

The Control and Prevention of Thiamine Deficiency Disorders: Report of a Regional Workshop

November 19 – 21, 2019
Luang Prabang, Lao PDR



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This report was written by Dr. Filomena Gomes, Dr. Megan Bourassa and Dr. Gilles Bergeron.

Executive summary

Thiamine deficiency remains a pressing public health issue and has been called the “forgotten scourge of Asia.” The lack of dietary diversity with reliance on staple crops with low thiamine content, or food preparation practices, such as milling grains and washing milled rice, in addition to postpartum food avoidances, are some of the causes of thiamine deficiency in Asia. Infantile beriberi, a disease caused by thiamine deficiency, presents during the exclusive breastfeeding period and without treatment commonly results in death within hours of clinical manifestation. There is also growing evidence suggesting sub-clinical thiamine deficiency may have a measurable, lasting impact on cognitive development and psychomotor functions.

On November 19, 20 and 21 2019, The New York Academy of Sciences (NYAS) convened a regional workshop in Luang Prabang, Lao PDR, as the first of two workshops seeking to address the key gaps in our knowledge of thiamine deficiency disorders (TDD) and to develop a model for control and prevention of TDD in the most affected countries. This first workshop included participation from several countries in the region where thiamine deficiency is a public health problem, including Lao PDR, Myanmar, Cambodia, Bhutan, Thailand, Vietnam and India (Assam and Kashmir). In addition, international thiamine experts and representatives from local and international governmental and non-governmental organizations, academic institutions, and the US Centers for Disease Control and Prevention accounted for a total of 40 workshop participants.

The first day of this 3-day workshop included sessions on thiamine biology and nutrition, clinical deficiency, and assessment of thiamine deficiency in a population and possible interventions to improve thiamine status. On the second day, a comprehensive landscape analysis of individual countries was presented by a representative of each country delegation, based on data compiled before the workshop (e.g. clinical case reports of beriberi and clinical surveillance data, surveys assessing dietary intake of thiamine and thiamine biomarkers, relevant policy documents, programmatic environment, and national health delivery architecture). The second day also included a session on planning large-scale surveys for the inclusion of assessment of thiamine deficiency, followed by a session on surveillance and monitoring. The third day focused on knowledge gaps that need to be addressed in order to reduce the global burden of thiamine deficiency, and each country group presented the main lines of action needed to initiate or improve upon a TDD control and prevention program in their country. The country groups also identified their commitments to be pursued by next workshop (in late 2020).



Acronyms

BMGF	Bill & Melinda Gates Foundation
ETKAC	Erythrocyte Transketolase Activity Coefficient
HMIS	Health Management Information System
IFA	Iron and Folic Acid supplements
NYAS	New York Academy of Sciences
MMS	Multiple Micronutrient Supplements
MNP	Multiple Micronutrient Powders
SBCC	Social and Behavior Change Communication
TDD	Thiamine Deficiency Disorders
ThDP	Thiamine Diphosphate
TIPs	Trials of Improved Practices
TRD	Thiamine Responsive Disorders
UNIMMAP	UNICEF/WHO/United Nations University international multiple micronutrient preparation
WG	Working Group
WRA	Women of Reproductive Age

Day One (November 19)

SESSION 1 – INTRODUCTION

Opening ceremony

Dr. Bounpheng Philavong

The workshop started with Dr. Sengchanh Kounnavong welcoming participants and inviting Dr. Bounpheng Philavong, Director General of the Department of Hygiene and Health Promotion (Ministry of Health) to open the event. Dr. Philavong highlighted the challenges that Lao PDR faces with regard to thiamine deficiency, recognizing that it is highly prevalent in Lao PDR, where “white sticky rice is eaten all day,” and stressing that pregnant and post-partum women are particularly at risk because of the dietary restrictions targeting that group in rural areas. The prevalence of thiamine deficiency is likely to be underestimated because of the limited capacity of healthcare professionals to identify and treat TDD. Dr. Philavong advocated for the need of an appropriate surveillance system and to assess thiamine status especially among women of reproductive age (WRA). Fortification of fish and soy sauce should be considered, in conjunction with strategies to tackle food taboos among pregnant women.



Workshop objectives and introductions

Dr. Gilles Bergeron

Dr. Bergeron described the aim of this workshop as laying out the technical basis for recognizing and addressing TDD. The workshop was structured to maximize contributions by all participants, help each national delegation design their individual country action plans to address TDD, and establish a long lasting global network of people working together to reduce the global burden of thiamine deficiency – a “community of practice” on thiamine.

The thiamine working group: antecedents

Dr. Ken Brown



Dr. Brown offered background information on thiamine deficiency, including the discovery of beriberi in the 19th and 20th centuries as a diet-related disease. He also discussed his encounters with beriberi in Thailand in 1971, when he - as a medical student - observed an infant with congestive heart failure due to thiamine deficiency and his marked improvement within hours after receiving an injection with thiamine. Later, while reviewing more recent data (2012-19) from Laos, he noted that many hospitals were receiving cases of infantile beriberi every week, prompting him to formulate the idea of a Thiamine Task Force. This group was subsequently convened in 2017 by the NYAS, with support from the Bill & Melinda Gates Foundation (BMGF), to estimate the global burden of thiamine deficiency, to prepare a “roadmap” for reducing or eliminating the disease burden, and to identify data gaps and research needs. The conclusions and recommendations of this Task Force were published in a scientific paper entitled “[Thiamine deficiency disorders: diagnosis, prevalence, and a roadmap for global control programs](#)”.

With funding from the BMGF, NYAS is now engaged in a number of research projects to reduce the global burden of thiamine deficiency such as: comparing thiamine biomarkers and their relationship with clinical disease, generating data on the prevalence of TDDs in sub-Saharan Africa, determining the appropriate level of maternal thiamine supplementation during lactation, and supporting Asian countries in the development of TDD surveillance, control and prevention programs.

Take-away messages:

- The prevalence of **thiamine deficiency** and occurrence of **infantile beriberi** remain unacceptably high in parts of Asia and likely elsewhere, although information is limited.
- Countries should invest in **assessing population thiamine status** and **the prevalence of TDDs** to determine the true extent of the problem, identify key target groups, and provide baseline data for future program evaluation.
- Where a public health problem is identified, **interventions should be implemented** to prevent and treat TDD.



SESSION 2 – THIAMINE BIOLOGY AND NUTRITION

Moderator – Mr. Laigden Dzed

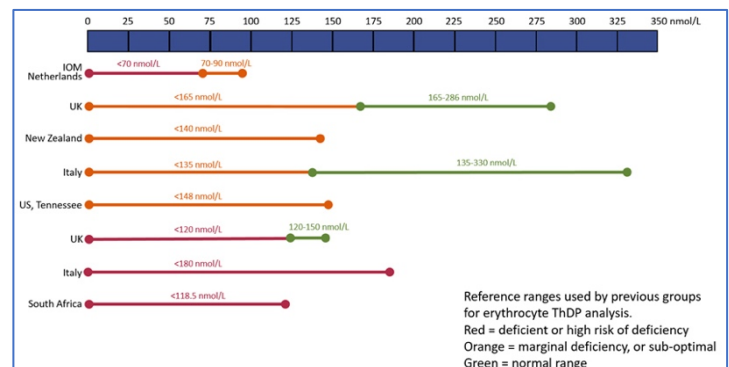
Biochemistry and biomarkers

Dr. Megan Bourassa



TDDs result from complex biochemical imbalances. To convey the processes at play, Dr. Bourassa explained that thiamine is absorbed (mostly in the small intestines), metabolized (in the liver), and transported (in the erythrocytes). She also explained the essential roles of thiamine within all cells, including energy production, carbohydrate and amino acid metabolism, and synthesis of nucleotides. Cells with the highest metabolic rates (e.g. in the brain and heart) are particularly affected by thiamine deficiency.

In whole blood most of thiamine is in the form of thiamine diphosphate (ThDP) with 80-90% of it being located in erythrocytes. As a result, ThDP from either whole blood or erythrocytes is a commonly used biomarker of status. The other available thiamine biomarker is the erythrocyte transketolase activity coefficient (ETKAC), which is an indirect, but functional measure of thiamine status based on enzymatic activity. While there are well established and widely accepted cut-off values for ETKAC indicative of thiamine deficiency, it is a less commonly performed assessment than ThDP. However, there is a wide variation of reference ranges



for ThDP used by different groups (figure on the right¹).

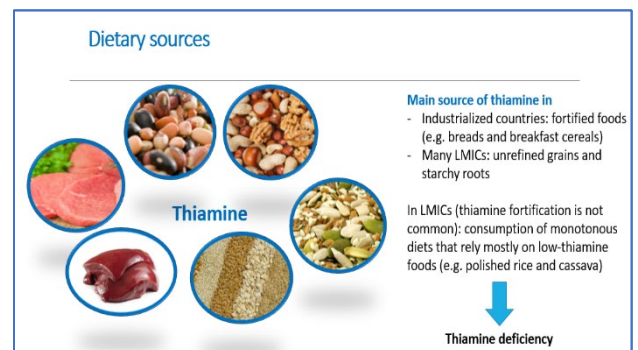
It is unclear which biomarker is better at detecting thiamine deficiency, because there is no broadly accepted cut-off for ThDP and the values do not always correlate well with clinical symptoms. Currently, the NYAS is leading a research project to determine which biomarker is more sensitive at detecting thiamine deficiency especially in the lower range of values, using specimens from a dose-response trial in Cambodia. Separate research (not led by NYAS) is also ongoing on the use of dried blood spots to measure thiamine blood levels, which could reduce the need for a cold chain and simplify sample processing in the future.

Dietary sources and requirements

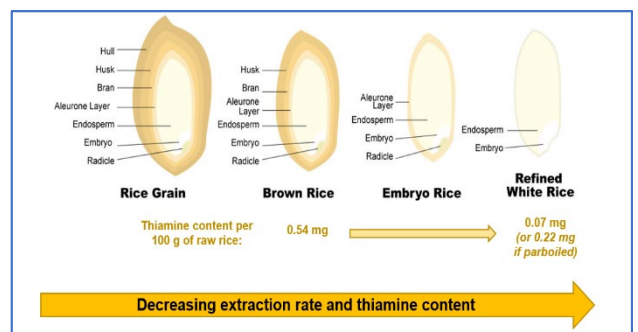
Dr. Filomena Gomes



In this presentation, Dr. Gomes covered the thiamine requirements, dietary sources and the factors that may reduce thiamine content in foods. Requirements for thiamine vary between age groups (the FAO/WHO Recommended Nutrient Intake being 1.1mg/day in women and 1.2mg/day in men), and are increased during pregnancy (1.4mg/day), lactation (1.5mg/day) and periods of increased metabolic activity. These requirements can be met by consuming good sources of thiamine, including pork meat, liver, wholegrains, pulses (e.g. lentils, peas), seeds (e.g. sunflower seeds) and nuts (e.g. peanuts and pistachios) (figure on the right). The interaction with other nutrients has been documented, such as consuming thiamine with vitamin C may have a protective role for thiamine. Magnesium is known to be a cofactor for the enzyme transketolase, and it has been reported that if both thiamine and magnesium deficiency coexist the symptoms of thiamine deficiency could not be suppressed with thiamine administration until magnesium deficiency was corrected².



Several factors can reduce the thiamine content in foods or its bioavailability. Food processing and cooking techniques such as dehulling of rice (i.e. removal of the external layers of the rice grain, which are rich in thiamine - figure on the right), or washing rice and discarding the water reduce thiamine content in foods. Also, thiamine is heat sensitive, water soluble, and is destroyed in neutral and alkaline conditions. In addition, anti-thiamine factors can affect thiamine absorption. Thiaminases found in some foods like raw or fermented fish inactivate thiamine, while other foods (e.g. betel nuts and tea leaves) act as thiamine antagonists and reduce the bioavailability of thiamine.



¹ Whitfield KC, Smith G, Chamnan C, Karakochuk CD, Sophonneary P, et al. (2017) High prevalence of thiamine (vitamin B1) deficiency in early childhood among a nationally representative sample of Cambodian women of childbearing age and their children. PLOS Neglected Tropical Diseases 11(9): e0005814. <https://doi.org/10.1371/journal.pntd.0005814>

² Dyckner T, EK B, Nyhlin H, Wester PO. Aggravation of Thiamine Deficiency by Magnesium Depletion: A Case Report. Acta Med Scand. 1985;218(1):129-131. doi:10.1111/j.0954-6820.1985.tb08836.x

SESSION 3 – CLINICAL DEFICIENCY

Moderator – Dr. Roshine Koshy

Thiamine deficiency disorders

Dr. Philip Fischer and Dr. Casey Johnson



Dr. Fischer and Dr. Johnson from the Mayo Clinic explained that the clinical features of thiamine deficiency have been known for a long time, but diagnosis has evolved from the old classification of wet vs. dry beriberi to a more recent classification with five different patterns of thiamine deficiency: acute cardiologic form, aphonic form, pseudo meningitic form, encephalopathy, and peripheral neuropathy³ (figure on the right). Some workshop participants commented further that this recent classification does not include all the potential thiamine deficiency symptoms (e.g. cardiac symptoms in adults).

Acute Cardiologic Form	Aphonic Form	Pseudo Meningitic Form	Encephalopathy	Peripheral Neuropathies
<ul style="list-style-type: none"> • Peak prevalence in breastfed babies of 1–3 months of age • Colic • Restlessness • Anorexia • Vomiting • Edema • Cyanosis and breathlessness with signs of heart failure leading to death • Pernicious form or Shoshin Beriberi • Sudden cardiogenic shock 	<ul style="list-style-type: none"> • Peak prevalence in 4- to 6-month-old infants • Initially hoarse cry until no sound is produced while crying • Restlessness • Edema • Breathlessness and death 	<ul style="list-style-type: none"> • Peak prevalence in 7- to 9-month-old infants • Nystagmus (involuntary eye movement) • Muscle twitching • Bulging fontanelle • Convulsions • Unconsciousness 	<ul style="list-style-type: none"> • Generally older children or adults but also seen in infants • Psychomotor slowing or apathy • Nystagmus or ophthalmoplegia • Ataxia • Impaired consciousness • Eventually coma and death 	<ul style="list-style-type: none"> • Older children or adults • Pain • Tingling or loss of sensation in hands and feet (peripheral neuropathy) • Muscle wasting with loss of function or paralysis of the lower extremities • Loss of ankle and knee reflexes • Cranial nerve impairment

The speakers showed what a classic infantile beriberi looks like (explained on the text box on the right) and reviewed the multiple reports of this condition in many South Asian countries. For example, a verbal autopsy study conducted in Prey Veng, Cambodia in 2005-2008 showed that 45% of infants who died in their first year of life had signs and symptoms of beriberi.⁴ However, many research questions and challenges related to thiamine deficiency diagnosis, prevention and treatment remain. For instance, many markedly “biochemically thiamine deficient” children do not present clinical symptoms, and others have concurrent illnesses that can act as confounding factors. In addition, thiamine deficiency may predispose infants to more severe infections as the administration of thiamine helps them overcome the infection.

What does classic infantile beriberi look like?

- Previously healthy, 2-4 months old
- Vomiting, irritability over a few days but no fever
- Respiratory distress, tachycardia
- Hepatomegaly
- Dysphonia, hoarseness
- Cyanosis and grunting
- Cold extremities, mottled skin
- Death within a few days

Haridas, G. "Infantile beriberi in Singapore during the latter part of the Japanese occupation." *Arch Dis Child*. 1947 Mar;22(109):23-33.
Thavarekai, O and J. Whitaker (1954) "Childhood thiamin deficiency in Northern Thailand." *American Journal of Clinical Nutrition* 18: 275-277.
Luxemburger, C., N. J. White, et al. (2003). "Ber-beri: the major cause of infant mortality in Karen refugees." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 97(2): 251-255.

