Summary of the Second Meeting of the Global Thiamine Alliance
By Hallie Kapner

Overview

On March 9 and 11, 2021, the Nutrition Science Program at the New York Academy of Sciences (NYAS), with support from the Bill & Melinda Gates Foundation, virtually hosted the second meeting of the Global Thiamine Alliance—an international group of pediatricians, nutritionists, physicians and surgeons, psychologists and public health experts dedicated to reducing the global burden of illness and mortality associated with thiamine deficiency. What began in 2017 as a Task Force charged with investigating the prevalence and disease burden of thiamine deficiency and identifying knowledge gaps has become a robust collective of researchers working to fill those gaps through studies spanning multiple continents. Among the topics of interest are developing a case definition for thiamine deficiency, verifying global and in-country prevalence of low thiamine status, and developing surveillance and prevention strategies.

Following the first meeting of the Global Thiamine Alliance in 2019, the group recommended use of the term *thiamine deficiency disorders* (TDDs) to collectively describe the wide-ranging clinical manifestations of thiamine deficiency across age groups. It is used accordingly herein.

Speakers

Hilal Ahmed, MD, Government Medical College
Shawn Baker, MPH, U.S. Agency for International Development
Dare Baldwin, PhD, University of Oregon
Ken Brown, MD, University of California, Davis
Megan Bourassa, PhD, NYAS
Kathleen Chan, MSc, University of California, Davis
Gwyneth Cotes, MPH, Hellen Keller International
Philip Fischer, MD, Mayo Clinic and Sheikh Shakhbout Medical City
Gary Gibson, PhD, Burke Neurological Institute, Weill Cornell Medicine
Filomena Gomes, PhD, NYAS
Tim Green, PhD, South Australian Health and Medical Research Institute
Sonja Hess, PhD, University of California, Davis
Laurent Hiffler, MD, Cellular Nutrition Research Group
Vijay Anand Ismavel, MS, MCh, Makunda Christian Leprosy and General Hospital
Maria Elena Jefferds, PhD, Centers for Disease Control and Prevention

Sengchanh Kounnavong, MD, PhD, Lao Tropical and Public Health Institute
Elisabeth Mates, MD, PhD, VA Sierra Nevada Health System
Jeffrey Measelle, PhD, University of Oregon
Mahesh Mummadi, MD, National Institute of Nutrition
Geoffry Smith, PhD, International Life Sciences Institute
Kyly Whitfield, PhD, Mount Saint Vincent University
Frank Wieringa, MD, PhD, Institut de Recherche pour le Développement

Key Takeaways

TDDs are highly prevalent in Southeast Asia and are a likely under-recognized problem in other regions including parts of India and Africa. TDDs are a significant cause of infant mortality in Southeast Asia, and emerging research indicates that even subclinical thiamine deficiency harms neurocognitive development, with potential lifelong impacts. Low thiamine intake or utilization is also implicated in Alzheimer's disease, and may be an underappreciated cause of falls and delirium in adults, and morbidity among some children and adolescents in high income countries.

Despite existing knowledge gaps, the Global Thiamine Alliance members agree that there is adequate data to motivate action to address thiamine deficiency in regions where thiamine intake is low, either through supplementation of pregnant and lactating women, food fortification, or a combination of both.

The group coalesced around several areas of priority to advance the field and aid countries in addressing TDDs. These include ongoing research to understand the relationship between biomarkers of thiamine status and clinical presentations of TDDs; local prevalence studies, including greater surveillance of symptoms associated with TDDs in hospitals and communities; advancing research on the potential impacts and implementation of thiamine-fortified salt; and continued exploration of the links between low thiamine intake in early life and cognitive development.

I. Introduction

Thiamine, also known as vitamin B_1, is an essential co-factor in four enzymatic processes involved in carbohydrate metabolism and energy production. Thiamine "keeps cells running," said **Megan Bourassa**, explaining that thiamine deficiency has the greatest impact on cells with high metabolic demands, including those in the heart and brain. Thiamine deficiency affects multiple organ systems and produces a range of symptoms that can be easily misdiagnosed, especially in areas where thiamine deficiency is less commonly reported. Risk appears highest where polished white rice is a dietary staple, as the polishing process removes the thiamine-rich husk of the rice kernel. In recent years, Bourassa reported, TDDs have become a topic of concern outside Southeast Asia, with outbreaks in Kiribati, Bhutan, Kashmir and Assam. Such outbreaks reinforce the possibility of a "serious unrecognized prevalence of thiamine deficiency" beyond the regions typically associated with this issue.

Thiamine deficiency: knowns and unknowns

Philip Fischer provided an overview of the known presentations, complications, and treatments for thiamine deficiency as well as a number of significant "unknowns" that impact patient outcomes. Thiamine deficiency is a dangerous condition that is highly prevalent in some parts of the world. According to Fischer, "in some parts of some countries, it's almost uniform." It is a major cause of under-5 death in Cambodia, where about half of children who die before age 1 are believed to have a thiamine deficiency disorder.[1] One study of Cambodian infants and their mothers revealed that thiamine deficiency is "endemic," as nearly all newborns and nursing mothers studied met criteria for biochemical thiamine deficiency, even those with no symptoms of beriberi.[2] In Myanmar, beriberi accounts for 6% of deaths among preschool-aged children, and 17% of infant deaths.[3]

Thiamine deficiency may be most readily identified when it presents with the classic symptoms of infantile beriberi, including hoarse cry, tachypnea, tachycardia, enlarged liver, listlessness and anorexia. [4] However, Fischer explained, "the manifestations [of thiamine deficiency] are diverse and multiple, affecting most parts of the body." TDDs can affect all age groups, causing metabolic acidosis, heart failure, neurologic complications ranging from encephalopathy to developmental delays, and peripheral nervous system disorders such as peripheral neuropathy, ataxia, and muscle weakness.[4,5] Heterogeneities in disease presentation can complicate diagnosis, as many of these symptoms are associated with other illnesses.

