so we will provide funds to cover transport & accommodations to seek care at this hospital.

STATISTICAL ANALYSES

Randomization and blinding

Participants, field data collectors, study investigators, and data analysts will be blinded to the randomized groups. Randomization was stratified by health centre, with randomly permuted block sizes of 4 and 6 to randomize to one of four treatment codes (two codes corresponding to each intervention group). A computer-generated randomization schedule will be prepared by an independent scientist not associated with the study, who will then determine which treatment code corresponds to which treatment group (this will be shared only with the supplement manufacturer, *Factors Group*, who will manufacture and package tablets).

Sample size

To detect a mean difference of 3 points in the MSEL score with 90% power ($d=0.16$, two-tailed $\alpha=0.05$), we would **require N=1,972 participants, 986 per group**, to detect the main effect on our primary outcome, MSEL-ELC at 18 months postnatal. This sample size assumes 10% perinatal losses after 12-16 weeks (details on estimated pregnancy loss and infant mortality in *Considerations for randomized controlled trials* section, below) and allowing a further 10% loss to follow-up at 18 months. This calculation is based on the smallest significant MSEL effect in the previous thiamine trial, when comparing 1.2 mg vs. 10 mg (Measelle et al., 2021). A 3-point difference in the MSEL-ELC is realistic based on the results of our previous study (Measelle et al. 2021) and would constitute a difference plausibly considered clinically meaningful (Alam et al. 2020; Primbs et al. 2023).

A sample size for the biological sample sub-set was calculated based on thiamine status defined by ETKac from our previous trial (Gallant et al. 2021). Assuming an approximate 50% reduction (46% vs 24%) in the proportion of infants at moderate or high risk of thiamine deficiency (ETKac >1.15) in the 10 mg thiamine supplemented versus 1.2 mg group in the previous trial, the proposed study would require a sample size of **105 per group, or n=210** to achieve a power of 90% at a two-sided p-value of 0.05.

Statistical analysis plan

Primary outcome: Scores on the MSEL-ELC at 18 months will be compared between groups using a linear regression model, with adjustment for health center, gestational age at enrolment, and birth anthropometry, and using generalized estimating equations with an independence working correlational structure to account for multiple births. The effect of treatment will be described as a mean difference with a 95% CI. In all analyses, missing outcome data will be addressed using multiple imputation, performed separately by randomized group using chained equations.

Secondary outcomes

Descriptive statistics for sociodemographic, diet, and health information collected from the questionnaires and anthropometric measures will be used to describe the sample, and relevant covariates such as parity, wealth status, gestational age, and birth anthropometry will be used as covariates. Like the MSEL scores, a single, standardized

mean score on the GSED (the Developmental Score or D-Score) will be analyzed using linear regression models, adjusted for relevant covariates. A continuous measure of infant looking time/attentional preference during the VPC will also be analyzed using linear regression models, adjusted for relevant covariates.

All outcomes will be analyzed on an intention-to-treat basis, where all participants will be analyzed according to their allocated treatment group regardless of compliance. A secondary 'per-protocol' analysis will be performed on a subset of participants who consumed $\geq 75\%$ of supplements over the study period. We will run all analyses with and without multiple births to verify whether outcomes are impacted. A p-value of 0.05 will indicate statistical significance.

Data management and security

Participants will be given a unique numeric study ID code, not derived from personal identifiers; this code will link all data collected from this individual. All data will be collected directly on tablets using structured forms designed specifically for this study. Video data for the VPC task will be uploaded onto the secure, password-protected Mount Saint Vincent University server before being deleted from recording devices. Data will be reviewed daily by the field data collector and coordinator before secure download and integration with the larger database. Data management and security procedures, including assurance of confidentiality, will adhere to the Canadian Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans (TCPS2 CORE) guidelines.

