INFANTILE BERIBERI

TECHNICAL REPORT: EVIDENCE REVIEW OF THE RISK FACTORS AND PREVENTION IN LAO PDR

BASED ON EVIDENCE AVAILABLE
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LIST OF ABBREVIATIONS

ANC	Antenatal Care
CNS	Central nervous system
Lao PDR	Lao People's Democratic Republic
MCH	Maternal and Child Health
MDG	Millennium Development Goal
MNCH	Maternal, newborn and child health
MoH	Ministry of Health
NGO	Non-Governmental Organisation
SIDS	Sudden infant death syndrome
TDP	Thiamine Diphosphate
UN	United Nations
UNICEF	United Nations International Children's Emergency Fund
WHO	World Health Organization

EXECUTIVE SUMMARY

Beriberi is the clinical manifestation of thiamine (Vitamin B1) deficiency. In infants, beriberi is almost always a result of breastfeeding from a thiamine deficient mother. This rapid onset, acute disease is typically seen in infants aged between one and five months, is characterized by cardiac complications and is usually fatal within a few days if not treated. Asian populations for whom the staple diet is polished white rice have historically been most affected by thiamine deficiency; prevalence rates and mortality from beriberi were high in parts of East and South-East Asia from the late 19th century , a time which marked the beginning of widespread rice milling (6). The incidence of infantile beriberi in industrialized countries virtually disappeared after the introduction of thiamine fortification of cereals in the 1940's. Today, infantile beriberi is largely confined to pockets of South East Asia and nutritionally vulnerable groups such as refugees (8) as well as infants fed thiamine deficient formula (9). In Lao PDR, thiamine deficiency in pregnant and lactating women is prevalent. Infantile beriberi has been recognized in Lao PDR since the 1960s however interest in the disease as a significant public health issue peaked in the early 1990's when a marked increase in infant deaths due to beriberi was noted; the increase was possibly linked to a shift in rice preparation techniques from traditional hand-pounding to machine-milling which was occurring in the parts of the country at that time.

The risk factors for maternal thiamine deficiency and infantile beriberi in Lao PDR are multiple; evidence for these are emerging from epidemiological studies in Lao and similar populations. Likely risk factors for infantile beriberi in Lao PDR are related to rice preparation methods, maternal consumption of products containing thiaminase -an enzyme which breaks down thiamine- suboptimal infant feeding practices and inadequate dietary diversity, the latter exacerbated by maternal adherence to postpartum food taboos.

Studies evaluating prevention strategies for infantile beriberi are scarce; in the literature that does exist, the focus is on approaches which aim to increase maternal thiamine status for which there are multiple methods. Fortification of rice is technically possible and promising as a cost-effective solution however its implementation in Lao PDR is currently unlikely to be feasible (11). Maternal supplementation with thiamine has been shown in multiple studies to improve maternal blood and breast milk concentrations. However in order for the infant to benefit, supplementation needs to be sustained over time (12, 13). Thiamine supplementation for pregnant and lactation women together with nutritional education have been provided for over a decade in certain rural regions of Lao PDR by 'Save the Children' and the Burnet Institute; there is anecdotal evidence that where coverage has been high, the incidence of beriberi has been low.

There is no formal national strategy for the control of infantile beriberi in Lao PDR and Vitamin B1 supplementation is not included in the National Maternal and Child Health plan (MNCH) (14). In Myanmar, maternal supplementation has been integrated into nation-wide antenatal and postnatal care packages in an effort to address infantile beriberi(15); evaluation of the program (unpublished data) has shown reduced prevalence of maternal thiamine deficiency in supplemented women compared to those un-supplemented.

Based on the evidence for risk factors, incidence and prevention of infantile beriberi, routine maternal thiamine supplementation coupled with nutrition counselling is also called for in Lao PDR. It is hoped that with increased awareness of infantile beriberi and its causes and prevention among Government policy makers, Non-Governmental Organisations (NGOs), multilateral agencies and health workers in Lao PDR and through coordinated efforts, progress towards elimination of this fatal yet preventable disease could be made.