Multi-System Presentations of Thiamine Deficiency

Smith *et al.* Thiamine deficiency: a clinical perspective

Table 1. Organ system manifestations of thiamine deficiency as seen at different ages in various geographical areas

Geographic setting	Metabolic	Cardiorespiratory		Neurologic				Musculo-skeletal	Gastro-intestinal
	Acidosis	Heart failure	Dysphonia	Encepha-lopathy	Develop-mental delay and hearing loss	Peripheral neuro-pathy	Ataxia	Weakness and atrophy	Vomiting

Imaging can reveal evidence of cardiac dysfunction[6] and neurologic changes[7] associated with beriberi to aid in diagnosis, but is not always accessible in low and middle income countries (LMICs) and some findings may not be evident until thiamine deficiency is severe.

While "thiamine deficiency is always treatable," said Fischer, it is not always curable. Patients often show rapid improvement after thiamine administration, yet some suffer long-term effects of severe or prolonged thiamine deficiency.[8] There is no standard treatment protocol for TDDs. Dosing regimens, routes of administration, and duration of treatment vary in studies and in practice around the world.[5]

Despite high prevalence of TDDs in some areas, the underlying pathophysiology is not well understood. This contributes to ongoing challenges in clinical recognition of these disorders. Improvements in diagnostics, along with the establishment of treatment protocols, may improve patient outcomes.

II. Thiamine Deficiency in High-Income Countries

Thiamine deficiency in adults

Thiamine deficiency is considered rare in high-income countries (HICs) due to dietary diversity and widespread food fortification. When it does occur, it is often in the setting of alcoholism, due to reduced thiamine intake and intestinal absorption. "Absent a history of alcoholism, the varied symptoms of thiamine deficiency... may be attributed to other conditions and can be misdiagnosed," said **Filomena Gomes**, who presented the results of a literature review assessing adult thiamine deficiency unrelated to alcoholism in HICs.[9]

Gomes and her collaborators reviewed 81 cases of confirmed adult thiamine deficiency that occurred between 1999-2020. Patients ranged in age from 19-75, and from severely underweight to obese. While underlying conditions varied, 94% of patients had at least one condition (e.g. cancer, gastrointestinal diseases, heart failure, and obesity) that caused decreased nutrient absorption, increased thiamine losses, or increased thiamine requirements. These include disease-related malnutrition accompanied by significant weight loss, complications following bariatric surgery, chronic use of diuretics to manage heart failure, or lack of thiamine in parenteral nutrition formulas. The remaining 6% of patients followed highly restrictive diets or experienced food insecurity.

Table 2. Pathophysiologic mechanisms that can lead to thiamine deficiency in adults

Pathophysiologic mechanisms	Causes
Increased thiamine requirements	Malignancy
	Fever and infection/sepsis
	Refeeding syndrome
	High-carbohydrate diets
Increased thiamine losses	Hemodialysis and peritoneal dialysis
	Chronic diuretic therapy
	Prolonged vomiting
	Prolonged diarrhea
Decreased thiamine intake or absorption	Alcoholism
	Bariatric surgery
	Malnutrition
	Restrictive or poor quality diet
	Parenteral nutrition (inappropriate formulation)
	Hyperemesis gravidarum
	Foods containing thiamine antagonists and thiaminases

Delays in diagnosis or misdiagnosis were common in this review. Treatment with thiamine resulted in partial or complete recovery in all but three cases, which were fatal.

Previous systematic reviews of adult thiamine deficiency in HICs have focused on a single presentation, such as Wernicke encephalopathy. As Gomes explained, this review highlights the many clinical manifestations of thiamine deficiency, as well as the variety of patients at risk. "This is not a resolved problem," she said, and thiamine deficiency is "present even where it is not expected."

Pediatric thiamine deficiency

Pediatric thiamine deficiency is often considered "anecdotal" in HICs, said **Laurent Hiffler**, but a new literature review tells a different story. Hiffler shared the results of the first review[10] of pediatric thiamine deficiency in recent years, in which he and his collaborators examined 480 cases of TDDs across newborns, infants, children, and adolescents from 2000-2020.

In a stark departure from the trend in LMICs, where infants are most often affected, nearly 70% of cases in Hiffler's review occurred in children and adolescents. The most common presentations were Wernicke encephalopathy (28%) and lactic acidosis (18.5%), although ataxia (12%), ocular abnormalities (6.5%), heart failure (6.5%) and several other symptoms were observed.