³ Whitfield, K.C., Bourassa, M.W., Adamolekun, B., Bergeron, G., Bettendorff, L., Brown, K.H., Cox, L., Fattal-Valevski, A., Fischer, P.R., Frank, E.L., Hiffler, L., Hlaing, L.M., Jefferds, M.E., Kapner, H., Kounnavong, S., Mousavi, M.P., Roth, D.E., Tsaloglou, M.-N., Wieringa, F. and Combs, G.F., Jr. (2018), Thiamine deficiency disorders: diagnosis, prevalence, and a roadmap for global control programs. *Ann. N.Y. Acad. Sci.*, 1430: 3-43. doi:10.1111/nyas.13919

⁴ Greta Kauffman, Debra Coats, Somonn Seab, Mark D Topazian, Philip R Fischer, Thiamine deficiency in ill children, *The American Journal of Clinical Nutrition*, Volume 94, Issue 2, August 2011, Pages 616–617, <https://doi.org/10.3945/ajcn.111.018457>

Hemoglobinopathies and the risk of thiamine deficiency

Dr. Frank Wieringa



Thiamine deficiency may be associated with other pathologies. Using data from the Cambodia National Micronutrient Survey, where blood samples were collected from 719 women of childbearing age (15-49y) and their young children (n=761, 6-69 months) in 2014, Dr. Wieringa explained first that mean erythrocyte ThDP values in these groups were 150 and 174 nmol/L respectively⁵, with significant deficiency among both groups, but especially in children under 12 months of age. Second, Dr. Wieringa explained how, using the same data, he explored the association between hemoglobinopathies and thiamine deficiency. Hemoglobinopathies, such as sickle cell disease and thalassemia, are inherited changes in the structure, function or production of hemoglobin, which happen to be highly prevalent in Southeast Asia, including between 30 and 60% of the Cambodian population. Looking at the association between hemoglobinopathies and micronutrient deficiencies in children, Dr. Wieringa showed that there is a higher prevalence of thiamine deficiency in any form of hemoglobinopathies when compared to those without hemoglobinopathies (table below, highlighted in yellow).

Variables	Normal Hb		HbE_Heterogygote		HbE_Homogygote		β_thalasemie		Other		Total		P-Value
	n	%	n	%	n	%	n	%	n	%	n	%	
Iron stores(Fer<15µg/L)	10	6.3	7	3.9	1	5.0	0	0.0	24	8.1	42	6.3	0.42
Iron Def erythropoeitin (stFr>8.3mg/L)	65	41.1	84	47.2	12	60.0	8	80.0	186	62.8	355	53.6	<0.001
Vitamin A Deficiency (<0.70µmol/L)	18	11.4	10	5.6	4	20.0	0	0.0	22	7.4	54	8.2	0.07
Vitamin A Marginal (<1.05µmol/L)	41	26.0	48	27.0	10	50.0	2	20.0	62	21.0	163	24.6	0.04
Vitamin B1 Deficiency (<120	22	13.5	34	18.6	7	33.3	4	36.4	75	24.4	143	20.9	0.008
Vit B1 Marginal (<150)	50	30.7	75	41.0	9	42.9	7	63.6	124	40.4	266	38.8	0.08
Folate Deficiency (<10nmol/L)	12	7.6	22	12.4	3	15.0	0	0.0	22	7.5	59	9.0	0.23
Vitamin B12 (<150 pmol/L)	5	3.2	3	1.7	0	0.0	0	0.0	5	1.7	13	2.0	0.74
Zinc Deficiency (<7.65µmol/L)	39	27.1	48	31.2	7	38.9	3	33.3	99	36.5	196	32.9	0.36
Zinc Deficiency marginal (<9.9µmol/l)	92	63.9	97	63.0	14	77.8	5	55.6	186	68.6	394	66.1	0.51
Iodine Deficiency (<100 µg/L)	106	68.0	126	71.6	12	66.7	5	55.6	179	60.3	429	65.3	0.17

The cause of this association has not been confirmed, but it could be due to the higher turn-over of erythrocytes observed in hemoglobinopathies, leading to higher losses of thiamine. The public health consequences of this association also remain to be defined but could imply higher attention for populations suffering from hemoglobinopathies.

⁵ Whitfield KC, Smith G, Chamnan C, Karakochuk CD, Sophonneary P, et al. (2017) High prevalence of thiamine (vitamin B1) deficiency in early childhood among a nationally representative sample of Cambodian women of childbearing age and their children. PLOS Neglected Tropical Diseases 11(9): e0005814. <https://doi.org/10.1371/journal.pntd.0005814>

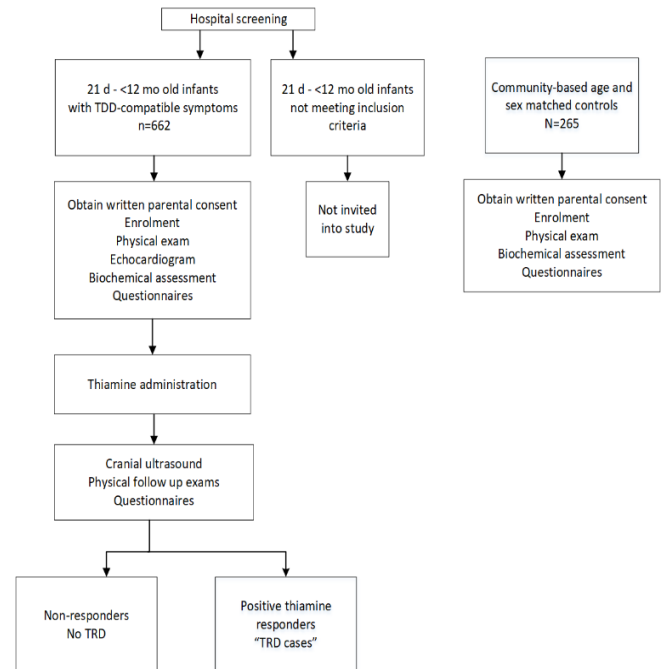
Developing a case definition

Dr. Taryn Smith

Dr. Smith is currently coordinating a study to establish a case definition of thiamine responsive disorders (TRD) among infants in Lao PDR. Given the lack of clear diagnosis, TDD are often suspected rather than confirmed, and a final diagnosis is often based upon positive response to thiamine administration, hence the focus of this study on TRD.

The complex study design (picture on the right) includes a large sample size of infants (hospitalized at the Lao Friends Hospital for Children) under 18 months of age (previously was under 12 months, as shown in figure at the right, but was expanded to include more children) (n=662), their mothers (n=662) and a community-based age and sex matched infant mother pairs (n= 265). Hospitalized infants who meet the broad inclusion criteria receive 100 mg thiamine per day for minimum for three days. Based on results from follow-up assessments for 48-72 hours, they are then classified into responders (TRD cases) or non-responders.

In addition to the development of a case definition for TRD, this ongoing study aims to define thiamine biomarker cut-offs (ThDP and ETKAC), as well as risk factors and predictors associated with TRDs (e.g. maternal and infant dietary practices, socioeconomic status, etc.). Data collection is anticipated to be completed by December 2020.



Lao Friends Hospital for Children's clinical experience in managing TDD

Dr. Lisa Rynn

Dr. Rynn, Medical Director at Lao Friends Hospital for Children in Luang Prabang, shared her clinical experiences in managing TDD at this hospital, which opened in 2015. She first described the typical (and often seen) case of an infant recently admitted to the Emergency Department with thiamine deficiency, namely a 2-month-old with severe respiratory distress, enlarged liver, poor perfusion and weak pulse. His mother reported following the local taboo diet, consisting almost exclusively of white rice, and experiencing numbness in her hands (a manifestation of being probably deficient in thiamine herself). The mother also reported that she had previously lost a child of about the same age to a similar "illness" (cause not identified) but didn't visit the hospital at the time, making Dr. Rynn suspect that this prior death might be an uncounted victim of thiamine deficiency. After receiving 100mg of intramuscular thiamine the symptoms affecting the infant showed gradual improvement within a few hours. He was ready for discharge within 48 hours.



Dr. Rynn next shared the case of another 9-month old infant recently seen in the Emergency Department with diagnosis of beriberi. Like the prior example, the mother reported a very restricted diet and mentioned that the child's own introduction to complementary feeds consisted only of rice soup. This suggests that not only exclusively breastfed infants, but also children during the complementary feeding period, are a group at risk of thiamine deficiency.

The table on the right shows the number of patients with a diagnosis of "beriberi" (and related deaths), identified through the electronic medical record system of this hospital between 2017 and October 2019. This sample had an average age of presentation of 5 months (the older patient being 12 years old), was composed mostly of males (mean 56%); Hmong ethnicity was most common (mean 55%, vs. 28% Khmu and 15% Lao). No particular association was detected with seasonality, and the acute cardiologic form (wet beriberi) was shown to be more prevalent.

Year	Number of cases of beriberi	Number of deaths due to beriberi	Average age at presentation
2017	372	6	5.1 months
2018	435	3	5 months
2019	342	5	4.6 months

Dr. Rynn also shared her current practices regarding the treatment and prophylactic supplements administered to both children and her mothers, complemented with educational sessions on thiamine deficiency for mothers attending the neonatal unit of the Lao Friends Hospital for Children.

SESSION 4 – ASSESSMENT OF THIAMINE DEFICIENCY IN A POPULATION

Moderator – Dr. Saipin Chotivichien

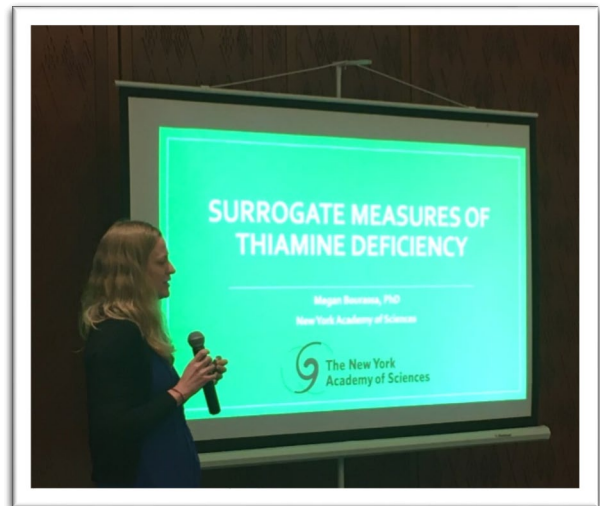
Surrogate measures of thiamine deficiency

Dr. Megan Bourassa



The lack of solid diagnostic criteria for TDD and the knowledge gaps related to thiamine biomarkers create problems in identifying populations at risk of being thiamine deficient. In this presentation, Dr. Bourassa reviewed the set of surrogate measures for thiamine deficiency proposed by the Thiamine Working Group (WG)⁶ which include:

- 1) **Infant mortality:** A telltale sign that the population may be affected by TDD is when population data shows peaks in curves of infant mortality at 3 months and 6 months of age. Infants may be born with some thiamine reserves from the prenatal period, but metabolic changes in the first few months of life increase their thiamine requirements. If left unaddressed this may lead to rapid increase in mortality among those cohorts.
- 2) **Dietary assessment:** National surveys or other studies may be used to identify populations where dietary thiamine intake are below the recommended levels.
- 3) **Food balance sheets:** Inadequate availability of thiamine in the national food supply, e.g. through the identification of countries where the average level of thiamine availability is below 1.2 mg/capita/day (assuming no thiamine

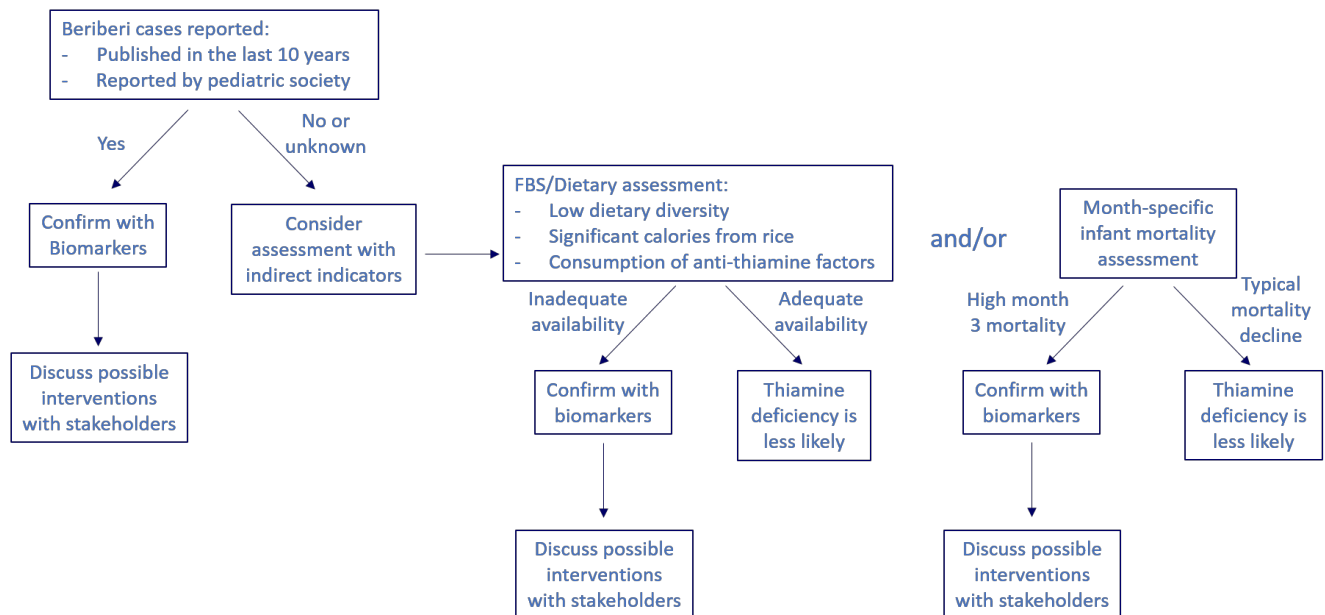


⁶ Whitfield, K.C., Bourassa, M.W., Adamolekun, B., Bergeron, G., Bettendorff, L., Brown, K.H., Cox, L., Fattal-Valevski, A., Fischer, P.R., Frank, E.L., Hiffler, L., Hlaing, L.M., Jefferds, M.E., Kapner, H., Kounnavong, S., Mousavi, M.P., Roth, D.E., Tsaloglou, M.-N., Wieringa, F. and Combs, G.F., Jr. (2018), Thiamine deficiency disorders: diagnosis, prevalence, and a roadmap for global control programs. Ann. N.Y. Acad. Sci., 1430: 3-43. doi:10.1111/nyas.13919

fortification program is in place); or countries where >50% of energy comes from low-thiamine staple crops (e.g. polished rice)

- 4) Household consumption and expenditure surveys: can be used to estimate aggregate household and per capita thiamine intake
- 5) Case reports of TDD: can be captured through retrospective reviews of medical records in hospitals or clinics

These surrogate measures were compiled into a decision tree (graph below), offering an approach to assess a country's risk of TDDs and the actions that the country may consider to prevent/control TDD cases.



Assessment of TDD in populations: biomarker and dietary intake assessments

Dr. Filomena Gomes



If the surrogate measures discussed in the previous presentation suggest that the population is at risk of thiamine deficiency, then an assessment should be carried out to determine whether thiamine deficiency is indeed a public health problem that requires action. Dr. Gomes explained how such an assessment could be conducted through a large-scale (regional/national) population survey, which may include several modules:

- 1) Biomarker assessment: *the gold standard to assess thiamine status and determine prevalence of thiamine deficiency.*

This module captures data on demographic characteristics, pregnancy and lactation status, breastfeeding practices and use of formula, use of nutrition supplements containing thiamine, symptoms of thiamine deficiency, and information related to blood specimen collection.

- 2) Dietary intake and local food practices assessment: *to determine the causes/etiology of thiamine deficiency.*

This module captures data on drugs that may deplete thiamine, food processing and preparation methods that increase losses of thiamine, foods that contain anti-thiamine factors, consumption of foods fortified with thiamine or foods that could be good vehicles for fortification, a 24-hour dietary intake recall and a food frequency questionnaire to assess the consumption of specific items over a longer time period (one month).

This large-scale survey targets WRA and infants under 12 months. Examples of those surveys are provided in the [Technical Reference Materials](#).

SESSION 5 – INTERVENTIONS TO IMPROVE THIAMINE STATUS

Moderator – Dr. Lwin Mar Hliang

This session focused on interventions that a country may consider to improve the thiamine status of a population. The types of interventions considered here include food fortification, supplementation, and education to healthcare providers and consumers to change food processing and consumer behaviors associated with thiamine deficiency.