I. INTRODUCTION

1.1 Purpose and scope of this report

In several regions of rural Lao PDR, where 'Save the Children' have been active in maternal and child health (MCH) programming for decades, they have responded to high infant mortality rates (IMR) and observational evidence of prevalent infantile beriberi. They have done this through the provision of vitamin B1 supplementation to pregnant and lactating women as part of their antenatal care (ANC) and postpartum care package. In the Sayaboury province where this has been functioning well for the past 13 years, infantile beriberi is now reportedly rare. Based on this experience, the Burnet Institute includes routine B1 supplementation in its support to the District Health Department in the Vilabouly District, Savannakhet Province. However in other regions, where ANC attendance and supplementation coverage are lower, infantile beriberi remains a problem.

Routine thiamine supplementation in currently not part of the Ministry of Health (MOH) MNCH strategy and thiamine deficiency among pregnant and lactating women is estimated to be highly prevalent in Lao PDR (10, 16). Moreover, several NGOs with a presence in Lao PDR including 'Save the Children' expect that thiamine deficiency and therefore infantile beriberi may be set to increase in line with the observed acceleration in the change over from rice hand-milling to machine milling (the latter technique is more proficient in removing the thiamine-containing rice husk).

These factors have prompted 'Save the Children' to commission the Burnet Institute to carry out a technical review of the evidence for the prevention of infantile beriberi with particular focus on maternal thiamine supplementation and nutrition counselling in order to stimulate sector discussion and to advocate for and inform the potential scaling up of prevention strategies in Lao PDR.
The technical report is based on a rapid review of the black and grey literature and as such does not include an in-depth quality analysis of each identified publication.

1.2 Methods used

A comprehensive literature search was conducted using three base search engines: Google Scholar, PubMed and the Cochrane library. Further grey literature was accessed via web searches and from colleagues in Lao PDR. The following key words were included in the literature search in various combinations:

thiamin/thiamine/vitamin B1/beriberi/infantile beriberi/deficiency/supplementation/Lao PDR/ fortification/food taboos/postpartum practices/maternal/rice

All relevant studies were included, however the search focused on Lao PDR and surrounding countries. Evidence for the prevention of infantile beriberi are presented in both table format (listed by study and including a description of the design, study population, objectives and key findings) and narrative forms.

1.3 Background

1.3.1 Thiamine – an essential micronutrient

Thiamine (Vitamin B1) is a water soluble vitamin essential for human metabolism. It is present in at least small amounts in most food groups (17) however the richest sources are "wheat germ, yeast extracts, meat…legumes and green vegetables" (18). A diet lacking in diversity and based excessively

on highly refined cereals such as rice, in which much of the thiamine has been lost during milling has long been recognized as the primary cause of thiamine deficiency at a population level. For this reason it has historically most commonly affected Asian populations for which polished rice is the staple and thiamine fortification is not established and widespread.

Thiamine deficiency has long been identified as a significant "cause of morbidity and mortality globally" (19). Body stores of vitamin B1 are depleted within two weeks of inadequate intake (6, 20) with clinical symptoms appearing within three months (8). The most well-recognized and life-threatening syndrome of symptoms resulting from severe thiamine deficiency is beriberi. In adults, beriberi typically presents in two forms; 'dry' beriberi is characterized by symptoms of the peripheral nervous system while the more acute version, 'wet beriberi' involves cardiac dysfunction and commonly features oedema (6).

Less is known about the pathogenesis and clinical features of beriberi in infants however it is widely accepted that the cause is primarily breastfeeding from a thiamine deficient mother. Pregnant and lactating women are at particular risk of thiamine deficiency; the thiamine requirements of this group are increased most markedly in the third trimester of pregnancy (16). In cases of maternal deficiency, signs of beriberi can appear in the breastfed infant within a few weeks of birth with presenting cases usually infants aged between one and five months. Infantile beriberi is almost always the 'wet form' characterized by rapid onset respiratory distress and cardiac complications which usually lead to death within a few days without treatment (18).

While infantile beriberi is the most overt sign and fatal form of severe thiamine deficiency - incidence can be used as an indicator of the burden of thiamine deficiency in a population(6, 18) – subclinical infantile thiamine deficiency has been linked to other adverse morbidity and mortality outcomes in the short-term (10) and long term (21). In the short-term, several authors have suggested a link between maternal thiamine deficiency and intrauterine growth retardation (22, 23) and sudden infant death syndrome (SIDS)(24), the former with well known long-term adverse consequences.