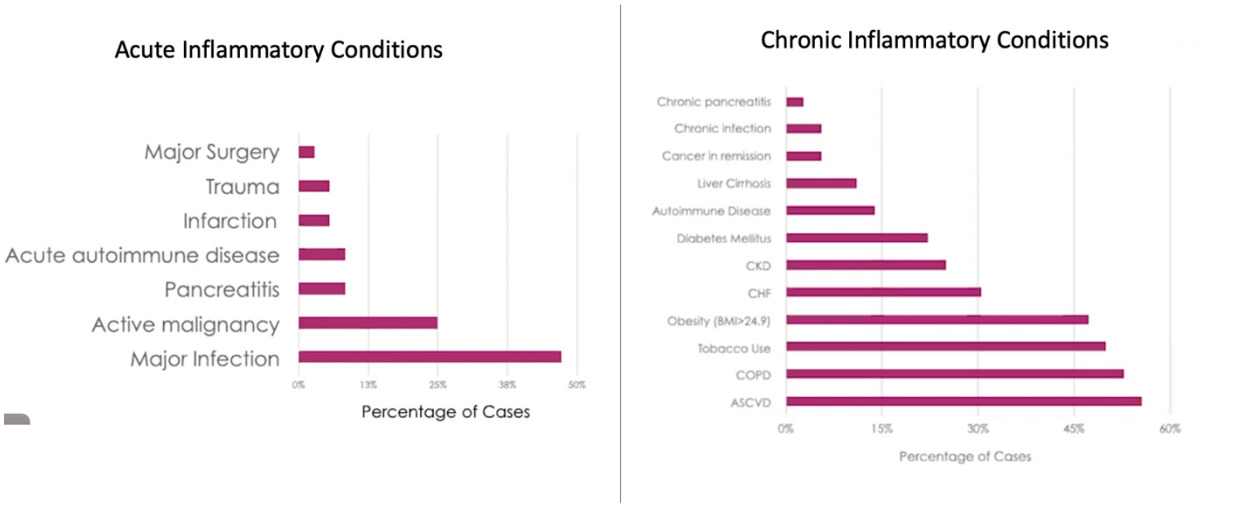
The team identified 11 categories of predisposing factors for thiamine deficiency, some specific to certain age groups, such as eating disorders, especially anorexia, and others which occur across age groups. These include congenital issues that impact thiamine transport or absorption and long-term sequelae of thiamine deficiency in infancy. Similar to adult populations, infants and children with acute illnesses associated with significant weight loss or malnutrition, or those receiving parenteral nutrition, are at risk for thiamine deficiency, as are diabetic and obese adolescents due to a mismatch between thiamine intake and metabolic demand. While not included in this review, Hiffler noted that especially vulnerable populations in HICs, such as migrant families, are also at greater risk for thiamine deficiency.

This report does not reflect the magnitude or prevalence of thiamine deficiency in HICs; however, it captures both a large number of predisposing factors and spotlights a shift in the groups most likely to be affected in HICs compared to LMICs.

Thiamine deficiency in hospitalized veterans

A retrospective case series of hospitalized veterans[11] suggests that thiamine deficiency may be an underappreciated cause of weakness, falls, and delirium in non-alcoholic hospitalized patients. **Elisabeth Mates** described a review of 36 hospitalized patients at the Veterans Administration Sierra Nevada Health Care System in Reno, NV, with plasma thiamine levels ≤7 nmol/L (reference range 8-30 nmol/L). The cohort was 92% male, with an average age of 74.5 years. Patients most commonly presented with muscle weakness and falls (75%) neuropsychiatric symptoms including delirium and delusions (72%), gastrointestinal symptoms (53%), and ataxia (42%).

In accordance with the review of TDDs in HICs presented by Dr. Gomes[9], Mates' study found that conditions that increase metabolic stress, increase thiamine losses (vomiting, diarrhea, dialysis, diuretics) or result in decreased thiamine intake (food insecurity or anorexia), are important etiologies for thiamine deficiency. Metabolic stress appears to be an "especially important risk factor," said Mates, who explained that a majority of patients (83%) had two or more acute inflammatory conditions such as infection or active malignancy, as well as multiple chronic inflammatory conditions including coronary artery disease, chronic obstructive pulmonary disease, tobacco use, obesity, and heart failure. Additionally, 75% of patients in this cohort had lost at least 5% of their baseline weight within the previous 12 months.



While the majority of patients improved with thiamine treatment, these cases were associated with higher health care costs, both to diagnose thiamine deficiency (specialty consults, neuroimaging) and to manage recovery (skilled nursing facilities, home care).

This study is just the latest to suggest that thiamine deficiency may be a significant issue in hospitalized patients. Previous reports of thiamine deficiency in adult hospitalized patients[12,13,14,15,16] indicate a potential prevalence as high as 10-25%, a number Mates described as "outstanding." "A prevalence study in this population is needed," she said.

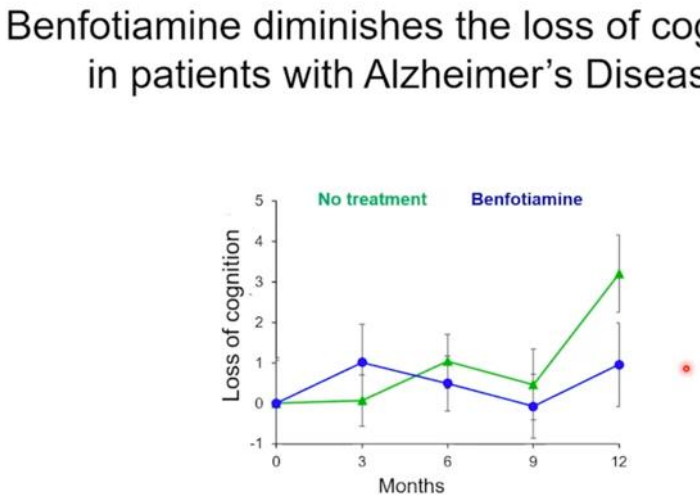
Thiamine in Alzheimer's disease

Few cells in the body demand as much energy as those in the brain, as **Gary E. Gibson** explained, noting that while the brain accounts for just 2% of body weight, it utilizes 20% of the body's glucose and oxygen. Thiamine-dependent enzymes are key regulators of brain glucose metabolism, and a reduction in the activity of these enzymes is evident in the brains of Alzheimer's disease (AD) patients. In addition to the accumulation of beta-amyloid plaques and neurofibrillary tangles, glucose hypometabolism is a "major marker" of AD, Gibson said,[17] noting that decreases in brain glucose utilization precede the onset of AD symptoms bby decades.