Food fortification: pros & cons

Dr. Tim Green



For more than 100 years food fortification has been used to increase the intake of a certain nutrient in a population. Dr. Green explained the pros and cons of this strategy (text box below) and offered guiding principles on the use of food fortification to ensure that the lowest possible amount is used to meet the needs of the target population. Aspects to consider in doing so include:

- The form of the nutrient to ensure its stability, bioavailability, safety, etc.
- The selection of a vehicle, which would ideally be a food staple, with consumption patterns consistent across the population and amenable to centralized processing.
- The amount to add should be based on current and target intakes of the nutrient, its distribution across the population, and the upper safety limits for this nutrient.
- Monitoring is essential to verify that the intervention is achieving its goal, to identify obstacles such as side effects, and to understand the sustainability of the program in its given context.

Fortification	
Pros	Cons
<ul style="list-style-type: none">• Passive• No behaviour change• Compliance not a problem• Continuous delivery• Cost-effective• Proven efficacy	<ul style="list-style-type: none">• Safety• Imbalance in other nutrients• Rough Instrument• Right to choose• Bioavailability• Food vehicles are often not consistent with Healthy Eating Guidelines

Supplementation: how, when, and how much

Dr. Kyly Whitfield



Dr. Whitfield's presentation addressed considerations in the rollout of supplementation as a way to improve the thiamine status of a population, namely:

1) Dietary Reference Intakes⁷ (table below).

The Recommended Dietary Allowance for thiamine in pregnant women in Southeast Asia is slightly higher than the equivalent value established by the Food and Nutrition Board, Institute of Medicine (1.5 mg/day vs. 1.4 mg/day, respectively).

Group	DRI (mg/d)	Rationale
Men	EAR: 1.0 RDA: 1.2	heaviest weighting of evidence was placed on a thiamine depletion-repletion study conducted among n=7 men in a metabolic unit in the late 1970s
Women	EAR: 0.9 RDA: 1.1	decreased from men's value by 10% based on body size and energy needs
Pregnancy	EAR: 1.2 RDA: 1.4	+30% increased growth in maternal and fetal compartments + 10% for increased energy utilization = 0.27 \cong 0.3 mg/d
Lactation	EAR: 1.2 RDA: 1.4	+ 0.16 mg into milk + 0.1 mg for energy cost of milk production = 0.26 \cong 0.3 mg/d

DRI: Dietary Reference Intakes. EAR: Estimated Average Requirement. RDA: Recommended Dietary Allowance

2) WHO recommended supplementation regimen for the treatment of thiamine deficiency (in major emergencies)⁸. These vary between mild (10 mg/day for 1 week, followed by 3-5 mg/d in following 6 weeks) and severe thiamine deficiency, which are divided into infants (25-50 mg IV immediately, 10 mg/d IM for 1 week, and 3-5 mg orally for 6 weeks) and critically ill adults (50-100mg IV immediately, 3-5mg orally for 6 weeks).

3) Delivery

- Intravenous: thiamine hydrochloride given as a 100mg IV bolus is safe⁹
- Intramuscular: has been associated, albeit rarely, with adverse effects, which makes some scientific societies prefer IV delivery¹⁰
- Oral: less effective than IV or IM routes¹¹ (high doses go largely unabsorbed due to limits in gastro-intestinal absorption)

⁷ Thiamin' Food and Nutrition Board, Institute of Medicine. National Academy of Sciences, 1998

⁸ WHO 1999 Thiamine deficiency and its prevention and control in major emergencies (pp.24)

⁹ Wrenn et al 1989 Ann Emerg Med 18:867-870

¹⁰ Galvin et al 2010 European Journal of Neurology 17:1408-1418

¹¹ Frank 2015 Journal of Parenteral and Enteral Nutrition 39(5): 503 -520

- 4) Dosing for human milk delivery: 100 mg/d for 5 days is enough to replenish thiamine-deficient Cambodian mothers, but a longer supplementation period may be needed to correct thiamine deficiency in breastfed infants.¹²
- 5) Standard of care
- Dosing around the world: the “UNICEF/WHO/United Nations University international multiple micronutrient preparation” (UNIMMAP) formulation contains 1.4 mg of thiamine (RDA for pregnancy and lactation) and is being adopted by some countries’ antenatal programs. However, a variety of treatment regimens have been applied in different countries.
 - WHO Essential Medicines List: contains oral supplements with 50mg of thiamine; multiple micronutrient powders for children may or may not contain thiamine (at 0.5 mg/sachet).

Based on the above, Dr. Whitfield suggested the following options:

- For prevention:
 - Oral thiamine at relatively low doses (~2.5 – 5 mg/d), through pregnancy and lactation
 - Challenges with procurement of low dose thiamine preparations may be mediated via use of the UNIMMAP formulation
- For treatment regimens:
 - Treat infant directly (IV or IM) if clinical deficiency is suspected;
 - Follow-up with oral thiamine treatment.

Note that the currently ongoing study “Thiamine dose response in human milk with supplementation among lactating women in Cambodia”¹³ will help define the dose of thiamine required to optimize human milk thiamine concentrations, which will further inform future supplementation and fortification programs.

Education of healthcare providers and consumers

Dr. Filomena Gomes



This presentation discussed the education of healthcare providers, community health workers and the public in locations where individuals may be affected by or are at risk of TDD.

Certain eating behaviors, myths and food practices increase the risk of TDD. Formative research should be carried out to identify such issues and develop nutritional education and behavioral change communication that address aspects such as:

- 1) Restrictive diets/food taboos post-partum: Such beliefs, combined with the increased thiamine requirements during lactation, poses mothers and her breastfed babies at severe risk of TDD
- 2) The consumption of anti-thiamine factors: Fermented tea leaves, betel nuts and other products may inhibit the absorption or bioavailability of thiamine
- 3) The importance of food diversity and of increasing awareness and availability of thiamine-rich foods: Populations at risk of TDD should know about the local availability and affordability of thiamine rich-foods such as pulses, beans, groundnuts, etc. and be encouraged to increase their consumption

¹² Coats et al 2013 Am J Clin Nutr 98(3):839-44

¹³ Whitfield et al. BMJ Open 2019;9:e029255.

4) **Food processing and cooking techniques:** Simple methods, such as switching from refined white rice to whole grain or parboiled rice; or avoiding soaking/washing rice before cooking, can be promoted to improve the intake of thiamine. Examples of generic educational materials were developed by the NYAS team and can be adapted to national or regional contexts for the education of healthcare providers and consumers in reducing the risk of TDD. These materials include:

- For healthcare professionals:
 - “[Thiamine deficiency disorders: identification and treatment](#)”
 - “[Infantile beriberi: clinical symptoms and case studies](#)”
 - “[A guide to increase thiamine intake and prevent thiamine deficiency](#)”
- For pregnant women and lactating mothers:
 - “[The importance of thiamine during pregnancy, breastfeeding and infancy](#)” (leaflet on the right).

In health facilities where the use of videos is possible, training of healthcare professionals can also be supplemented with existing educational videos, e.g.: <https://youtu.be/QXLj45Kt-wU>



A study to evaluate the impact of health and nutritional education to address thiamine deficiency among pregnant and lactating mothers living in Assam and Tripura states

Dr. Mahesh Kumar Mummadi



Several suspected and confirmed cases of TDD have been documented in Assam and Tripura (two Northeast Indian states), particularly among infants, pregnant women and lactating mothers. A quick situational analysis showed that, in this area, betel nuts and fermented fish are widely consumed, and raw rice is washed repeatedly (4-5 times) before cooking.

Dr. Mummadi, a scientist at the Indian National Institute of Nutrition, presented a 2-year study that will be conducted on 1320 pregnant & lactating mothers living in selected districts of Assam and Tripura. The study has the following objectives:

- To study the prevalence of thiamine deficiency (through biomarkers in blood and breastmilk, assessment of dietary intake, verbal autopsies of infants who have died in the last 6 months) and associated factors, in this population
- To assess the impact of health & nutritional education on thiamine deficiency among this population, as a sustainable model of intervention. Pregnant women before 2nd trimester will be recruited and intervention will be given until the child is 6 months old.

Dr. Mummadi obtained approval by the national Scientific Advisory Committee and is seeking funding to initiate this study.

Day Two (November 20)

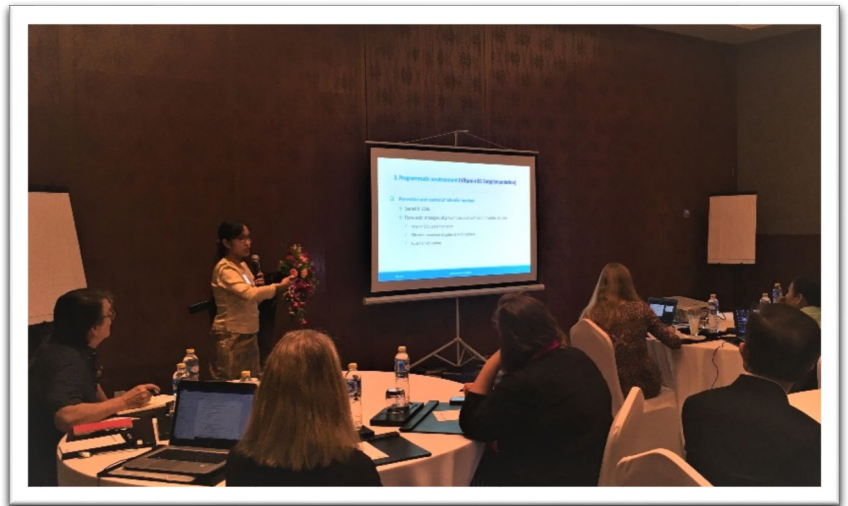
The second day of the workshop was divided in two parts. The first set of sessions were devoted to presentations by each participating country of their individual situation with respect to TDD. The second part focused on data aspects, namely: how to conduct surveys and how to establish monitoring and surveillance systems to support the fight against TDDs.

SESSION 6 – LANDSCAPE ANALYSIS OF INDIVIDUAL COUNTRIES

Moderator – Dr. Kyly Whitfield

In this section, a comprehensive landscape analysis of individual countries was presented by a representative of each country delegation, based on data collected before the workshop.

These national data on preliminary estimates of TDD, policy environment, programmatic environment, and the national health system infrastructure should help each country configure a TDD Control and Prevention program tailored to their needs and context.



Myanmar

Dr. Lwin Mar Hlaing



Myanmar is one of the few countries with a thiamine deficiency control and prevention program in place. Dr. Hlaing, the Acting Director of the Myanmar National Nutrition Center, shared the country's experience from discovery to action.

Preliminary estimates of TDD in Myanmar

In 2003 a cause specific, under-five mortality survey suggested that beriberi was the fifth leading cause of death among infants 1-11 months of age (7.1%). Shortly after, a hospital-based beriberi surveillance conducted in 2005 showed that case fatality rate was 5.9% among 2-3-month old infants.

In 2008, a community-based survey showed that thiamine deficiency (assessed by ETKAC) affected 6.8% of pregnant women and 4.4% of lactating women.

In 2014 a study on under-five mortality using a standard verbal autopsy questionnaire (WHO) revealed that beriberi was the second leading cause of death among infants 28-days to 1-year old and that half of these deaths occurred at home.

Programmatic environment

In 2006, a control and prevention program of infantile beriberi was initiated that included thiamine supplementation, effective treatment of patients with TDD and nutrition education (text box on the right). Thiamine related information was included in the Standardized Health Message Booklet and in the maternal nutrition component of the Community Infant and Young Child Feeding Counselling Package.

❑ Vitamin B1 supplementation

- ❖ Prevention of infantile beriberi
- ❖ 10mg daily dose of vitamin B1 to pregnant and lactating women (starting from 9th month of pregnancy until 3 months after delivery)

❑ Effective treatment

- ❖ IM injection of vitamin B1 50-100 mg stat dose
- ❖ Followed by oral 10mg BD Vitamin B1 for 2 weeks and 10mg daily for 1 month

❑ Nutrition education

- ❖ Thiamine-rich foods, proper cooking methods, maternal nutrition

Data from the Health Management Information System (HMIS) 2018 show that there were 1.1 infants with beriberi per 1000 live births, and 72% of pregnant women and over 85% of post-natal and breastfeeding mothers received thiamine supplements. The Myanmar Micronutrient and Food Consumption Survey from 2018 will soon bring more information on the thiamine status of WRA, pregnant and lactating women.

Rice fortification with multiple micronutrients, including thiamine, was approved in 2016; and the national rice fortification policy is now in its final draft. The fortified rice program will be used in sports institutes, nursing training schools, government hospital meal programs; in pre-school children in kindergartens. However, the program faces serious challenges:

- Only a few of the country's rice millers are engaged in rice fortification program (15 out of >2,000). Those will reach only 1% of the total population in Myanmar.
- There are only two fortified kernel producers. They have to import the premix which increases the cost of the product. The next step of the rice fortification program is to set up a mandatory minimum (approximately 10%) in the production of fortified rice by large and medium-sized millers. This goal will be supported by the provision of limited subsidies and inducements to private producers and phased in over the next 3-5 years.

Salt fortification: Universal salt iodization was adopted in 1989, but adequate iodization is not followed by most producers. A legislative statement on iodization of salt is being drafted.

Home fortification with micronutrient powders: This program is limited to children 6-23 months and is not universal.

Prenatal multiple micronutrient supplementation (MMS): These supplements were introduced in 2016 to replace iron and folic acid supplements (IFA) and are locally produced since 2019.

Other relevant information

The Multi-sectoral National Plan of Action on Nutrition 2019-2023 aims to reduce all forms of malnutrition in mothers, children and adolescents, and thiamine supplementation and food fortification are among the key interventions covered by this Plan.

Lao PRD

Dr. Chandavone Phoxay

Dr. Phoxay, Director of the National Nutrition Center, covered the landscape analysis for Lao PDR.



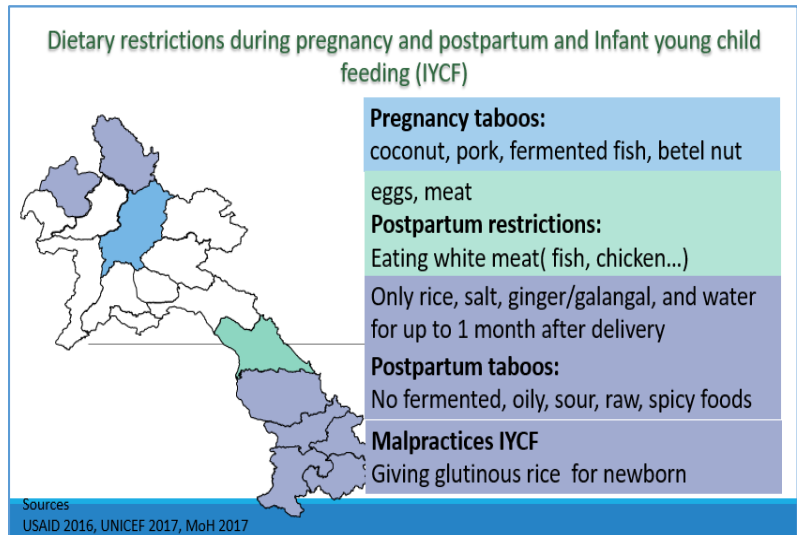
Data and information on TDD

In 2008 a survey conducted in the two Lao PDR sub-districts with highest and lowest infant mortality indicated that the low concentration of thiamine in the blood and milk of mothers was strongly suggestive that infantile beriberi due to thiamine deficiency was the principal cause of the infant mortality in the study regions¹⁴. In 2010-16 the provision of thiamine supplementation to mothers by the International Support and Partnership for Health (2010-2016) resulted in reduced mortality¹⁵.

Pre and postnatal dietary restrictions are well documented in Laos and vary from region to region (and presumably between ethnic groups) – figure on the right. In addition, approximately 70% of energy intake comes from white rice¹⁶, and minimum adequate dietary diversity is not achieved in children aged 6-23 months.