While the longer term implications of infantile thiamine deficiency has not been extensively studied, the role of thiamine in central nervous system (CNS) development has prompted research, largely on animals into the impact of intrauterine or early life thiamine deprivation on cognitive and physical development(9). In a cohort of Israeli children exposed to thiamine deficiency as infants due to consumption of thiamine-depleted formula were found to have delayed motor development and

A mother in Luang Prabang walks to the health clinic with her family.
Nam Bak District in Luang Prabang Province

language acquisition (9) and a higher incidence of epilepsy (25) in comparison to a healthy control group. In another study, children in a Thailand refugee camp in which "delayed visual maturation" was observed, exposure to thiamine deficiency was identified as a possible cause (5, 26). Thiamine deficiency in infancy could well be an un-recognized underlying contributing factor in impaired cognitive development in children of populations in which thiamine deficiency is endemic(21) and therefore a perpetuating factor in the malnutrition-poverty cycle.

1.3.2 Beriberi : a brief history and extent of the problem

Documentation of beriberi dates back centuries however it was first recognized as common disease in the late 19th century in East and South East Asia (6). Infantile beriberi was first described in Japan around 1888 (27). This point in time marked an increase in infantile deaths from beriberi across many Asian countries which persisted well into the 20th century; in 1910, 40% of infant deaths were attributed to beriberi in the Philippines, while rates were also high in Japan (3.5 deaths per 1000 live births(28) in (6), Malaysia and Thailand (6). The surge in beriberi incidence in Asia at this time coincided with the introduction of wide-spread rice milling and the switch from brown to white rice (27). Once the cause was recognized, public health campaigns, economic growth and better access to dietary diversity lead to control over the disease in many Asian countries. In Western developed regions, thiamine deficiency virtually disappeared with the widespread introduction of whole flour and fortified flour around the mid-20th century (6) after such time beriberi received far less research attention.

Today, global prevalence estimates for infantile beriberi are not available; there are no cause-specific mortality indicators for beriberi in current World Health Organization (WHO) global health statistics however it remains a known important public health problem in pockets of South-east Asia and in vulnerable populations such as refugees (8). In the late 1980's, infantile beriberi was recognized as the leading cause of infant deaths in refugees of Karen ethnic origin in northern Thailand where the disease was the leading cause for infant mortality; the IMR was very high at 18%(29). There were also several other reports of infantile beriberi in refugee populations in the early 1990's in Ethiopia, Guinea, Nepal and Djibouti (8).

While the burden of infantile beriberi in refugee settings has been, in general, well documented, in stable environments in which thiamine deficiency in pregnant and lactating women is endemic such as in Cambodia(30, 31) and Lao PDR (10), precise incidence rates are unknown. In these populations, the burden of infantile beriberi can be estimated from the prevalence of thiamine deficiency in the breast milk of lactating women and from the mortality trends in infants (6). In Myanmar, where a beriberi surveillance system has been implemented, infantile beriberi has been described as the "fifth leading cause of deaths of children" in their first year of life accounting for 7.12% of all infant deaths and almost 9% for those 6 months and younger (2003) (15). In a rural province of Cambodia (Prey Beng province) it is estimated that beriberi is the cause of up to 50% of infant deaths (31).

1.3.3 Infantile beriberi in Lao PDR

The high undernutrition burden in Lao PDR has been well documented; the national stunting prevalence stands at 44% (32). Infantile beriberi was recognized in Lao PDR as early as the 1920s as a significant cause of infant mortality and there were spikes of interest in the disease later in the 1960s and 1970s(33). Beriberi re-emerged as a recognized infant condition in the early 1990s when an increase in cases presenting at hospitals in the capital, Vientiane was noted (1). The rise in incidence appeared to be linked to the switch in many parts of Lao PDR from traditional hand-pounding of the rice to machine-milling, the latter being more proficient in removing the thiamin-containing rice husk.

With heightened awareness of beriberi, rapid treatment with parenteral thiamine became available across Lao PDR (1). Reports from one Vientiane hospital suggest that infantile beriberi remains prevalent (1, 10); between 2005 and 2008, around 54 infants per year were admitted with beriberi; the case-fatality rate was 6% (10). In certain rural areas there is anecdotal evidence of persisting infantile beriberi (10) however the precise extent of the problem and its relative distribution throughout the country is unknown; there is no official national surveillance system (10) and it is likely that in rural and hard-to-reach areas, infants may die before they reach a health facility and many cases go unreported.