Thiamine has been studied in the context of memory and cognitive performance, and animal studies confirm that thiamine deficiency induces physiologic changes and symptoms also seen in AD patients. These include abnormal brain glucose utilization, neuronal loss, memory loss, and plaque formation.[18]

Gibson and his collaborators have proposed glucose hypometabolism as a therapeutic target for AD. "This is a vast minority opinion," he said, yet a clinical trial[19] testing a drug that significantly boosts thiamine levels shows intriguing results.

Gibson and his team conducted a one year, double-blind, randomized, placebo-controlled trial of benfotiamine, a synthetic thiamine precursor that boosts blood thiamine levels 100x higher than thiamine itself. In 71 patients with mild AD and plaques, the treatment group maintained stable levels of cognition and brain function and experienced a reduction in advanced glycation end products. There were no adverse events reported. The researchers are exploring possibilities for conducting a large multi-center trial of benfotiamine.



III. Global Outbreaks of Thiamine Deficiency and Regions of Concern

Dietary intake data are not widely available for thiamine, which complicates efforts to identify areas at risk for TDDs. In an effort to flag regions of possible concern, the Thiamine Task Force considered several types of data, including food balance sheets, which indicate the amount of thiamine available in the local food supply;[20] per-country analyses of the percentage of calories that come from white rice;[21] and literature reviews of locations that have experienced outbreaks of TDDs over the past 40 years.[22] While parts of Asia and Southeast Asia feature prominently in these reviews, several unexpected countries and regions showed elevated risk for thiamine deficiency, including The Gambia, Madagascar, and parts of Latin America.

Thiamine status in The Gambia

White rice is a staple food in The Gambia, distinct from other West African nations, which rely on a variety of staples in addition to rice, including cassava, yams, and maize. Outbreaks of TDDs in the general population have occurred in the country, and **Megan Bourassa** noted that based on food balance sheet data, thiamine in the food supply is likely low. The country's climate is characterized by two distinct seasons: a "wet" season, during which agricultural activity is high but dietary diversity is reduced, and a "dry" harvest season, where food is more abundant.

Bourassa discussed the only recent study of thiamine status in The Gambia—an assessment of red blood cell samples from 277 women of childbearing age (18-40). Half the samples were collected during the wet season, and half from the dry season. Bourassa reports that 35.8% of women were likely thiamine deficient across both seasons, however, risk for thiamine deficiency jumped significantly in the wet season. About 48% of women were at high risk of deficiency during the wet season, versus 23% in the dry. This unique seasonal variability in risk may also impact the risk of TDDs in exclusively breastfed infants in The Gambia.

Thiamine deficiency in Madagascar

Data from a recent trial of fortified complementary food and responsive feeding in Madagascar highlight the challenges of designing interventions to reduce the risk of thiamine deficiency among high-risk populations. **Frank Wieringa** presented the (unpublished) results of a 9-month, 2x2 cluster randomized controlled trial of 800 infants ~6 months of age. The experimental cohorts received either responsive feeding, fortified complementary food (FCF) containing 0.35 mg thiamine/day, or both.

There is no universally accepted cutoff value to define thiamine deficiency,[20] but all participants had baseline thiamine levels far lower than children in Western nations. About 48% of infants had whole blood thiamine levels <70 nmol/L, which is 2 standard deviations below the mean in Western nations, and 9% had levels <50 nmol/L, consistent with levels reported in infantile beriberi.[2]

The interventions had little impact on thiamine levels after 9 months, with only the groups receiving FCF showing a statistically non-significant increase (+2.8 nmol/L). Several factors may explain this outcome, according to Wieringa, including low compliance, the possibility that higher levels of fortification are needed for FCF in this population, and even a reconsideration of the RDA for thiamine for children consuming high carbohydrate diets. The sachets used in this study contained 70% of the RDA for children ages 1-3—an amount intended to fill dietary gaps rather than supply a full day's worth of thiamine. "Apparently the gap was bigger than we thought," Wieringa said.

IV. Interventions to Address Thiamine Deficiency in Cambodia

Thiamine dose response in human milk with supplementation

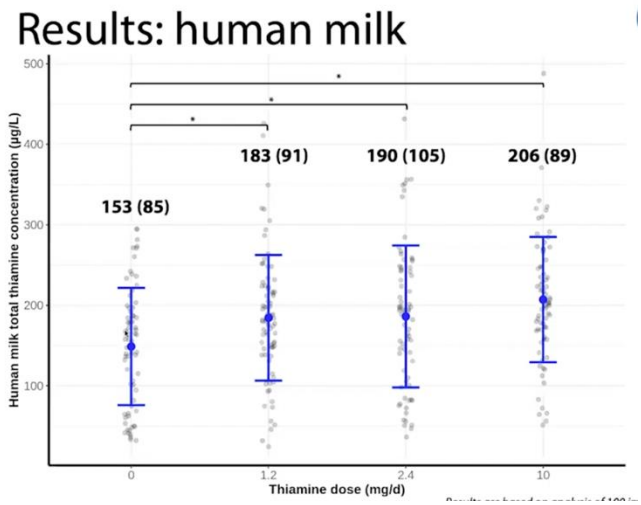
Some efforts to prevent infantile beriberi have focused on improving maternal thiamine status as a means of increasing thiamine concentration in breastmilk. As **Kyly Whitfield** explained, when a vitamin deficiency occurs during the exclusive breastfeeding period, "we need to take a step back from the baby and look at the mom." In Cambodia, a diet dominated by polished white rice and foods rich in thiaminases, such as the fermented fish paste prahok, along with betel nut chewing, are likely contributors to low thiamine status in lactating mothers.[9] Infants consuming low-thiamine breastmilk are at high risk of TDDs,[23] either in the form of infantile beriberi or impaired cognitive development as a result of low thiamine in infancy.[2]