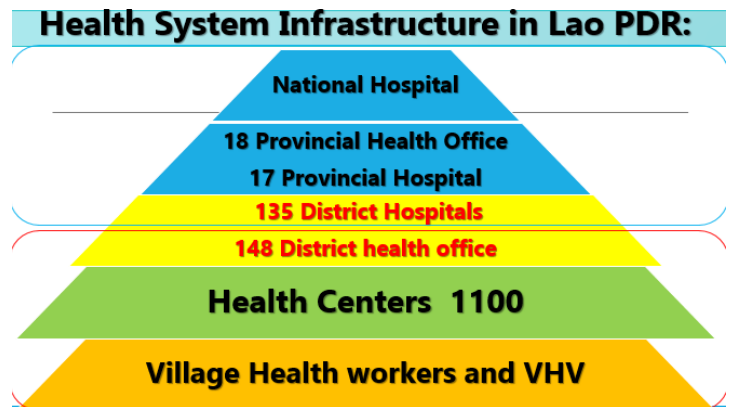
Programs

The 2025 National Nutrition Strategy and Plan of Action for 2016-2020 identified 22 priority interventions. The first is “the promotion of the consumption of iodized salts and micronutrient fortified food, and thiamine supplementation for pregnant and lactating mothers in the high-risk communities”¹⁷. Among the fortifiable food products commonly consumed in Lao PDR, salt is the food product with the highest coverage. However, although there is a mandatory salt iodization policy, iodine deficiency is still high (49%). There is also a distribution of micronutrient powders (containing 0.5 mg thiamine/sachet) among children between 6 months and 5 years of age.



National health system

The Health System Infrastructure is presented on the right. The Village Health Workers deliver nutrition education to the population, and thiamine supplements are given in maternity wards in some provinces (but this program is not well established). Dr. Phoxay identified some challenges, e.g. limited data, lack of confirmed diagnosis of beriberi and diagnosis being based on symptoms that overlap with other diseases.



¹⁴ Nakano et al (2008) High Infant Mortality Presumably Due to Thiamine Deficiency in Lao PDR, Journal of International Health. 23(1):33-42

¹⁵ ISAPH report 2010-2016

¹⁶ Lao Food Consumption FAO 2014

¹⁷ National Guidance on Micronutrient supplementation in Lao PDR., MoH and UNICEF, 2018

Cambodia

Dr. Chea Mary



The landscape analysis for Cambodia was presented by Dr. Chea Mary, Manager of the National Nutrition Program.

Preliminary estimates of TDD in Cambodia

Available surveys on thiamine deficiency and consumption and intake¹⁸ show that the proportion of thiamine deficient Cambodian women and children (using the lower cut-off of eThDP < 120 nmol) is 27% and 15%, respectively. These numbers increase to 78% and 58% if the higher cut-off of eThDP < 180 nmol is used. The population has an average thiamine intake of 0.58 mg/day, and 63% of the energy consumed by Cambodians comes from non-fortified white rice.

Various studies conducted in Cambodia contribute significant additional information to the national understanding of thiamine deficiency. First, levels of thiamine in rural Cambodian populations are lower than those among urban populations¹⁹. Second, the diagnostic criteria for infantile beriberi does not seem to correlate with blood thiamine indicators²⁰. Third, women who consumed thiamine-containing fish sauce have higher concentrations of thiamine in their blood and breastmilk, and their infants had higher thiamine status in blood, when compared to a control population²¹.

Programmatic Environment

The current fortification policies for several food products and their degree of compliance were discussed (table on the right). The level of compliance of salt iodization has improved over time, but 64% of the coarse salt tested is not yet iodized at the required level.

A home-based fortification program with Multiple Micronutrient Powders (MNP) was started in 2011 for children but was discontinued in 2015 due to funding and compliance issues.

Currently, a national IFA supplementation program is in place for WRA including pregnant and lactating women, and there is a national vitamin A supplementation program for children aged 6-59 months.

National health system infrastructure

The national health system is structured into different levels (national, provincial and operational district) and includes a variety of facilities (nine national hospitals to 1,141 health centers). Currently, none of the existing national laboratories have the capacity to analyze thiamine biomarkers.

Budget for Health Sector

The annual budget for the health sector (including nutrition services delivered through health facilities and communities) between 2016 and 2020 is progressively increasing, and budget gaps should decrease over this period of time. However, funding for nutrition-specific programming, such as fortification and supplementation, remain quite low.

Fortification environment		
Fortification	Environment/regulation	Scale
Salt iodization	Sub Decree 69 – mandatory	National program
Fish sauce and soya sauce fortifying with iron	Proclamation for the production and consumption of iron fortified fish sauce and soy sauce. No.048 NCN – voluntary	National program
Rice fortification vitamins A, B1, B3, B6, Folic Acid, B12, Iron, Zinc	No regulation	Small scale with support from WFP and RACHA
Thiamine fortifying with iron fish sauce	No regulation	Pilot stage, support from UBC and HKI
Degree of fortification compliance		
Items	Total producers	Producers declared complying
Table salt production	200	200
Refined salt production	25	25
Fish sauce and soya production	90	53
Rice production	At least 1 rice mill machine in every village	No regulation

¹⁸CDHS and Micronutrient Survey 2014; Whitfield et al (2017) PLOS Negl Trop Dis 11(9): e0005814; Gibson & Cavalli-Sforza 2012 Food and Nutrition Bulletin 33(3 Suppl): S214-20; based on the analysis of the food balance sheets (FAO, 2011) and the global food fortification data (<https://fortificationdata.org/interactive-map-fortification-legislation/>)

¹⁹ The Journal of Nutrition 2016 145(1):147-48. doi: 10.3945/jn.115.225599.147

²⁰ J. Pediatr. vol. 161,5 (2012): 843-7. doi:10.1016/j.jpeds.2012.05.006

²¹ JAMA Pediatr. (2016).doi:10.1001/jamapediatrics.2016.2065

Thailand

Dr. Bancha Kakhong and Dr. Saipin Chotivichien



Dr. Kakhong, Deputy Director-General of the Ministry of Health in Thailand and Dr. Saipin Chotivichien, Director of the Bureau of Nutrition in the Department of Health, began their exposé by reviewing the decentralized structure of the Thai National Health System. Following this introduction, they moved to the programmatic aspects of the nutrition program in Thailand.

Preliminary estimates of TDD

The incidence of diagnosed TDD cases in Thailand tends to be concentrated in specific population groups, namely fishing crews, prisoners and industry workers (table on the right). Aside from those populations, thiamine consumption appears to be adequate across all parts of the Thai population.

Laboratories in the Thai healthcare system (particularly in large hospitals) have the ability to measure thiamine status. Infant mortality data, when analyzed by month, shows a progressive decline from the 1st to the 12th month of age, suggesting that thiamine deficiency is not an issue in this age group.

Published Thai Studies Indicative of Thiamine Deficiency

Year	Province	Class / Category	Total No. of Cases		
			Reported Cases	Reported Deaths	Total
APR. 2005	Samut Sakhon	Fishing crew	11	2	13
JUL. 2006	Samut Sakhon	Fishing crew	22	28	50
NOV. 2011	Bangkok	Prisoners	11	4	15
JUL. 2013	Chachoengsao	Industry workers	17	3	20
DEC. 2014	Northeast Thailand	Prisoners	79	28	107
JAN. 2016	Samut Prakarn	Fishing crew	9 (Thai 8, Cambodia 1)	2 (Thai)	11
JAN. 2016	Ranong	Fishing crew	26 (Thai 7, Cambodia 19)	6 (Thai 1, Cambodia 5)	32

The Department of Health promotes healthy eating to prevent micronutrient deficiency among all age groups. Despite the low prevalence of TDD in Thailand, the Division of Occupational and Environmental Disease, under The Department of Disease Control, is in the process of setting up a pilot reporting system in five provinces to monitor thiamine deficiency in high risk groups (e.g. fishing crew).

Programmatic Environment

Regarding fortification²²:

- Mandatory fortification includes vitamin A for condensed milk, and iodine for salt, fish sauce, soy sauce and salt brine. Voluntary fortification includes vitamins B1, B2 and B3 for rice, with thiamine content not less than 0.4 mg in 100 g of pre-cooked rice (or 26.67% Thai Recommended Dietary Intake).
- The food production process is decentralized and supervised by provincial health offices.
- Equipment to fortify rice with thiamine is not provided by national authority, but manufacturers (almost all private) can afford the equipment to do so (mixing machine, vitamin sprayer with hot air current, etc.).

Regarding supplementation: IFA supplements are provided to WRA. IFA and iodine supplements are provided to pregnant and lactating women (with a coverage of 77% for pregnant women). Iron supplements are provided to young children (6 months to 5 years) and school aged children (with a coverage rate of 48% and 22%, respectively²³).

²² Notification of the Ministry of Public Health No. 150 (1993)

²³ Health Data Center, MoPH, 14 Nov., 2019

Vietnam

Prof. Dr. Le Thi Hop



Prof. Dr. Hop, Director of the Vietnamese National Institute of Nutrition, provided an overview of the current state of knowledge on thiamine deficiency in Vietnam, nutrition policies and interventions in Vietnam and stressed that the specific objectives of the 2020 National Plan of Action for Nutrition include the reduction of micronutrient deficiencies.

There are a few current fortification and supplementation policies that include thiamine, such as: food fortification with micronutrient powders for babies²⁴ (0.04 mg to 0.2 mg of thiamine/100g), wheat flour fortification with 2.5 mg of thiamine/kg of wheat flour²⁵, and MMS for pregnant and lactating women containing 1.4 mg of thiamine per tablet.

An analysis of the trends of Food Consumption of Vietnamese People between 1985 and 2010 showed that rice consumption decreased while other major sources of carbohydrates (e.g. bread and noodles), fat, animal foods (meat, fish, eggs and milk) increased. Thiamine intakes in adults also increased, reaching 1.1 mg/capita/day in 2010, suggesting that most of the adult population in Vietnam has adequate intakes of this vitamin (table on the right). However, the mean intake of thiamine in children is only 72% of the recommended dietary allowance.

Trends of Vitamins Intake of Vietnamese People from 1985-2010

Vitamins	1985	1990	2000	2010
B2 (mg)	0.45	0.36	0.53	0.7
PP (mg)	11.0	10.0	11.56	14.3
C (mg)	40.0	53.2	72.5	85.1
B1 (mg)	0.82	0.69	0.92	1.1
Vit B1/1000 kcal	0.42	0.39	0.48	0.57

There are two ongoing pilot studies on food fortification, supported by ILSI:

- Fish sauce fortified with iron
- Rice fortified with micronutrients (iron, zinc, thiamine, folic acid and riboflavin)

In addition, GAIN is supporting additional fortification programs, e.g. fish and soy sauce fortified with iron, involving 16 food companies.

Dr. Hop concluded that despite the improvement in both quantity and quality of food consumption, the Vietnamese population still faces several micronutrient deficiencies, and there is a paucity of national data on thiamine deficiency that justifies conducting a national survey to determine the population's thiamine status. Results from a recent micronutrient survey will likely be available in March 2020.

Bhutan

Dr. Mimi Lhamu Mynak



In this presentation, Dr. Mynak, a Bhutanese pediatrician at the Jigme Dorji Wangchuk National Referral Hospital, described how thiamine deficiency – particularly among of infants and children – has been discovered and managed in Bhutan. She started by describing the three-tiered health care service delivery system and the laboratory capacity to perform thiamine biomarker analysis at the Royal Centre for Disease Control in Thimphu.

²⁴ MOH Decision 6289/2003/QĐ-BYT

²⁵ MOH Decision 6289/2003/QĐ-BYT

Programmatic Environment

Nationwide supplementation and fortification programs include:

- IFA, calcium, vitamin A supplementation for pregnant and lactating mothers (coverage is 100% and compliance is over 80%)
- Vitamin A supplementation for children
- Iodized salt: iodine deficiency disorders eliminated as a public health issue since 2003
- Fortified rice: distributed to government boarding schools
- Micronutrient powders (including thiamine) for young children aged 6-23 months (recently launched, will reach scale by June 2020)

Existing nutrition policy documents include: the Food and Nutrition Security Policy of Bhutan 2014, Food-based Dietary Guidelines 2010, Bhutan Dietary Guidelines for School Children 2015, Accelerating Actions for Reducing Undernutrition Among Women and Children (2017 -2019), and National Nutrition Strategy and Action Plans (2019-2023), in the draft form.

Estimates of TDD in Bhutan

a) School children

A number of outbreaks of peripheral neuropathy were reported in Bhutan since 1998, although it is unclear whether these cases were TDDs (table on the right). The last outbreak, in 2011 affected school children and drew more attention, as 2 of the students died (with features suggestive of congestive cardiac failure), and other students were referred to clinical care in Assam, where they received the diagnosis of thiamine deficiency.

Despite some follow-up interventions, such as strengthening of the school feeding program and a one-off thiamine supplementation provided to school children, Bhutan continued to report sporadic outbreaks of peripheral neuropathy in boarding school children.

A study conducted in 2014 in 7 districts found a high prevalence of thiamine deficiency in schoolchildren at baseline (51%), and this number increased when in schools to 90% in midterm and 92% after midterm²⁶.

In 2018 rice fortified with vitamins A, B1, B3, B6, B9, B12, iron and zinc was distributed to school children and covered all boarding schools in 2019.

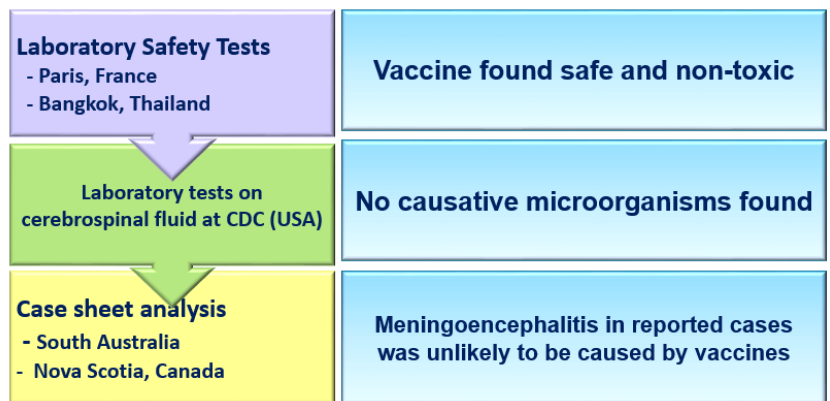
Year	Number of cases	Categories
1998	60	Young soldiers, recruits and civilians
2003	11	Young soldiers, recruits and civilians
2004	36	Soldiers + Civilians
2006	20	School Children
2007	12	School Children
2008	14	School Children
2010	75	Monks
2011	34	School Children

b) Infants

The pentavalent vaccine was introduced on September 1, 2009, and nine infant deaths with temporal relation to vaccine were reported. The vaccine was suspended on October 23, 2009, and an in-depth investigation was conducted with help from WHO (figure on the right).

The vaccine, which was proven to be safe, was reintroduced in January 2011, and surveillance for acute encephalitis was initiated. The common clinical features captured in this surveillance included vomiting, irritability, respiratory distress and bilateral symmetrical basal ganglia and thalamic infarcts. Two thirds of the affected infants were 0-6 months of age, and 61% of these cases (of meningoencephalitis/encephalopathy) were fatal. This is nearly twice the level of fatality cases from any cause seen at the

Summary of vaccine testing and case sheet review



²⁶ Laigden et al (2015) Bhutan Health Journal. 1(1): 49-56

pediatric intensive care unit (35%), and there was a peak of cases seen between August and October that corresponds with the time period in which anti-thiamine containing ferns are consumed (July to September). In addition, between 2014 and 2017 several samples were tested for a variety of viral diseases and infections (most of which were negative) and the possible diagnosis changed to metabolic encephalopathy, but the causes of that disease remained unknown.

In 2018 a volunteer pediatric intensivist from Germany spent three months in Bhutan and worked with Dr. Mynak to understand the causes of metabolic encephalopathy. After some research and the suspicion that the disease could be attributed to thiamine deficiency, it was decided to start empirical treatment with thiamine (50-100 mg IV, followed by 10 mg oral supplements for 10 days) for all babies presenting with features of encephalopathy, beginning in September 2018 in the Pediatric Department where Dr. Mynak works. This initiative resulted in a dramatic improvement of symptoms, a reduced stay in the Pediatric Intensive Care Unit, and a significant reduction in mortality rates (table below).

TDD in children – post introduction of thiamine (in Sep 2018)					
	Total admission PICU	Mortality	Meningoencephalitis cases	Mortality in Meningoencephalitis	
<ul style="list-style-type: none"> ❖ Immediate improvement in the sensorium 24 hours ❖ Reduced respiratory support ❖ Reduced stay in the PICU ❖ Pulmonary hypertension improved ❖ Drastic reduction in mortality 	Sep 2017 – Aug 2018	295	102 (34 %)	67	38 (58%)
	Sep 2018 – Aug 2019	281	44 (16%)	45	8 (18 %)

Dr. Mynak concluded that the (frequently fatal) disease she was observing in the Pediatric Intensive Care Unit was a thiamine responsive disease. The diet in Bhutan is predominantly based on polished rice that is washed repeatedly, tea is consumed with meals, and chewing of betel nuts and consumption of ferns is very common.