Timeline of activities

	Winter	Spring	Summer	Fall	Winter	Spring	Summer	Fall	Winter	Spring	Summer	Fall
Activities	Year 1				Year 2				Year 3			
Obtain ethics approvals, and register clinical trial	✓											
Develop data collection tools and training tools	✓											
Procure supplements, neurocognitive assessment test supplies	✓											
Train field data collection staff and coordinator		✓	✓									
Recruitment, enrolment, and randomization			✓	✓								
Data collection			✓	✓	✓	✓	✓	✓	✓	✓	✓	
Data cleaning, statistical analysis, and interpretation										✓	✓	
Dissemination: manuscript preparation & submission, academic conferences												✓
Dissemination: village-level knowledge translation; dissemination workshop with key												✓

Study team

Grant contributor	Study role
Dr. Kyly Whitfield, Mount Saint Vincent University	Co-Principal investigator, trial lead: Will oversee all research (maintain clinicaltrials.gov, all ethics certificates, design and execution of all study tools, supervision of postdoctoral fellow and graduate students, responsible for data management, storage, and dissemination, responsible for finances). Over 10 years experience with field research in Cambodia and other low- and middle-income countries (including PI on the previous trial) with a specific expertise in thiamine (e.g. lead author on Global Thiamine Alliance's Roadmap, Whitfield <i>et al</i> 2018 Ann NY Acad Sci 1430(1):3-43).
Mr. Hou Kroeun, HKI Cambodia	Co-Principal investigator, implementation lead: Responsible for overseeing all day-to-day research activities (Cambodian government research permissions, oversight of all data collection staff, interim data cleaning, storage, and management, day-to-day finances, etc). Was implementation lead on previous trial. Importantly, Kroeun will serve as liaison with our Ministry of Health & Ministry of Planning partners: Her Excellency Dr Prak Sophhoneary (MoH) and His Excellency Mam Borath (MoP). This government support and collaboration is essential to ensure that research findings can be integrated into future policy.
Drs. Jeff Measelle and Dare Baldwin, University of Oregon	Co-investigators: early neurocognitive development. As experts in early cognitive development, Measelle and Baldwin will head up the training and implementation for all cognitive assessments. They sit on several international consortiums for validation of cognitive tools for global use (e.g. ManyBabies Consortium; CREDI/GSED). Measelle has previous field experience in Lao PDR, and both were co-investigators on our previous trial in Cambodia.
Drs. Frank Wieringa, IRD; Tim Green, Flinders University / SAHMRI; Kim Rattana, Ministry of Health	Co-investigators: nutrition. Green and Wieringa have extensive experience in global nutrition research, with specific expertise in Southeast Asia, micronutrients, and maternal and child health interventions. Both were co-investigators on our previous trial, and bring invaluable experience to this study team. Dr. Rattana is a physician and the Director of the National Maternal and Child Health Center, Cambodian Ministry of Health. She brings extensive experience with maternal and child health in Cambodia.

Dissemination plans and future directions

As with our prior research in Cambodia, our dissemination plan will include the following:

- Publishing the results of our study in peer-reviewed scientific journals, and
- Presenting our findings in scientific and professional forums, including meetings with and at the request of Cambodian health officials, where we will present the results of our study in a balanced, research-focused manner.

Dissemination activities related to the proposed randomized controlled trial in Cambodia will not include lobbying or any form of legislative advocacy.

Our research will be vital as the Cambodian Ministry of Health continues exploring a shift from IFA to multiple micronutrient supplements (MMS) in pregnancy (Hoang et al, 2024). Currently, women receive 180 prenatal and 42 postnatal IFA tablets (Han et al, 2022), but the government is considering supplying UNIMMAP MMS as 180 tablets in pregnancy and 90 tablets postnatal.

The UNIMAPP MMS formulation contains 1.4 mg thiamine, but a one-size-fits-all UNIMAPP MMS is not appropriate in all countries. If our proposed study confirms that perinatal thiamine supplementation of 10 mg/d is beneficial to infant neurocognitive development, the Cambodian Ministry of Health could follow others' lead to distribute a customized MMS. Other countries have customized MMS to meet national needs; for instance, the UNIMMAP formulation distributed through government channels in South Africa was modified to contain less copper, and to add vitamin K (Monterrosa et al, 2018). The data generated by the proposed study thus holds potential to help ensure the life-long health and well-being of Cambodian mothers and infants going forward.

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