Food fortification may be an effective means to raise thiamine status of pregnant and lactating women, and Whitfield and a group of collaborators have published encouraging results of trials of thiamine-fortified fish sauce.[24] However, reports of TDDs in regions where fortifiable commercially manufactured fish sauce is not universally consumed prompted a new investigation of salt as a vehicle for thiamine fortification. Whitfield discussed a multi-pronged study of 335 mother-child pairs, which included a dose-response trial[25] to determine the level of fortification needed to optimize breastmilk thiamine; an assessment of salt consumption by target populations in Cambodia; and cognitive assessments to understand the link between thiamine intake in infancy and neurodevelopment.

For the dose-response trial, lactating mothers were supplemented daily with 1.2 mg (EAR for lactating women) or 2.4 mg (EARx2) of thiamine or 10 mg (positive control) in pill form—or a placebo— from 2-24 weeks postpartum. Maternal blood and breastmilk samples were collected at baseline and 24 weeks, with additional milk samples taken at 4 and 12 weeks. One infant blood sample was collected at 24 weeks. Total thiamine concentration of breastmilk, as well as whole blood thiamine and erythrocyte transketolase activity, were measured and compared across the trial arms.

Dose-response results
The team determined that 2.35 mg thiamine/day was required to increase breastmilk thiamine concentration to 90% of the estimated maximum human milk thiamine concentration (191 µg/L).[26] However, the confidence interval was wider than expected, which Whitfield attributes to significant variability among women in response to thiamine. This is not a new finding, as prior studies have shown that nutrient content of breastmilk varies greatly among women in response to supplementation.[27]

Supplementation results
Despite variations, breastmilk thiamine was higher in all supplemented groups versus placebo. There were no significant differences among those receiving 1.2, 2.4, or 10 mg of thiamine, and all supplemented women had breastmilk thiamine comparable to mothers in thiamine-replete countries.



Similarly, whole blood thiamine levels in all supplemented women were higher than the placebo group, with a significant difference only between the lowest (1.2 mg) and highest (10 mg) cohorts. Erythrocyte transketolase activity also showed that the placebo group was far likelier to be at high risk for deficiency than any of the supplemented groups.

Babies of supplemented mothers had similar whole blood thiamine levels and erythrocyte transketolase activity showed that placebo infants were at higher risk of deficiency. The only significant difference among infants was between the placebo and 10 mg supplementation cohort.

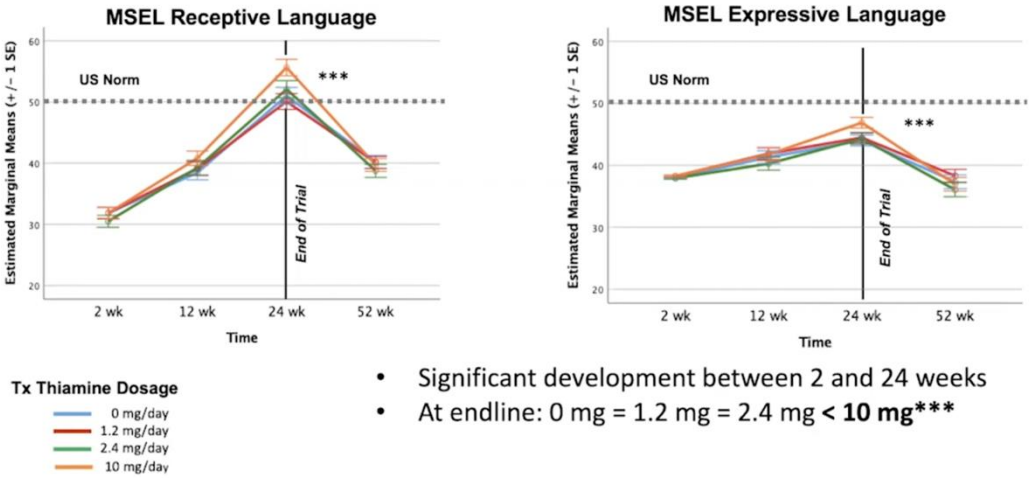
The researchers concluded that a 1.2 mg daily supplement was sufficient to boost breastmilk thiamine to levels seen in replete populations.

Effect of thiamine supplementation on cognitive and language development

Neurodevelopment during the first 1,000 days sets the stage for all future brain development, 80% of which is completed in the first 5 years of life. “We have a narrow window to get it right,” said **Jeffrey Measelle**, noting that the “neurodevelopmental costs” of thiamine deficiency both pre- and postnatally have been well-characterized in animal studies[28,29,30] as well as in longitudinal studies of Israeli infants who were fed thiamine-deficient formula.[31] These include gross and fine motor deficits[32] and ophthalmologic abnormalities,[33] but some of the most significant impacts are in the domain of language development.[34]

Measelle introduced early results of the cognitive assessments conducted as part of the trial described by Dr. Whitfield.[25]26 The findings reinforce the notion that early life thiamine status impacts language development. Among the many cognitive domains assessed by Measelle and collaborator **Dare Baldwin**, expressive and receptive language were the only ones in which statistically significant differences were seen between the infants of mothers receiving the highest doses of thiamine supplementation (10 mg) and the lower dose or placebo cohorts. Distressingly, according to Measelle, a final cognitive assessment at 52 weeks— 6 months after

discontinuation of supplemental thiamine for mothers— showed a dramatic decline in language skills for all children.