Since then all children admitted with meningoencephalitis or encephalopathy and isolated pulmonary hypertension in her department received thiamine. Echocardiography is performed within 24 hours of admission in suspected cases of thiamine deficiency, and district medical officers were also sensitized on the use of thiamine in sick infants.

In May 2019 a prospective case-controlled study was initiated at the National Referral Hospital and includes assessment of thiamine biomarkers in infants as well dietary history of their mothers.

Comments: It is very likely that vaccines produce a systemic inflammatory response that may lead to symptoms of thiamine deficiency, which requires further investigation and considerations to provide thiamine concomitantly with the vaccine.

Assam

Dr. Roshine Koshy



Dr. Koshy, the Medical Superintendent at the Makunda Christian Leprosy and General Hospital in Assam, Northeast India, provided her regional and clinical perspective of thiamine deficiency, followed by data collected from Dr. Mummadi (Scientist at the Indian National Nutrition Institute) who provided a national landscape analysis of thiamine deficiency.

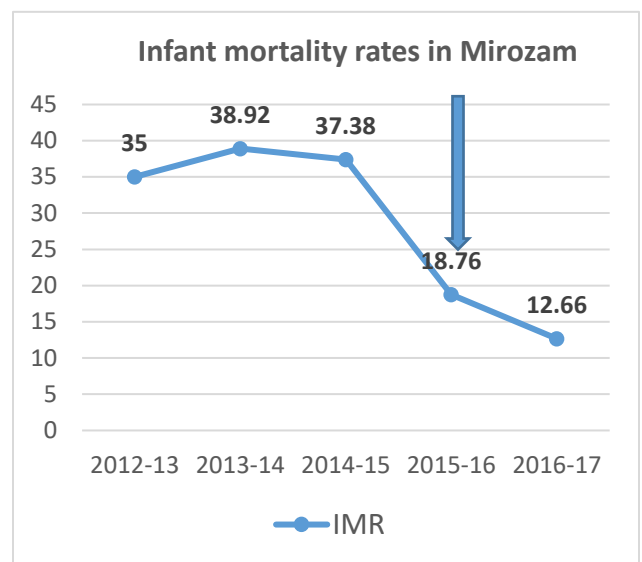
In 2018 Dr. Koshy conducted a retrospective review of the clinical presentation and electrodiagnostic features of 24 peripartum women presenting with peripheral polyneuropathy during a 6-month period, showing improvement in clinical symptoms after administration of thiamine²⁷. Of the 20 patients with follow up data 18 patients (90%) had improvement in neurological deficits, and 25% of patients also had concurrent symptoms of cardiac involvement (wet beriberi). All patients had a rice predominant diet (with 54% consuming polished rice) and frequently consumed tea, betel nut, and fermented or raw fish.

“Peripartum women are being brought to our hospital in wheelchairs [because of thiamine deficiency]. We included the “squat test” - the ability to get up from sitting position, on a chair, without support - as part of our screening protocol [for thiamine deficiency], which is being applied at this hospital and taught to our junior authors.”

Dr. Koshy has also encountered a number of infants with the classical presentation of cardiac form of infantile beriberi. Twenty-eight critically ill, exclusively breastfed infants were seen over a period of one year. Seventy percent required inotropic support apart from fluid resuscitation and 50% required invasive ventilation. After administering thiamine 92% of the infants showed dramatic improvement with resolution of shock within 24 hours (data not published – manuscript submitted for publication and to be presented at the 5th Micronutrient Forum Global conference, 2020).

Dr. Koshy also highlighted how infant mortality rates decreased dramatically in 2015 in Mirozam (bordering Assam and Myanmar) after the implementation of a policy to provide thiamine supplementation to pregnant women (figure on the right). However, there is no ongoing surveillance system in place.

Currently, there is a multicenter study (seven centers in India, including two hospitals in Assam) in collaboration with Oxford University to set up a surveillance of eight peripartum complications, including transient peripheral neuropathy. Over a period of nine months, 690 complicated pregnancies were seen at the Makunda Hospital of which 9% presented with transient peripheral neuropathy.



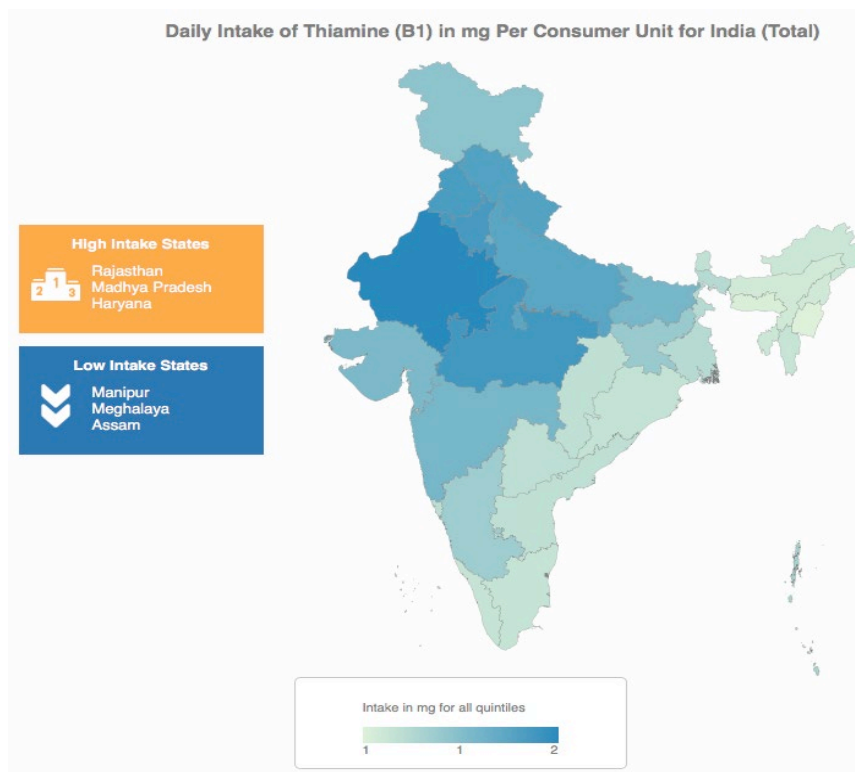
There are no national or regional guidelines on the diagnosis of and management of TDDs. At the Makunda Hospital, based on the available formulations for supplements and clinical experience, the following thiamine supplementation guidelines are used (table below):

²⁷ Koshy et al. CHRISMED J Health Res 2018;5:178-181

	Target group	Dose
Prevention	Antenatal (throughout pregnancy) and post-natal women (3 months postpartum)	Thiamine in form of vitamin B complex, 1 capsule per day containing 10 mg of thiamine
Treatment	Infantile cardiac beriberi	100 mg thiamine IV bolus, total of 7 days, followed by vitamin B drops containing 1mg per ml per day for a month
	Dry beriberi in adults	200 mg thiamine IV/IM for 7 days followed by 100 mg of thiamine for 1 – 6 months
	Wet beriberi in adults	400 mg thiamine IV twice daily for 7 days followed by 100 mg thiamine for 1-3 months
	All patients are counselled to avoid dry /fermented fish and betel nut	

The national nutrition survey data show that, on average, there is a daily intake of thiamine/capita/day of 1.14 mg, but these numbers are much lower in the States of Manipur (0.5 mg), Meghalaya (0.57 mg) and Assam (0.66 mg). The lower intakes of thiamine are seen in all Indian Eastern States (figure below).

The governance of the health system is divided between the union and state governments, and routine national and state level surveillance exist mainly for infectious diseases. Most of rural India accesses sub-health centers, rather than hospitals. Thus, the data on reported hospitalized cases of TDD may be just the “tip of the iceberg.”



The National Nutrition Strategy from 2017 focused on vitamin A, iron, iodine and zinc, but not thiamine. The minimum level of (voluntary) fortification with thiamine is set up for three food products (rice, maida and atta), but a mandatory fortification policy exists for salt with iodine since 1998 and with iron since 2018.

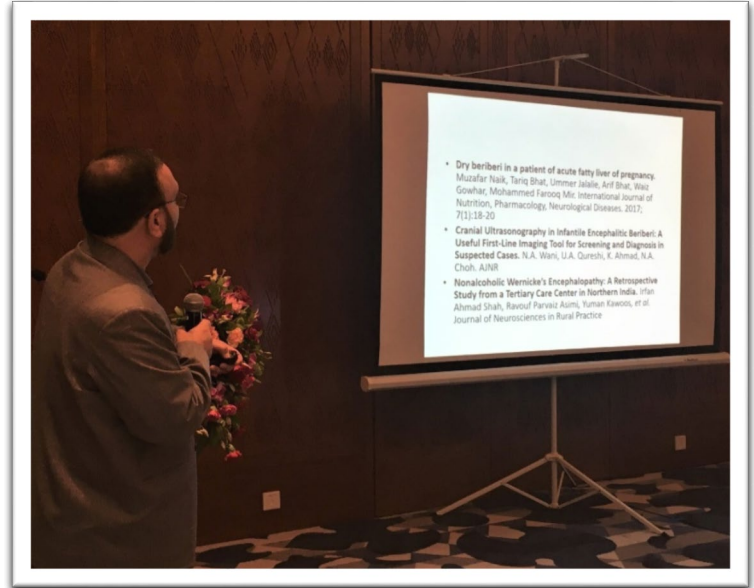
Iron and folic acid supplementation programs reach children (from 6 months to 10 years), adolescents, WRA, pregnant women and lactating women (with 70% coverage). As these are the most at risk populations for TDD, these programs could work as delivery platforms for an additional thiamine supplementation program.

Jammu and Kashmir

Dr. Shahzada Khan and Dr. Umar Amin Qureshi



Dr. Khan and Dr. Qureshi are two physicians from the Government Medical College, in the Department of Community Medicine and Department of Pediatrics, respectively. Dr. Khan started by sharing a number of recently published studies on thiamine deficiency/TDD, which were conducted in Jammu and Kashmir, in Northern India. These studies showed how TDD is affecting infants^{28,29,30,31,32}, older children³³, peripartum women^{34,35} and adults^{36, 37, 38}.

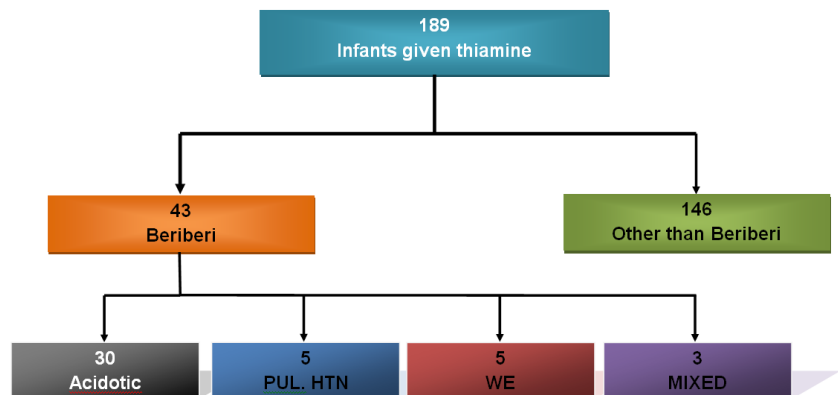


Regional data shows that the percentage of iodized salt is 99.5% in urban areas of Jammu and Kashmir, and 93.5% in the rural areas, suggesting that salt is a potential good (co)fortification vehicle for thiamine.

Dr. Qureshi showed the clinical and laboratory data on infantile beriberi that he gathered retrospectively in the Department of pediatrics at GB Pant Hospital, Srinagar, Kashmir. This includes previously documented infants with thiamine deficiency presenting with unexplained pulmonary hypertension, metabolic (lactic) acidosis and/or encephalopathy, admitted between January and December 2016.

Inclusion criteria were all infants from one month old onwards in whom parenteral thiamine was given at admission and whose final diagnosis of beriberi had been made by rapid response to thiamine and after exclusion of a relevant differential diagnosis.

The 43 infants who received the diagnosis of beriberi were extensively investigated and classified into four phenotypes of beriberi (figure on the right):



²⁸ Nazir et al. 2019. Indian Pediatr. 56(8):673-681

²⁹ Bhat et al. 2017. World J Pediatr. 13(5):485-488

³⁰ Wani et al. 2016. AJNR Am J Neuroradiol. 37(8):1535-40

³¹ Qureshi et al. 2016. 32(2):213-6

³² Javeed et al. 2017. 69(1):24-27

³³ Ganie et al. 2012. Indian J Endocrinol Metab; 16(4): 646–650

³⁴ Sheikh et al. 2019. Int J Adv Med. 6(3):662-667

³⁵ Naik et al. 2017. Int J Nutr Pharmacol Neurol Dis. 7:18-20

³⁶ Shah et al. 2019. Int J Res Med Sci. 7(5):1494-1499

³⁷ Shah et al. 2017. J Neurosci Rural Pract. 8(3):401-406

³⁸ Iqbal et al. 2019. Heart India. 7(2):68-73

- 1) Acidosis (n=30): mean age of 67 days, mean hospital stay of 7 days; presenting with vomiting, fasting/acidotic breathing, gasping, moaning, low blood pH (7.13), high lactate (5 to >15), acute respiratory failure (50%), cardiogenic shock (46%), severe metabolic acidosis (36%) and seizures (36%),
- 2) Pulmonary hypertension (n=5): mean age of 158 days, mean hospital stay of 4 days; presenting with decreased feeding, hoarseness of voice, tachycardia, irritability, low blood pH (7.26), slightly high lactate (mean of 5.62) and mean pulmonary pressure 52 mm Hg
- 3) Wernicke's encephalopathy (n=5): mean age of 190 days, mean hospital stay of 3 days; presenting with vomiting, low Glasgow Coma Scale, vacant stare, ptosis, normal lactate and blood pH, seizures and hyperechoic basal ganglia.
- 4) Mixed forms (n=3).

Dr. Qureshi noted that this is a secondary data analysis and infants who may have died of beriberi would not be part of the study.

In the last part of this presentation, Dr. Khan described a recent community based cross-sectional study, conducted in 2019, looking at the consumption of thiamine-containing food among population of Srinagar district in Kashmir. A population of 749 children and adults from 200 households and four different areas was studied, and a 24-hour dietary recall method was applied. The three most consumed foods were polished white rice, roti and cow's milk. More than 80% of the population was not meeting the daily thiamine requirements, which applied to both men and women.

Kiribati


Dr. Tim Green



Dr. Green presented the case of a TDD outbreak observed in Kiribati in 2014-2015 and the subsequent efforts made to control and prevent thiamine deficiency in this small Pacific Island country. The remote location of this country makes it dependent on imports for food (including canned foods) and leads to low dietary diversity, with a sub-optimal level of 0.66 mg of thiamine available/capita/day.

The emergence of thiamine deficiency in Kiribati was initially reported as an unusual and sometimes fatal illness³⁹. A study of etiology of the outbreak on the Kuria atoll identified 69 cases (prevalence of 7%), including 34 confirmed TDD and 35 unconfirmed TDD (text box on the right). Most were adults (median age 28 years), and 59 (83%) were male. The 10 female cases included eight pregnant and two lactating women. Seven adult males and two infants died (13% case fatality rate). Resolution of objective clinical signs (78%) or symptoms (94%) was identified within one week of starting treatment with 100 mg of thiamine hydrochloride and was assessed using the squat test, heel-walk test and lower extremity hypo- or areflexia. Risk factors included having a friend with TDD and drinking kava (a drink made from the ground roots of the plant *Piper methysticum*). Drinking yeast alcohol reduced the risk of disease.