Dare Baldwin shared data on correlations between infant thiamine status and performance on tasks integral to language processing, visual processing, and social interaction. The higher the thiamine dose a mother received, the better the infants' score in language preference tasks, visual comparison tasks, and assessments of joint attention and social engagement between mother and baby.

The prenatal period also emerged as an important factor in neurocognitive development. In this study, higher human milk thiamine concentration at 2 weeks postpartum was associated with better neurological status in infants and was predictive of better general and cognitive development at 24 weeks.

Salt as a potential vehicle for thiamine fortification

Kathleen Chan explained the final arm of the Whitfield trial, which explored the feasibility of salt as a vehicle for thiamine.[35] Salt has been utilized successfully as a vehicle for iodine in Cambodia and is widely consumed year-round across all age and socioeconomic groups. Its suitability as a means to reach lactating women with enough thiamine to improve their status and potentially prevent infantile beriberi is dependent in part on the amount of salt these populations consume, and in what form (table salt vs condiments).

Chan detailed the process of assessing overall household salt intake and intake specific to lactating mothers during the exclusive breastfeeding period. Methods included questions about daily salt usage; measures of household salt disappearance; repeat maternal 24-hour urine sodium concentrations; and repeat 12-hour observed weighed salt and condiment intake records for mothers.

Results from various methods of measuring salt intake were in close agreement. Mean use of salt per the disappearance study was 11.3 g/person/day, with some seasonal variation. Values from the 24-hour urinary sodium concentrations estimated salt intake at 9 g/person/day, while

the condiment and salt use observation study indicated usage of 9.3 g/person/day. Importantly, 70% of observed salt intake came from table salt.

The team modeled the usual salt intake distribution among lactating women, arriving at an estimate of 7-8 g/day. Using the optimal dose from the dose-response trial (1.2 mg/day), the team determined a fortification dose of 275 mg/kg of salt using a modified EAR cut-point method,[36] which aims to increase intakes above the EAR while minimizing excess intake. As there is no upper intake level for thiamine, the team set the limit at 10 mg/day. Future work includes stability testing of iodine-thiamine salt, as well as cost analysis, acceptability testing, and efficacy trials.

V. Lao Thiamine Project: Updates and Preliminary Data

Researchers from the Lao Thiamine Project presented progress updates on the study's mission of developing a case definition of thiamine responsive disorders (TRD) among infants and young children.

Sonja Hess offered preliminary results from a prospective study[37] of hospitalized infants and young children in Luang Prabang, which aims to identify common clinical features and risk factors among patients who respond positively to thiamine administration.

The study included 452 patients with a mean age of 4.3 months and high rates of exclusive breastfeeding (70%), all of whom presented with symptoms consistent with thiamine deficiency. Eligibility criteria included a wide range of symptoms, as Hess explained that "beriberi is likely the tip of the iceberg, and many more children may benefit from thiamine in the hospital."

Enrollment Criteria of Hospitalized Children

	N	%
N	449	
Difficulty breathing	319	71.0
Tachycardia#	278	61.9
Tachypnea*	203	45.2
Loss of voice / hoarse voice	179	39.9
Persistent crying	177	39.4
Enlarged liver (>2 cm)	139	31.0
Reduced oxygen saturation (<92%)	112	24.9
Convulsion	40	8.9
Loss of consciousness	30	6.7
Nystagmus/abnormal eye movement	17	3.8
Muscle twitching	13	2.9
Acute paralysis	2	0.4

Study participants were given thiamine in the hospital alongside other medical care as necessary, and their response to thiamine and overall condition was monitored closely for the first 72 hours. Children also received an echocardiogram and cranial ultrasound to look for changes consistent with TDDs. Maternal blood and breastmilk and infant blood samples were also taken, and mothers participated in a questionnaire covering diet, health, and demographic information.

Following case report review by a pediatric team with expertise in tropical medicine, study participants were assigned a "TRD Score" denoting the likelihood that their condition was caused by low thiamine. The scale included classic beriberi, probable TRD, possible TRD, and unlikely TRD. These scores formed the basis of a predictive model correlating the incidence of symptoms with response to thiamine administration. Based on preliminary results, Hess is "optimistic," and notes that the team aims to adapt the model into a practical TRD diagnostic tool "similar to an APGAR score" for low-resource settings.

About 61% of the first 338 patients analyzed had positive TRD scores, either classic beriberi (22%) or probable TRD (38%). In an unexpected finding, Hess reported that 46% of participants had abnormal cranial ultrasounds, with findings consistent with thiamine deficiency. Additional review of these imaging studies is currently underway, as the high prevalence of abnormalities is "very concerning," said Hess.

Late this year, blood and breastmilk samples will be analyzed to determine which biomarkers and cutoffs may be associated with TRD in this population. Ultimately, all data will be compared to a community cohort of frequency-matched mother-child pairs to identify risk factors that may be predictive of TRD.

Thiamine supplementation in health centers in Lao PDR

While the WHO guideline does not recommend thiamine supplementation for pregnant and lactating women or children under age 5, the Ministry of Health in Lao PDR has implemented a national policy of supplementation to address high prevalence of infantile beriberi. Supplementation is integrated into routine antenatal care where available. Additional recommendations include nutrition education to promote the consumption of thiamine-rich foods and reduce intake of thiaminases, and community engagement to modify "taboo diet" practices common in the region.

The Lao Thiamine Project assessed the implementation of the national supplementation policy at health centers in Luang Prabang and the surrounding provinces. Researchers queried 691 mothers regarding their use of supplements during pregnancy and lactation. They also contacted the health centers where the mothers received antenatal care to learn about local supplementation practices. **Sengchanh Kounnavong** reviewed the results, which indicate high frequency of supplementation during pregnancy and lactation.

Among 86 health centers, all reported providing some form of supplementation to pregnant and lactating women at each ANC visit. About 74% reported supplying an iron-folic acid (IFA) +

B1 supplement, while about 20% supplied only IFA. A minority of clinics (2%) provided multivitamins. 94% of health centers provided thiamine supplements for the first 3 months of lactation. Those that did not often cited supply issues.

Mothers' own reports reflect high levels of supplementation during pregnancy (84%), but rates of supplementation during lactation were much lower, at just 17%.

VI. Thiamine Deficiency in India

Update from Jammu and Kashmir

New data on thiamine intakes in pregnant women in Jammu and Kashmir are paving the way for assessments to determine if prophylactic supplementation should be considered in the region, according to **Hilal Ahmad.** A cross-sectional study of 170 pregnant women interviewed at an antenatal clinic in Srinagar estimated mean thiamine intakes from food at 0.86 mg/day, with half of women consuming ≤0.56 mg/day, and 75% consuming ≤1.2 mg/day. The RDA for pregnant and lactating women is 1.4 mg/day.

Study participants had low dietary diversity, with heavy reliance on polished white rice. Ahmad reports that among this population, washing rice is "universal." Notably, socioeconomic status played a significant role in thiamine intake, with higher intakes among more affluent women. Urban women also had higher intakes than rural women.

In addition to a forthcoming study to consider the need for thiamine supplementation for pregnant women, Ahmad and his collaborators are preparing to launch a community-based study on the prevalence of subclinical thiamine deficiency in exclusively breastfed infants, and a study to identify clinical markers to differentiate thiamine deficiency-related neuropathy from Guillain-Barré syndrome. These studies follow a recently published paper[38] detailing the presentations of three clinically distinct forms of infantile TDDs common in Jammu and Kashmir.

Thiamine deficiency in Assam

Thiamine deficiency disorders are a prevalent and likely underestimated health problem in Assam, said **Vijay Anand Ismavel**, who described observing the associated symptoms for nearly 30 years among his pediatric patients "without realizing they were thiamine-related." Research on TDDs in the region has increased over the past decade. Some indicators suggest that thiamine deficiency may be more widespread in northeast India than in other areas of the country, with significant impacts on peripartum women,[39] infants, and children.[40]

Ismavel highlighted Assam's proximity to Myanmar and Bangladesh, and explained that his hospital serves a rural poor population with low dietary diversity and other risk factors for TDDs. "All states in northeast India have the same geography, ethnicity, and food habits, so we think this is likely to be much more prevalent than reported," he said. Recently completed studies in Mizoram,[41] Tripura, and even high-income areas of Assam support this hypothesis.

Patients in Assam present with the full clinical spectrum of TDDs[42], including infantile beriberi, neuropathy in peripartum women as well as other groups, cardiac issues including cardiomyopathy, heart failure, mitral regurgitation and pericardial effusion, and metabolic acidosis.

Ismavel and a team of clinicians have engaged India's National Institute of Nutrition as well as the government of Assam to raise awareness and funding to address TDDs. The team has maintained an active research agenda to advance these efforts, with one forthcoming study on maternal and infant biomarkers and their relationship to TDDs, and another on the response to thiamine among pregnant women with heart failure.[43] Community prevalence estimation studies are also planned.

VI. Future Needs of the Global Thiamine Alliance

A group discussion of future needs began with a resounding consensus that countries have no time to waste addressing thiamine deficiency. "We need to act now," said **Tim Green**, noting that thiamine has no upper limit and no associated safety concerns. "In the absence of harm—and some very strong suggestion of good," he said, "it is time to act. And if not through fortification, it should be through supplementation in pregnancy."

Alliance members agreed that adequate research exists on infantile beriberi alone to make a compelling case for supplementing pregnant and lactating women, implementing staple food fortification—or both—in regions where thiamine intake is low. New and emerging evidence indicates that adequate thiamine intake has benefits across the lifespan, from supporting cognitive development in infants and children to potentially slowing the progression of Alzheimer's disease.

In early life, "thiamine deficiency might be the new lead exposure," said Dare Baldwin, an analogy that reflects the evolution in thinking surrounding the dangers of lead. Outward signs of lead toxicity raised alarms, yet "only later did we understand that even low-level exposure was harmful for development," Baldwin explained. In aging populations, the potential public health impact of slowing or preventing cognitive deficits and dementia is "incredible," said **Maria Elena Jefferds**. "Don't limit [the discussion of benefits] to early life," she said.

Research Needs

Kyly Whitfield led a discussion of outstanding research needs, with an emphasis on reaching consensus on issues related to biomarkers of thiamine status and continued exploration of the neurodevelopmental effects of low thiamine intake in infancy.