Kuria Outbreak



SAHMRI
South Australia Health & Medical Research Institute

- Population 1000
- Households 190
- Outbreak affected 7% of population
- 69 cases suspected or confirmed
- 5 infants earlier had suspected infantile beriberi

Consecutively, Dr. Green and Dr. Whitfield led a cross-sectional household survey (in collaboration with the WHO and the Kiribati Ministry of Health) to come up with a sustainable method to combat beriberi in Kiribati. All households in Kuria with a pregnant woman or a child under 59 months of age were considered for inclusion. The sample was composed of 17 pregnant women; 17 lactating women; 70 WRA, 84 children aged 6-59 months and 93 adult men. Thiamine deficiency (based on ThDP cut-off of <95nmol/L) affected 30% of women, 24% of men and 15% of children. Based on dietary intake

³⁹ Nilles et al. 2018. Re-emergence of thiamine deficiency disease in the Pacific islands (2014–15): A case-control study. PLoS ONE 13(6): e0198590

data, thiamine inadequacy was 22% among WRA, more than 50% for pregnant and lactating women and 44% among men. Results showed a high prevalence of alcohol consumption, which is especially problematic given the higher thiamine requirement among heavy drinkers. In light of the limited potential for dietary diversity and limitations associated with rice fortification in this country, possible interventions to prevent TDD include supplementation and fortification of salt. However, some steps will be required before introducing salt fortified with thiamine (list of steps enumerated on the right).

Where to next?



- Convince powers that be that salt fortification does not increase salt intake
- Introduce salt fortification
 - Measure salt intake
 - Pilot study on Kuria where we replace all salt in market stalls with thiaminized and iodized salt
 - Institute sodium reduction strategies
 - Measure beriberi cases during that year
 - Measure thiamine in blood before and after
 - Measure salt intake before and after

SESSION 7 – PLANNING A LARGE-SCALE SURVEY FOR THE ASSESSMENT OF THIAMINE DEFICIENCY

Moderator – Dr. Mahesh Kumar Mummadi

Introduction

Dr. Gilles Bergeron

While there is enough information to justify intervention in countries affected by TDD, better data on population thiamine status are needed if countries are to establish effective TDD control and prevention programs. This session covered methodological issues in the preparation of large-scale surveys and when establishing surveillance programs.

Planning large-scale micronutrient survey integrating thiamine assessment

Dr. Fabian Rohner



Dr. Rohner discussed several considerations for planning a large-scale survey that integrates the assessment of thiamine status and/or intake. His presentation offered guidance on the following aspects:

- **Defining the scope of the survey** by collecting available data from previous national surveys, smaller scale surveys, etc. to document indicators of interest in the target populations.
- **Sampling considerations**, including the need for regional and national level stratifications. The final sample size will determine the cost of the survey, hence its budgetary feasibility, its duration and whether there is sufficient national capacity to carry it out.
- **Piggy-backing on other surveys** may lead to substantial cost savings but reduces flexibility in determining the sample and in documenting associated conditions of TDD.
- **Planning for logistics requirements** must address options for supply procurement and assessment of national and international laboratories' capacity.
- **Paying attention to protocol finalization, ethical approval and the development of questionnaires**
- **Planning the field work**, including the strategy to guarantee cold chain, blood processing (centralized vs. decentralized), as well as supply procurement.
- **Specifying the implementation protocol** including the selection of sampling units (households or individuals), logistics and quality control.
- **Integrating thiamine as a biomarker** (figure on the right).

Integration of thiamine as a biomarker

- Survey design:
 - Can household approach be used as sampling unit?
 - Need to oversample?
- Questionnaire-related:
 - Special modules? How much added time?
- Specimen collection:
 - EDTA or Heparin tubes vs. serum tubes
 - Special cold chain requirements
- Sample processing:
 - Special specimen processing requirements
 - Special cold chain requirements

SESSION 8 – SURVEILLANCE AND MONITORING FOR TDD

Moderator – Dr. Chandavone Phoxay

Program design, monitoring and evaluation and surveillance systems

Dr. Maria Elena Jefferds



Dr. Jefferds, from the U.S. Centers for Disease Control and Prevention, provided an overview of the design of monitoring, evaluation and surveillance systems, particularly as applied from a prevention lens:

Design

- Surveillance and monitoring of TDD should aim to track disease incidence and the distribution of dietary inadequacy and deficiency through the collection and analysis of primary or secondary data.
- Some platforms like the Iodine Global Network, or the Food Fortification Initiative can provide technical or operational guidance that adapted for thiamine surveillance.
- Establishing such a system requires the full documentation of expected processes and pathways in data transmission.
- The design of interventions should include behavior change strategies to support adherence and resources to maintain those strategies.

Monitoring: assessing how the program (inputs, activities and outputs) is performing according to predefined criteria and targets. Two types of monitoring should be considered:

- Internal monitoring, typically using routine data (e.g. HMIS, Logistics Management and Information Systems (LMIS)), is meant to document and identify problems and improve program performance.
- External monitoring focuses on the objectives and outcomes of the program and relies on data collected/managed independently of the staff.

Evaluation: the assessment of program/project that covers its need, design, implementation, impact, efficiency and sustainability, so as to incorporate lessons learned into the decision-making process about the program and inform public policy.

Surveillance: the ongoing, systematic collection, analysis, interpretation and dissemination of data regarding nutritional status and nutrition programs in order to make policy and programmatic decisions that lead to improvements in the nutrition situation of a population.

The key points for monitoring and surveillance were presented (figure on the right).

Key points: Monitoring and Surveillance

- Nutrition data value chain
 - No one source of data to meet all needs – multiple needed
 - Analysis of country nutrition information landscape
- All interventions need internal monitoring
 - Often is HMIS/LMIS (DHIS2) or a parallel system (pilot)
 - Industrial fortification at mills
- Frameworks and technical monitoring & surveillance resources exist can be applied
- Work with stakeholders: focus, prioritize, collect and use to improve intervention effectiveness and make policy decisions

Day Three (November 21)

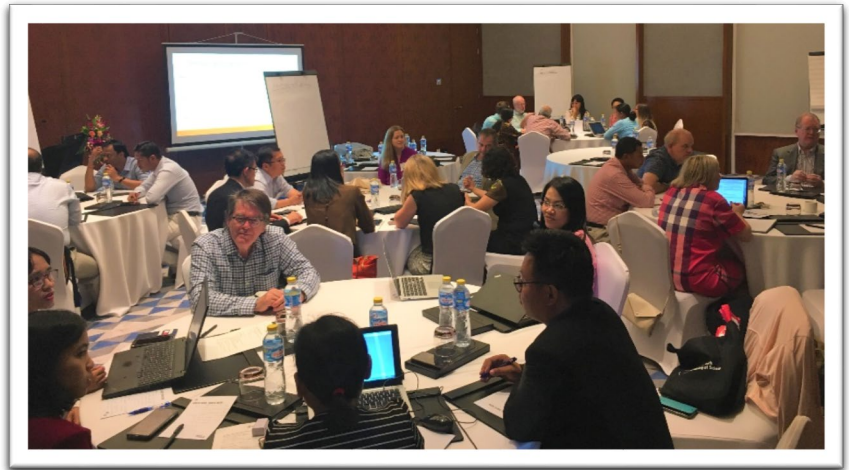
While days 1 and 2 focused on the presentation of materials, tools and experiences by participants, day 3 aimed at processing this information into actionable recommendations. Contrasting with the didactic presentations of the first two days, day 3 sessions were based on WG deliberations. Two WG sessions were organized: the first session emphasized thematic aspects related to addressing TDD. Participants voluntarily assigned themselves to the WG of their preference. The second session focused on country action plans, for which participants were assigned to their respective country's WG.

SESSION 9 – NEXT STEPS

Thematic working groups

Moderator: Dr. Megan Bourassa

In this exercise five thematic WG were organized around data, policy and advocacy, clinical issues, social and behavior change communication, and food fortification. Each group was asked to discuss the needs and knowledge gaps associated with each theme and to develop recommendations that would help overcome those gaps.



1) Data WG

The Data WG identified data needs and suggestions along the following dimensions:

Design of Surveillance Systems

- Assessment of thiamine status needs to be included into national surveys.
- Surveillance data needs to be broken down into specific areas.
- Simple symptoms indicative of early stages of beriberi (e.g. tingling in hand, squat test—the appropriate clinical symptoms should be proposed by the Clinical WG) should be included into existing questionnaires or in clinical settings as part of screening in suspected high-risk areas. In India for instance, simple symptom questions should be included in the [IDSP](#) (integrated disease surveillance program under HMIS), which gets updated every week.



Planning of surveys

- Many countries (e.g. Laos, India) do not have baseline data on their population's thiamine status. Baseline surveys such as the micronutrient survey in Vietnam should be carried out in all countries, at least in high risk areas (as identified by the number of clinical cases).
- A multiple-country systematic review of existing clinical reports of TDD cases should be carried out as a step in generating the evidence to support policy making.
- This should be followed by a baseline TDD prevalence study in high risk areas.
- To better understand the extent of the problem, other sources of data should be used, e.g. infant mortality rates, food balance sheets, food consumption surveys, etc.

Minimum criteria for public health concern

- Cut-offs for thiamine deficiency need to be developed, similar to what was developed for Vitamin A deficiency (e.g. based on the "night blindness" clinical symptom). For TDD readily identifiable symptoms (e.g. tingling in hand, squat test, etc.) should be used.
- The cut off for action is tricky: a cut-off of 20% to declare public health concern may be too high; yet a single case of infant death attributed to thiamine deficiency should be considered as a public health concern.

What data is needed to piggy back on other surveys?

- Adding thiamine to existing/ongoing micronutrient surveys: Many large surveys, e.g. India's Comprehensive National Nutrition Survey conducted in partnership with UNICEF, do not assess thiamine status but should be added, first in the high-risk areas and then expanded to the whole country if the initial inclusion proves useful.
- Recognizing how difficult it is to add new questions to surveys like the DHS or to existing HIMS, formative research should be done to translate the disease name into locally-recognized terms (in the same way as night blindness is for vitamin A). For instance, the term beriberi is derived from the Sinhalese word meaning "extreme weakness." Perhaps there are already local terms for beriberi that can be included in surveys, which might allow for quick detection without having to go through the process of full case definition.

2) Advocacy and policy WG

The WG identified the following advocacy and policy questions:

What messages or information do we need to communicate and how?

- An immediate need is to create threshold estimates/indicators of when TDD reaches the level of public health concern.
- For advocacy purposes, the costs and consequences of TDD must be understood both in the immediate (mortality) and longer term (e.g. cognitive development).
- There is a need to convince policy makers in understanding that TDD interventions are low cost, that results can be obtained rapidly with treatment, and that such actions can be incrementally added to existing programs. They don't need to be established as big programs on their own.
- Effective advocacy should make it personal by involving clinicians who bring compelling stories.
- Using existing data and systems, surveillance and case reporting at healthcare facilities for TDD cases is needed
- In the longer term, we should work on developing global guidance/recommendations, as this will be critical to make changes at the national level.

Who to target for advocacy?

- Government officials (many of whom are present in the workshop) and government institutions
- Professional associations (pediatrics, nutrition), who have not been involved in these discussions so far
- Health services, to generate information for advocacy (some examples were already presented in this workshop)
- We must raise awareness among stakeholders such as donors, civil society organizations.
- WHO/UNICEF are key allies at the country level, as they are respected and viewed as credible.
- Regional associations (in particular ASEAN, the Association of Southeast Asian Nations, given the current prevalence of TDD in Southeast Asia) should be made aware of the issues.
- Media can be very powerful in creating awareness (particularly if there are TDD outbreaks), but only if done responsibly with a focus on key positive messages to avoid the sense of panic.

What strategies to use in rolling out advocacy messages?

- Develop evidence briefs with burden estimates
- Revise the cost effectiveness estimates; develop policy focused communications (burden vs. estimates)
- Engaging allies, not just nutritionists
- Raise awareness among health providers: could target small number to start, does not need to be the whole healthcare system; generate evidence/stories and collect more data to better identify actual burden
- Communications and media:
 - To be guided by government counterparts, using key messages
 - Should focus on the positives, e.g. low cost, low risk, rapid recovery of affected children (offer an effective positive story!)
 - Needs to be creative about dissemination of findings: go beyond the usual articles and one-off dissemination events, bring individual stories and make it more personal
 - Develop engagement strategy with WHO/UNICEF

Comments: The NYAS secretariat should prepare proceedings of this workshop for the WHO (country offices), showing that this is a critical problem that needs immediate attention; individual countries should also voice their concerns directly to WHO.

3) Clinical issues WG



This WG started by outlining the need to improve case definitions because:

- There is a broad spectrum of clinical manifestations across ages with overlap between presentations of varying severity (e.g. children at a certain age group can present with both neurological and cardiac symptoms).
- The existing WHO-based classification of clinical manifestations of TDD (available in the [technical reference materials](#) and shown below) has some important gaps: for example, it does not cover some neurological manifestations in infants (such as ptosis - i.e. drooping or falling of the upper eyelid - and vacant stare) and several cardiac manifestations affecting adults is missing.
- The WG proposed using a common case definition to be applied in hospitals and community settings for clinical diagnosis and treatment in hospitals and for surveillance in hospitals and the community.

The WG, composed mainly of clinicians, suggests four categories for case definitions:

Acute Cardiologic Form	Aphonic Form	Pseudo Meningitic Form	Encephalopathy	Peripheral Neuropathies
<ul style="list-style-type: none"> • Peak prevalence in breastfed babies of 1-3 months of age • Colic • Restlessness • Anorexia • Vomiting • Edema • Cyanosis and breathlessness with signs of heart failure leading to death • Pernicious form or Shoshin Beriberi • Sudden cardiogenic shock 	<ul style="list-style-type: none"> • Peak prevalence in 4- to 6-month-old infants • Initially hoarse cry until no sound is produced while crying • Restlessness • Edema • Breathlessness and death 	<ul style="list-style-type: none"> • Peak prevalence in 7- to 9-month-old infants • Nystagmus (involuntary eye movement) • Muscle twitching • Bulging fontanelle • Convulsions • Unconsciousness 	<ul style="list-style-type: none"> • Generally older children or adults but also seen in infants • Psychomotor slowing or apathy • Nystagmus or ophthalmoplegia • Ataxia • Impaired consciousness • Eventually coma and death 	<ul style="list-style-type: none"> • Older children or adults • Pain • Tingling or loss of sensation in hands and feet (peripheral neuropathy) • Muscle wasting with loss of function or paralysis of the lower extremities • Loss of ankle and knee reflexes • Cranial nerve impairment

1. Clinically confirmed cases (applicable only in hospital settings)

- Symptoms suggestive of TDD (refer to table on the right, but first make sure that the gaps/missing information are addressed in this table) AND
- Clinical response to thiamine AND
- Present dietary risk factors: exclusively breastfed infants/ patients with low food diversity/restrictive diets in mothers AND
- No alternative diagnosis at discharge

2. Clinically suspected cases (most likely to be found in hospital settings)

- Symptoms suggestive of TDD (refer to table above but first make sure that the gaps/missing information are addressed in this table) AND
- Unclear whether improvement is in response to thiamine or to other aspects of treatment AND
- Present dietary risk factors: exclusively breastfed infants/ patients with low food diversity/ restrictive diets in mothers AND
- Alternative diagnosis may be under consideration

3. At risk cases (most likely to be found in the community)

- No TDD related symptoms AND
- Present dietary risk factors: exclusively breastfed infants or those with low food diversity or restrictive diets in mothers

4. Unlikely cases

- No TDD symptoms AND no dietary risk factors



With regards to treatment, the WG suggested the following guidelines:

PEDIATRIC POPULATION

- If symptomatic: parenteral thiamine (intravenous or intramuscular): at least 100 mg/day until the infant can take oral supplements, then oral thiamine supplements of at least 10 mg daily for at least two weeks and until diet is adequate (through complementary feeding and/or breastfeeding mother who is adequately supplemented)
- If asymptomatic: oral thiamine, at least 10 mg daily, until diet is adequate (this applies to at risk infants, i.e. exclusively breastfed infants, infants whose mothers have symptoms of TDD and/or following dietary restrictions, or infants with low levels of thiamine biomarkers but do not present clinical symptoms)
- Treatment of the baby includes treatment of the mothers with a tablet of 100 mg/day of thiamine for at least six weeks

ADULT POPULATION

- Gaps were noted (as above)
- Use the existing guidelines for the treatment of alcohol-related thiamine deficiency as a reference
- Data on what has been clinically practiced may be different and should be compared to the existing guidelines for the treatment of alcohol related thiamine deficiency.