Biomarkers and cutoffs

The lack of both agreed-upon cutoffs for thiamine deficiency and correlations between biomarkers of thiamine status and TDDs is a longstanding issue. Methods for assessing thiamine status are time and resource-intensive and may provide little insight into the prevalence of

TDDs, as not all thiamine-deficient individuals present with symptoms of illness. Genetics may play a role in this, as **Phillip Fischer** noted, but this has yet to be studied.

Collectively, these factors complicate efforts to gauge population-level thiamine status beyond estimates available from food balance sheets and food frequency questionnaires. This information is likely critical in motivating countries to take action. Several members of the group stressed the importance of developing guidance around biomarker data, along with a rapid test for thiamine status.

Early life thiamine intake and neurodevelopment

Study results presented by Whitfield, Measelle, and Baldwin indicate the need for more research into the dose of thiamine necessary to achieve breastmilk thiamine concentration high enough to *both* prevent beriberi and support cognitive development. While a 1.2mg dose appears sufficient to prevent beriberi, improvements in cognitive development outcomes were only apparent at a 10mg maternal supplemental dose. Whitfield and Measelle commented that more work is needed to understand how maternal thiamine status pre-pregnancy and during gestation may affect these outcomes, as this may shift both the required supplemental dose and duration of supplementation. Longitudinal studies of infant cohorts may also help shape a supplementation (or fortification) strategy.

Several participants emphasized the benefits of a more multidisciplinary approach to addressing these issues moving forward. “There’s an incredible amount of [relevant] science going on among people who know little or nothing about public health aspects,” said **Geoffry Smith**, advocating for greater engagement with colleagues working across cell biology, neurology, physiology and other disciplines.

Implementation questions and challenges

Tim Green proposed several outstanding questions and challenges surrounding implementation of interventions to address thiamine deficiency. Discussion topics ranged from treatment and prevention protocols to fortification and cost-effectiveness analyses.

Treatment and Prevention

The lack of standardized treatment protocols for TDDs poses multiple challenges. Patients may not be receiving optimal treatment, and variations in dose, timing, duration, and mode of delivery complicate analyses of response to thiamine among patients with confirmed or suspected TDDs. Green suggests that existing protocols—including details of who is treated, when, at what dose and delivery mechanism, and whether factors such as alcohol use or carbohydrate intake are considerations, be compiled and reviewed by clinicians with expertise in TDDs to produce treatment protocols for infants, children, and adults.

Thiamine fortification may be an effective means of preventing TDDs, but the practice is uncommon. Salt has emerged as a desirable vehicle, as it is centrally processed, accessible,

utilized across all age groups, and most countries have existing salt fortification infrastructure. Additional studies are needed to determine if stability or organoleptic issues arise with double-fortified salt, and to settle on an optimal fortification dose. Green also emphasized the need to demonstrate why population-level measures should be adopted rather than a targeted approach through supplementation.

Cost-effectiveness

Motivating countries to take action requires cost-effectiveness data that is not yet available for thiamine. Even with thiamine's high safety profile and low cost, "it usually comes back to money," Green said. Building the case requires data on prevalence of TDDs, how many cases may be prevented through interventions, and hard costs of different interventions. Human capital costs should also be considered, said Green, as deficits in cognitive development can ripple throughout the life course, with potentially significant effects on GDP.

Kenneth Brown suggested a potential strategy for countries aiming to avoid "the dilemma of interpreting biomarkers" while making a case for action on thiamine deficiency. He described an approach similar to that of vaccine trials, where a high-risk group in a region—in this case, lactating women—all receive supplementation, then local hospital caseloads are monitored accordingly. Regions like Assam, which already monitor hospital prevalence of TDDs, may be positioned to use such a strategy to demonstrate the impact of supplementation.

Another cost and feasibility consideration is whether thiamine could or should be integrated into IFA supplements that are already in distribution, or into the UNIMMAP formulation at a higher dose than is currently included (1.4 mg).

Advocacy

Shawn Baker issued a rallying cry in the meeting's concluding session, urging the group to prioritize several actions for gaining allies and advancing action on thiamine deficiency.

"We clearly need to have a burden statement," said Baker, suggesting that infant mortality and longer-term impacts on child health and development could be used to model disease burden, along with available information on biomarkers, hospital case reports, and food intake surveys. Baker drew analogies to efforts to build a case for vitamin A supplementation, noting that a clear "tipping point" emerged, whereby countries with certain levels of under-5 mortality were targeted for vitamin A supplementation, even in the absence of evidence of deficiency. A similar tipping point for thiamine is less clear, he said, but developing a consensus around a set of data points (hospital prevalence and others) may be a useful tool for countries to evaluate the need to address or further investigate TDDs in their population.

Ultimately, broader action on thiamine will require engagement with WHO and UNICEF, but in the short-term, Baker suggested building support among regional health organizations, such as ASEAN, whose members include many countries at high risk for TDDs. **Kenneth Brown** noted that medical professionals are also key allies and should be a focus of educational outreach to

improve diagnosis and recognition of the clinical presentations of TDDs. Baker noted that pediatricians were powerful advocates in the community and with policymakers while building support for vitamin A programs.

The meeting concluded with a discussion about the need to prioritize one or two tasks as the focus of action on thiamine. There was agreement among the group that these agenda items could reasonably be:

1. Build upon existing supplementation infrastructure for pregnant and lactating women, whether MMS (with a higher dose of thiamine) or IFA (with added thiamine), and
2. Develop fortification solutions.

Baker acknowledged that addressing TDDs is far more complex than this initial agenda, but stressed the importance of focusing on a short list of goals at this stage. "If we can't boil it down to a couple of prioritized asks to policymakers, we're not going to go to scale fast enough," Baker said, "and too many kids are going to die in the interim."

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