The WG suggested specific needs related to education and sensitization, namely:

- Messages should state that TDD are preventable and easily treatable but potentially fatal if left untreated.
- Prioritize the education of healthcare professionals (individually and through professional societies), deliver community health education (to fit the needs of lay people), and advocate for appropriate government intervention

The WG further proposed guidance in relation to supplementation, namely:

- Target high risk groups, such as pregnant and lactating women, children at risk of deficiency, subpopulations at risk of TDD (e.g. prisoners and fisherman)
- Dose: minimum as per the RDA, but in clinical practice 10 mg once a day is a widely available and used
- When: to prevent infantile beriberi, supplement during antenatal period (at least in the third trimester) and postnatal period (at least 3-6 months)
- Should be coupled with dietary advice to improve diet diversity and ultimately increase thiamine intake
- Until a universal thiamine fortification policy has been adequately implemented, supplement all groups

Comments: it may be safer to refer to breastfed infants (vs. exclusively breastfed infants) as a group at risk in the proposed case definitions. In the educational messages it is important to add the long-term negative effects of thiamine deficiency on the neurological/cognitive development of the child. Instead of proposing supplementation during the postnatal period for 3-6 months, it is better to say through 6 months or beyond, until there is assurance that the infant is receiving enough thiamine from the diet (complementary feeding).

4) Social and behavior change communication (SBCC) WG

This WG identified the following needs related to SBCC:

1. Develop key messages

Conduct formative research:

- To explore dietary patterns among the general population and at-risk groups and to identify food taboos
- To understand influencing factors leading to poor diet, barriers to diversity (cultural issues)
- To understand who the influential people are
- To develop trials of improved practices (TIPS) and conduct them locally or by region



2. Key message to be included

2.1. Develop messages targeting the general population around:

- The general need for dietary diversity and the specific inclusion of thiamine-rich foods
- Barriers to improve practices (e.g. the belief that the more rice a person eats, the stronger the person will be) and risk behavior including common food taboos
- Encourage cooking methods that preserve the thiamine contained in food

2.2 Develop counseling on infant and young child feeding to ensure that an adequate amount of thiamine is provided

- Maternal diet/nutrition: frequency of meal, recommended amount, food taboos
- Breastfeeding: early initiation of breastfeeding, exclusive breastfeeding, continued breastfeeding
- Complementary food: frequency, amount, consistency, type of food (focusing on dietary diversity), hygiene (food safety during food preparation), responsive feeding

2.3 Develop guidelines on the prevention and treatment of thiamine deficiency

2.4 Develop messages highlighting the consequences of thiamine deficiency

3. Develop strategies to promote demand for services

- Establish linkages between the health system and their community
- Use mass media (e.g. radio, TV spots) and prepare Information, Education and Communication (IEC) materials that are sensitive to ethnic differences; develop group education and counseling materials as well as tailored individual counseling
- Promote the creation of support groups
- TIPS
- Facilitate community participation and ownership through the sharing of good practices, experiences and challenges via community talks; promote the inclusion and involvement of husbands and other family members in making good dietary choices; use positive deviant families

Comments:

All countries should already have messages and counseling for infant and young child feeding. Clarify that only minor adjustments may be needed to include thiamine-specific messages (i.e. incremental adjustments for existing programs). Highlight also that existing platforms shall be used to address the problem of thiamine deficiency.

5) Fortification issues



This WG identified issues and guiding principles for action in the establishment of such programs, as follows:

- Emphasize the high prevalence and the severe consequences associated with beriberi to justify the adoption of a fortification policy
- Thiamine fortification is safe (there are no risks associated with excess fortification).
- There is a need to decide on a target level for fortification (e.g. Recommended Dietary Allowance for lactating women (1.4 mg) vs. Estimated Average Requirement for [population sub-group] (Estimated Average Requirement is traditionally used to decide on levels for fortification)).
- There is a need to motivate action: Is there enough evidence that thiamine is an issue in this country? If yes:
 - The country needs to decide on the vehicle(s) that would provide high coverage (e.g. wheat is not an appropriate vehicle for many countries represented in this meeting; consider alternatives such as salt, fish sauce or bouillon cubes).
 - Work with government and industry group(s) to ensure mandatory fortification
 - Ensure adequate quality control and monitoring procedures are in place
 - Follow up with cases to assess whether fortification resulted in a decrease in TDD cases

Salt was presented as potentially good vehicle because of its wide reach, its consistent intake over time, and the fact that, as a condiment, intake does not increase with higher dietary intakes as is typical with staple food fortification (making for less variation between population sub-groups). However, there are potential limitations regarding how much thiamine can be added to salt. There may be a limit of 0.03 mg thiamine per 1 g salt (30 ppm) using the spray technique, which would not meet the Recommended Dietary Allowance with the consumption of 10 g of salt per day. Other fortification techniques, such as dry blending, may be considered but require an infusion of money for equipment. This WG identified some short-term tasks, including the need to:



- Determine the cost of bulk thiamine fortification (premix when bought in bulk)
- Assess the existence of nutrients provided by salt in the fish and soy sauces' factories to understand whether thiamine fortified salt would be used in the production of salt-containing condiments (i.e. fortify once and it will 'trickle' to other vehicles)
- Determine how much thiamine can be added to salt (is the actual limit 0.03 mg thiamine per 1 g salt?) and investigate organoleptic and technical issues related with the increase of thiamine concentrations

Comments:

Maybe there is an opportunity to optimize salt iodization while adding thiamine to salt.

Country group work

Moderator: Dr. Megan Bourassa

In the second session of day 3, individual country teams discussed and presented the main lines of action they considered necessary to consolidate a TDD control and prevention program in their country and to identify the commitments to be pursued by next meeting of the Thiamine Alliance at the end of 2020.

India (Jammu & Kashmir and Assam)

The situation analysis and next steps for India were presented as follows:



Clinical beriberi and prevalence data: Kashmir

- Existing hospital-based studies:
 - 8 published: infants and adults
 - Yet to be published: 1 (infants)
 - Case control (infants)
- Two planned community surveys (sub centers) targeting pregnant and lactating women (accepted and funded); infants (in process of getting approval)

Delegates will need to build the evidence by:

- Collecting the number of cases in hospital before and after supplementation with thiamine
- Enquiring with other hospitals (public and private) to expand the understanding of prevalence
- Conducting verbal autopsies in communities
- Analyzing infant mortality rates (1-6 months)
- Finding resources for a multi-center study on beriberi and support by a research team (including the states of Assam, Jammu & Kashmir and others)



Clinical beriberi and prevalence data: Assam (Tripura, Mirozam)

- Existing hospital-based studies:
 - 1 published (adult dry beriberi)
 - 2 abstracts accepted for presentation in Micronutrient Forum Global conference Bangkok 2020
 - Yet to be published: 2 articles (1 infantile beriberi; 1 wet beriberi in peripartum women)
- One planned community survey, targeting pregnant women, lactating mothers and infants
 - Conducted by the National Institute of Nutrition, Makunda Hospital, Silchar Medical College,
 - Accepted by the Scientific Advisory Committee of ICMR, but awaiting funding

Acknowledgement of beriberi as a public health concern by the government

- Kashmir has not yet communicated with the government
- Assam has already communicated to Health Secretary of both States and Districts of Assam and Tripura, as well as with the National Institute of Nutrition
- Next steps:
 - It would be helpful to have WHO and UNICEF speaking to State and District level based on evidence so far (support from NYAS to accomplish this task would be helpful).
 - The clinical delegates can prepare videos of cases that they have seen and would like to show them to the government.

Note: Communication between Assam and Kashmir is difficult due to the current political situation in Kashmir.

Proposed training to sensitize and educate (next steps)

- Prepare training for medical professionals at district and sub-district levels for early detection and management of cases of TDD
- Approach communities through primary and secondary health care facilities through existing programs
- Educate and supplement pregnant women, lactating women and infants (delivery model not defined)
- Develop videos offering standardized health education modules, one for community health care workers and one for the professional community
- Link with WHO/UNICEF to work on education/raising awareness in other parts of the country

Fortification

- This is a required intervention as the entire population needs to be targeted.
- Salt identified as the best vehicle for fortification with thiamine, as iodized salt is widely used in India
- Next steps are needed:
 - Find out sources of iodized salt in Assam, Tripura
 - Find out both public and private players in the field
 - Interact with the Food Safety Standards Authority of India (FSSAI) to help with introduction of thiamine fortification of salt (and possible interaction with WHO/UNICEF)

Cambodia

This country group stated their next steps as follows:



Bring thiamine awareness to stakeholders

- Focus advocacy efforts on three key areas: expand and strengthen salt fortification to include thiamine; expand antenatal/postnatal supplementation and review recommended formulation; integrate thiamine supplementation and surveillance into existing policies and programs
- Prepare evidence brief on thiamine and use it to spark a meeting with key stakeholders (MoH, UNICEF, WHO, World Bank, clinicians from two children's hospitals)
- Train healthcare providers to look for TDD during IMCI (Integrated Management of Childhood Illness) / C-IMCI (Community-based Integrated Management of Childhood Illness)
- Explore potential partnerships with children's hospitals for gathering additional information on suspected cases of TDD, to use for awareness-raising efforts



UNIMMAP

When UNIMMAP was previously being discussed thiamine was not considered a priority, so MoH settled on IFA. Calcium supplementation during pregnancy is now a priority for MoH, presenting an opportunity to review the current supplementation guidelines. There is a need to advocate to the Nutrition WG, WHO, UNICEF, and HE Dr. Prak Sophonneary for MMS (including thiamine and calcium), but need to consider the cost, procurement and the fact that UNIMMAP does not include calcium.

New IYCF guidelines and new Nutrition Roadmap (for next year)

- This is the ideal time to push for education on thiamine deficiency.
- Need to develop training for healthcare professionals and hospital staff as part of new IYCF training

IMCI and C-IMCI

- Focused on primary healthcare: There is a need to integrate key messages around signs of TDD; when to refer to hospital / treat with thiamine.
- Need to discuss this with WHO, to make sure that the messages are the same everywhere

Fortification

- With data from current dose-response study, will need to prepare a recipe with iodine-thiamine premix to be used for 'initial intervention'/'Phase I'. Ministry of Planning (MoP) indicated that fortification should start with the salt boilers (refined salt), and the next step would be working with all salt producers (refined and coarse salt)
- Use evidence to prepare document for Sub-Decree for mandatory fortification, and modify the existing Sub-Decree for Iodized Salt to include thiamine
- MoP indicated that the development of a point-of-care test to assess thiamine in salt would be beneficial for quality control and monitoring

Comments: the coverage/reach of the current IMCI program is an important factor to the effectiveness on integrating information about thiamine

Bhutan

The required next steps were identified as follows:



Immediate (1-2 years) commitments:

1. Generate and disseminate evidence on TDD to relevant stakeholders
2. Address TDD as one of the action points in the draft national nutrition strategy action plan (NNSAP 2019-2023)
3. Explore MMS for pregnant and lactating mothers
4. Roll out MNP for all children aged 6-23 months in Bhutan (reach 100% coverage in the next 2 years)
5. Sensitize health workers on TDD during health conferences, seminars, workshops (for example during the roll out of MNPs), etc.
6. Incorporate TDD in a flagship program in eight districts to reduce undernutrition in women and children, and use SBCC strategies (“Stop stunting” and “MoE”)



Medium term (3-5 years) commitments

1. Conduct a national micronutrient survey (this would be the first one in this country)
2. Explore the expansion of fortified rice (already used in schools) to other institutions, communities, etc.
3. Develop and implement SBCC on thiamine nutrition
4. Develop online surveillance system for nutritional disorders in the Royal Centre for Disease Control’s NEWARSIS

The following support from NYAS and others will be required:

- Institutional linkage for capacity building, evidence generation and knowledge sharing
- Funding support from developmental partners to carry out the interventions and provide technical backstops
- Develop burden estimates and clear guidelines on the management and prevention of TDD

Myanmar

This country group showed how some policies have been implemented to control and prevent TDD in Myanmar but also proposed further action plans and commitments in the following areas:



Supplementation

- MMS and thiamine supplementation policy are already in place, namely:
 - MMS (similar formulation to UNIMMAP) is provided to pregnant women, starting in the first ANC visit and continued until they reach 180 tablets.
 - 10 mg of thiamine daily is provided to pregnant women (from 9th month of gestation to 3 months after delivery)
- Aim to improve supplementation program, with focus on improving compliance (coverage is good, at 87%)
- Aim to expand provision of MMS to lactating mothers (aiming to 6 months after delivery)
- Aim to replace thiamine with MMS (and remove current high dose vitamin A supplementation) in post-natal mothers, which requires to:
 - Adjust formulation of MMS (locally produced), to increase thiamine content (currently is 1.4 mg)
 - Adjust current protocol of MMS supplementation
 - Consider the financing of this supplementation



- Aim to develop an investment case to close this gap: need an advocacy tool, explaining what Myanmar needs (i.e. stop vitamin A and thiamine, replace by and extend the use of MMS); clarify what the gap is and the justification for this action
- Aim to improve monitoring and evaluation (surveillance), in particular the compliance with the supplementation program (through home visits by midwives, though verification of empty bottles/blisters in ANC visits, and by including compliance data in HMIS)

Fortification

- Aim for double fortification of salt with iodine and thiamine (since there has been a universal salt iodization program in place since 1989)
- Technical questions to be answered: technical constraints of adding two micronutrients to salt (e.g. single premix with iodine & thiamine?); best fortification technique (salt iodization in Myanmar is through spray, most factories use manual spray); ideal level and formula of thiamine to be added to salt
- Policy change for double fortification of salt will require: map salt producers (67 salt producers are registered in Myanmar, but smaller producers may not be captured); planning phase, starting with large-scale producers (which are less than 10); setting industry standards by those large-scale producers and supporting the above by providing tax exemption for premixes (an innovation factor for producers to engage on fortification programs)

MNP

- With thiamine supplementation and double fortification of salt (iodine and thiamine) MNP will not provide additional benefit for thiamine specifically; if iron and other micronutrient deficiencies are to be taken into consideration, MNP should be considered as an intervention.

The delegates from Myanmar further identified support needed in the following areas:

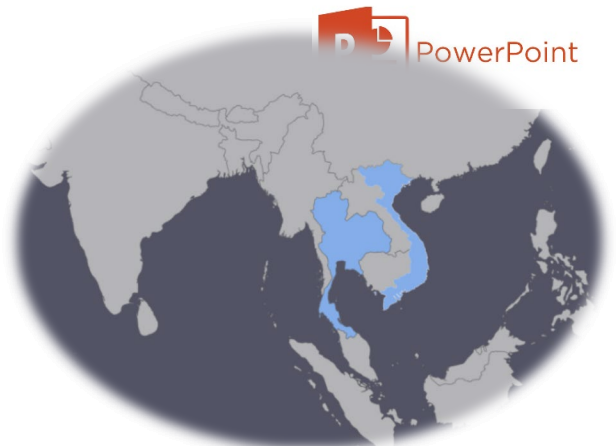
- Quality check for MMS (locally produced as well as for other products that enter the country), as it is not clear whether the product actually contains the nutrients that are claimed
- Slight adjustment to the formulation (e.g. to increase the content of thiamine)
- Identify a mechanism to get routine data on compliance of MMS
- Technical support for double fortification of salt

Comment: If there is a continuation of MMS during post-partum period, in principle there is no reason to provide vitamin A supplementation to newborns (another point in favor of the use of MMS for lactating women).

Vietnam and Thailand

Thailand and Vietnam presented jointly because of their similar contexts in terms of control and prevention of TDD and very few regular cases of TDD. Thailand showed the figure below and explained that the country already has a surveillance system, but proposes a new “one protocol for all nutrients”:

- Needs more data from clinicians to generate more knowledge, which may lead to a simplified screening of TDD; people should be the center of the decisions
- Proposes a nutrient risk screening focused on groups at risk (fishing crew, prisoners, lactating mothers and infants), to determine if a person is at risk or not.
 - If at risk, the person will be recommended for healthcare services, including biomarker assays. Data collected here will be sent to the government for policy formulation; will be used by research institutions to



determine next research questions; will be used by community workers to develop (consumption) behavior change interventions.

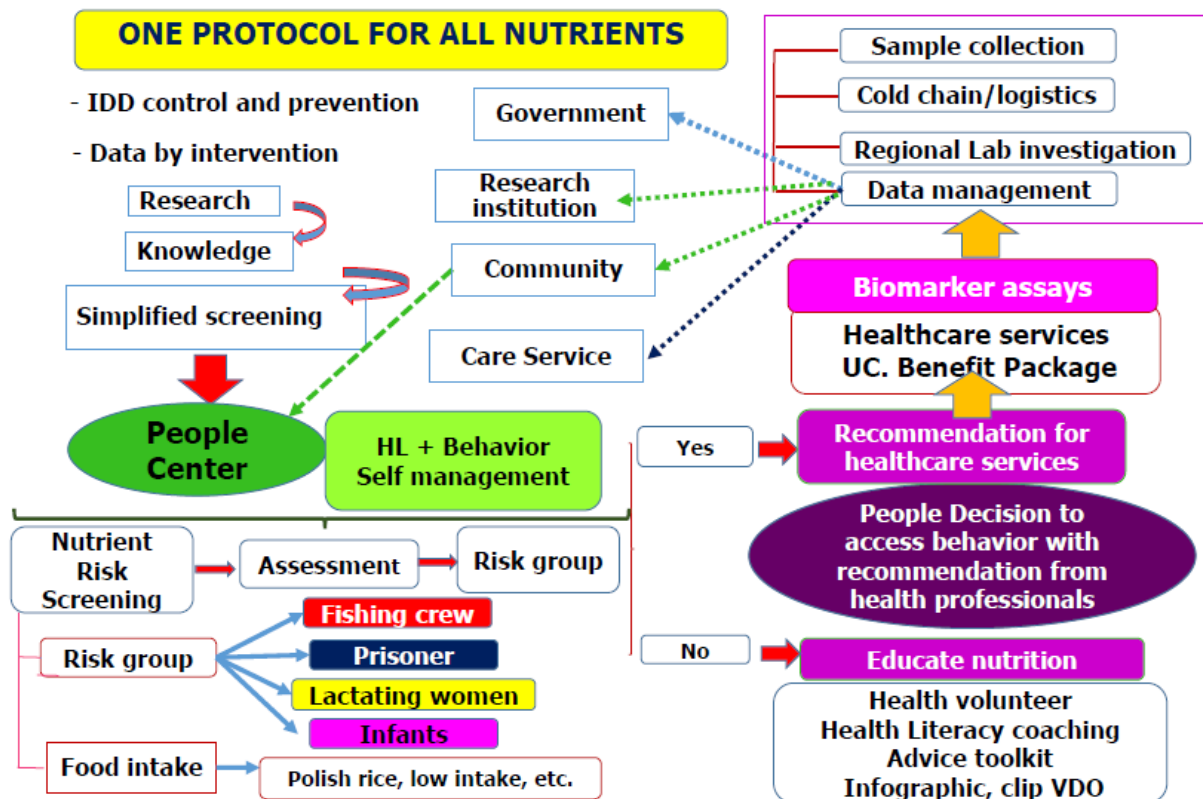
- If not at risk, education about nutrition will be provided by existing systems (health volunteer, health literacy coaching, advice toolkits, etc.)
- Thailand already carries out a food consumption survey and can work to add more information about thiamine intake in the existing survey questions.

Vietnam explained that there are some differences in the approach presented by Thailand, such as:

- Health literacy is not as good in Vietnam as in Thailand, therefore people are not making informed decisions themselves, but they are informed of current diagnosis and treatment.
- Technology is not as advanced in rural areas due to limited access to smartphones and internet, therefore health education is still based on printed leaflets. This would be the channel to educate people about thiamine deficiency.
- Vietnam does not have a Universal Healthcare System. Education of healthcare professionals about thiamine deficiency needs to be delivered at all levels, and there is a need for a simplified screening (test) of thiamine deficiency.

Key action points for Thailand and Vietnam:

- Main focus should be on SBCC
- Policy action by the respective Departments of Health will be needed
- Policy communication and short course training for healthcare professionals and health workers are necessary
- NYAS and global experts should support the development of effective simplified screening forms.



Lao PDR

This country group identified short, medium and long-term lines of action for Lao PDR, as follows:

Short-term: stakeholder awareness

The country knows that there is high prevalence of TDD, but a consensus is needed on whether or not to declare it a public health problem in need of a public health intervention. If so, there is a need for a policy brief for policy makers and advocacy for stakeholders. The criteria required to declare a public health problem remains to be defined: a re-analysis of infant mortality based on DHS data or HMIS would be helpful in indicating what the National Nutritional Surveillance sites should focus on (e.g. two villages per province if these villages are suitable in terms of potential sample size and epidemiology, or a clinic based, knowing that there may be several wards receiving TDD patients); whether sentinel sites should be set up with dedicated teams specifically trained on TDD, etc.



Short-term: capacity development and changing approach to supplementation

- There is a need to build capacity for case detection and management at the facility level. This will involve training on case definitions/detection and on treatment and an effort to integrate these with IMAM and micronutrient guidance implementation, including a review of existing training materials to specifically cover thiamine deficiency. Lao has 17 national hospitals and many more district hospitals and health centers, most of which do not know about case detection and management.
- Aim to switch from IFA to MMS: Pregnant and lactating women are currently receiving IFA + Vit A + Ca supplements. To switch from IFA to MMS, more evidence will be needed to advocate with policy and stakeholder. This evidence can be built on:
 - Model intervention: case management supplementation of MMS
 - Surveillance (coverage, compliance, incidence of TDD, infant mortality rates)

To be clarified: the distribution plan (modus operandi); the cost implications; what to do with the current newborn and postpartum vitamin A supplementation (postpartum supplementation would not be affected, since UNIMMAP stops at 6 months postpartum, but continuation for children requires further investigation); determine if supplements are part of food taboos in most susceptible ethnic groups. If Lao were to switch from IFA (government procured) to MMS, it should start with free distribution of MMS.

Short to medium-term: clinical training and fortification

- Requirements for clinical training and supply chain:
 - SBCC to include TDD; determine costs of integration of TDD component in both pre-service and in-service training;
 - Determine coverage and effectiveness of training: It may be worth starting a pilot in certain national/provincial hospitals, where some thiamine information already exists (but not sufficiently detailed) and then use “Training of Trainers” approach.
- Requirements for the District Health Information Software (DHIS) 2 system: determine the best thiamine status indicators and whether a one-off expansion of the set of indicators is enough
- Requirements for fortification: identify suitable vehicles (salt, oil, rice?); explore technological requirements and fortifiability; have food fortification guidelines in place and a technical WG to elaborate a fortification strategy plan;

determine how many people are buying rice millers products and assess the distribution challenges of having small millers in every village; determine whether school meals should be an entry point for fortified rice (right population? how is rice procured?).

Medium to long-term: large scale assessment of thiamine status

- Plan for a national micronutrient survey including indicators of thiamine status
- Research needed to determine whether thiamine content is enough in the UNIMMAP formulation
- Determine how to better use the DHIS 2 system to include thiamine data



Comments

Many countries mentioned the idea of adopting the use of the UNIMMAP formulation into prenatal care programs, but there is a question whether this formulation contains enough thiamine. There was a recent meeting in Washington DC about product specification of MMS, and one of the discussions was around the change of formulation (composition/amount of nutrients) to better fit the current knowledge of the nutritional needs during pregnancy, given that the UNIMMAP formulation was set up in 1999. However, we need to bear in mind that any change in formulation will need to go through many tests (e.g. stability testing, interaction with other nutrients), which may require a few years until we obtain a new formulation. In addition, while scaling up the product, the manufactures do not like to have multiple formulations. If we decide that a higher dose of thiamine is needed in an area of endemic deficiency, a solution could be to produce a South Asian version of UNIMMAP. This is a research question that needs to be addressed.

Dr. Brown: During the group discussions, we found out that the coverage of IFA is low; this means that the need is not only in switching from IFA to MMS, but also in the strengthening of the existing IFA program to reach good coverage.

Summary and next steps

Dr. Gilles Bergeron

After each country group presented their action plan for a TDD control and prevention program that would better fit the needs of their country, Dr. Bergeron shared with the workshop participants what he envisaged as being the next steps.



List of actions of what will happen:

- Countries will act on their individual lines of action (details are presented within this Workshop Report)
- The NYAS will commit to conduct several activities:
 - Compile, edit, disseminate the Workshop Report (inclusive of all PPTs; discussions; work group output; resulting general recommendations)
 - Consolidate the communications hub (by updating the [website](#) and establishing a mechanism for ongoing relation with all meeting participants, possibly by establishing WG)
 - Provide an update of the country commitments and present the proceedings of this workshop at the Micronutrient Forum 5th Global Conference 2020
 - Help individual country efforts to obtain third-party resources by preparing supportive materials
 - Reach out/engage with major organizations interested in micronutrient issues e.g. WHO, UNICEF (HQ/Country offices), [ASEAN](#), [SUN](#), [A&T](#), [Sight and Life](#), etc.
 - Seek integration of our thiamine work with micronutrient projects (e.g. [iZinc](#), [Iodine Global Network](#))

- Organize the second workshop, which will take the place in the Fall of 2020
- Seek alternate sources of funding, as the current BMGF funding approaches the end
- Commitments from other organizations (e.g. Frank will approach L'Institut de recherche pour le développement (IRD))

List of actions of what should or could happen:

- Prepare a series of publications, such as:
 - Scientific paper summarizing data presented during day 2 of this workshop, with the contribution of the workshop participants (targeting high-impact journal)
 - “State-of-the-art” (White) paper on issues, recommendations, knowledge gaps reported during the presentations of the thematic group discussions (on clinical issues, data issues, food fortification, SBCC, policy advocacy, etc.)
 - Sample Policy Advocacy brief
 - Compendium of case studies
- Develop a cost/effectiveness model (focusing on death averted - not DALY - by thiamine supplementation/fortification)
- Explore existing secondary data sources (DHS, NFHS IV, MICS) for evidence inviting further examination (e.g. month by month infant mortality in at-risk populations; burden of disease; etc.).
- Establish partnerships with medical schools, professional associations, etc.
- Host thematic WG (thiamine-specific components to go into survey/surveillance; ID research, etc.)

Comments from participants (on what should happen in the next 12 months):

- A few participants suggested we attribute a name for this thiamine network, e.g. Thiamine Global Network.
- Dr. Brown suggested the integration of a thiamine global WG under the umbrella of the Micronutrient Forum, without dividing it by world regions.
- Dr. Baker suggested an analysis of the global prevalence of thiamine deficiency and the global burden of the disease, and then conduct a cost-effectiveness analysis and identify the best fortification vehicle.
- Dr. Koshy raised the question about when to consider thiamine deficiency as a public health issue (as governments may not believe that the existing data is enough). Dr. Rohner suggested looking at thiamine deficiency data before and after the implementation of a thiamine supplementation program, and take this data to WHO. Dr. Fischer claims we already have compelling existing data showing that thiamine deficiency kills people and contributes to the disability of many more. Some participants volunteered to start a WG on this topic (clinical and data issues).
- Dr. Whitfield volunteered to work on the fortification issues (possibly in a peer reviewed paper), and Dr. Jefferds suggested the development of a technical brief where we summarize the current knowledge about thiamine fortification.
- Dr. Rohner suggested the need to identify key clinical symptoms of thiamine deficiency that can be included in large scale surveys or health information systems.
- Dr. Green explained that the cut offs to define thiamine deficiency should be based on the value that leads to the absence of symptoms, similarly to what has been done for other micronutrients.

Closing thoughts

Dr. Ken Brown

During the closing remarks, Dr. Brown started by reflecting on where we were when we initiated the thiamine Task Force and where we are now. He recognized that the knowledge shared by the different countries during this workshop shows that the problem of thiamine deficiency is widely spread at the population level, rather than being limited to a few isolated cases. Dr. Brown thanked all the workshop participants and organizers, who were all willing to share their data, knowledge and expertise, as well as Dr. Baker for his wisdom, vision and confidence to invest on a “suspected problem” that started with a very limited knowledge base.



“The level of energy and excitement of this group is really remarkable and inspirational”

Dr. Brown’s perspective on next steps include:

1. Need to do more advocacy for thiamine deficiency to generate more financial support which allows us to do more work on this project

Dr. Brown presented the number of under-five deaths attributable to vitamin and mineral deficiencies, according to the

Lancet Nutrition Series from 2013, which he considers to be significantly underestimated, and compared them with the revised estimates that he calculated. Thiamine deficiency was not considered for analysis by the Lancet Nutrition Series from 2013, and Ken took the data from Myanmar to estimate the under-five deaths attributable to the deficiency of this vitamin, but recognizes that this number is also an underestimate because it does not take into account all the

Revised estimates of number of U-5 deaths attributable to vitamin and mineral deficiencies

Micronutrient deficiency	Lancet Nutrition Series, 2013		Revised scenario	
	Deaths	% U5 deaths	Deaths	% U5 deaths
Vitamin A, children	157,000	2.3	157,000	2.3
Vitamin A, mothers	--	--	+?	+?
Iron, mothers	93,860	1.4	247,000	3.6
Zinc, children	116,000	1.7	116,000	1.7
Zinc, mothers	--	--	144,200	2.1
Folate, mothers	60,624	0.9	175,700*	2.5
Thiamine	--	--	>3500	>0.1
Vitamin D	--	--	?	?
Others (vit B12, selenium, others?)	--	--	?	?
All	427,486	6.3	843,400	12.0

Based on all SGA infants

Considers effects of maternal zinc on PTB

Based on new estimates of NTD prevalence

*Does not include elective termination of pregnancy for fetal anomalies

Brown KH et al. Food Nutr Bull, 2015

countries that are now known to be at risk of thiamine deficiency. A future close analysis of the data presented in this workshop would allow us to obtain better estimates of under-five deaths attributable to thiamine deficiency.

2. Country plans to tackle thiamine deficiency started in this workshop with rudimentary ideas, but need to be developed with greater detail and implemented
3. We need to establish topical WG on thiamine. Similar to what was discussed before, Dr. Brown envisions several such WGs, including:
 - a) WG on mortality/morbidity attributable to thiamine deficiency:
 - What is the likely burden of thiamine deficiency, and deaths attributable to TDD?
 - Considering costs of intervention programs (e.g. supplementation during pregnancy), what would be the cost per death averted and benefit-cost ratios of these interventions? In the case of folate, it is a very attractive number, being comparable to the cost per death averted of bed nets (in countries with malaria).
 - What are the remaining research needs to refine or improve these estimates over time?
 - b) WG on thiamine-specific status and coverage indicators that should be included in surveys/surveillance
 - The identification of simplified indicators of thiamine status (e.g. signs of peripheral neuropathy, oculomotor disorders, other?) and comparison with gold standards (e.g. nerve conduction studies?) to define specificity and sensitivity of the indicators, are urgently needed.
 - The interpretation of biomarkers of thiamine status should be done by consolidating the results of ongoing research as it becomes available
 - c) WG on criteria to initiate program activity:
 - What data (e.g. reported number of cases of thiamine deficiency) are needed to motivate action (intervention and/or population assessment)?
 - d) WG on guidance for thiamine supplementation, to determine:
 - Appropriate formulation, dose, duration of supplementation for specific target groups
 - Research needs to support new recommendations (developed on previous point)

- e) WG on guidance for thiamine fortification, to determine:
- Appropriate vehicle selection, form of thiamine, target and level of fortification
 - Quality control, industry compliance

Meeting closure

Following Dr. Brown's concluding comments, the NYAS team brought the meeting to closure, clarifying that going forward the WGs will be constituted and invited by NYAS to meet periodically by teleconference and establish work packages according to the availability of participant WG members.

Feedback from workshop participants

How did the participants perceive this workshop?

The following feedback was collected from an anonymous survey completed post-workshop in December 2019.

"One of the most interesting workshops I have been to in some time - good mix of sharing, preparatory work, and presentations. I learned a lot and returned home with much clearer ideas for what we can do to address thiamine deficiency in Cambodia"

"It was absolutely totally fantastic!"

"Excellent country reports, group discussions, and opportunities for networking and developing future plans".

"Superb information, much of it not in the medical literature yet. Great networking"

"It made us realize that thiamine deficiency is an issue and that we need to do something about it"

"I started out as a real novice in the area of thiamine and I left having a much deeper understanding of the issues and the potential way forward"

"The workshop was very valuable in bringing to the table the voices of practitioners who are dealing with this issue in real-life settings"

Organizer and Participant List

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