While research interest in infantile beriberi has increased over the past two decades in response to the re-identification of the disease, the public implications of thiamine deficiency remains "under-recognized" in Lao PDR (34). Infantile beriberi is not mentioned in the United Nations (UN) country analysis report 2012-2015 (35) while the Lao social indicator survey of 2011/12 did not collect information related to the disease (36).

With considerable population movement in Lao PDR from resettlement and village consolidation, it is feasible to expect that pockets of new vulnerabilities will occur over coming years; communities in which thiamine deficiency may not have been a significant problem in the past may start to experience higher prevalence. In addition, Lao branches of several NGOs - Save the Children, Burnet, Swiss Red Cross – have seen the shift from the hand-milling to machine-milling of rice occurring slowly over the past two decades. However, observations through regular field visits are that the rate of change in the past 2-3 years is increasing substantively and the expectation is that thiamine deficiency will increase at a similar rapid pace.

II. EVIDENCE REVIEW FOR RISK FACTORS AND PREVENTION OF INFANTILE BERIBERI

2.1 Causes of and risk factors for infantile beriberi

The root cause of infantile beriberi is undeniably maternal thiamine deficiency (29). Breast milk concentrations of thiamine are highly dependent on maternal thiamine consumption and are "substantially reduced by maternal depletion"(37). The recommended daily intake of thiamine for pregnant and lactating women is 1.4 mg (Institute of Medicine US – in (38)). There is evidence that this group in parts of Lao PDR do not meet this requirement with diet alone; in the outskirts of Vientiane 96.6% of lactating mothers who took part in a cross-sectional survey had inadequate thiamine intakes (2). At a Cambodian rural health clinic, dietary thiamine for mothers of infants diagnosed with beriberi was adequate for only 4% (30).

Text Box 1: Likely risk factors for infantile beriberi in Lao PDR

- **Maternal diet high in machine-milled 'sticky' (1,2) rice and lacking in dietary diversity.**
- **Longer rice soaking and cooking time (1)**
- **Adherence to postpartum food taboos (2-4)**
- **Maternal consumption of thiaminase-containing food (5)**
- **Suboptimal feeding practices (2, 7)**
- **High dietary carbohydrate intake(2), hard physical labor (1)and infection all increase maternal thiamine requirements**
- **Lower maternal education level (1, 10)**

Factors thought to contribute to low thiamine intake in pregnant and lactating women in Lao PDR are listed in Text Box 1. Most importantly, their diets frequently lack diversity and are 'excessively based on glutinous rice' (2). Highly refined cereals ,"if eaten in isolation do not contain enough thiamine to support human life"(6), therefore populations which rely heavily on these for calories are at risk of thiamine deficiency. The amount of thiamine left in rice at the point of eating depends on the methods for refining and cooking. Polished rice is the staple diet in Lao PDR and it is often eaten in 'sticky' form. Sticky rice preparation requires longer soaking and cooking times than other types of rice which likely further reduce the Vitamin B1 content. A diet high in sticky rice was observed in mothers of cases of infantile beriberi in the outskirts of Vientiane and around 90% of these consumed machine-milled and unfortified rice (this figure was similar for controls) (1). In the same study, the mothers of cases were more likely to soak and cook their rice for a longer period than the controls (1).Further, other researchers have found that it is common practice in parts of Lao PDR for sticky-rice to be soaked for more than eight hours. (3).

According to the World Health Organization (WHO), thiamine deficiency occurs in a community when there is not enough access to foods rich in micronutrients such as 'fruit, vegetables, animal products and fortified foods"(39). Dietary diversity already known to be inadequate for a proportion of the population in Lao PDR can be further restricted in lactating women by widely practiced post-partum traditions which include adherence to food taboos(2-4). In a Vientiane survey, 93% of lactating mothers reported restricted intake of 'meat, fruits and vegetables for up to 2-3 months postpartum'(2) while in a rural community in one particular ethnic group, the diets of some postpartum women were restricted to only rice and salt(4). A diet disproportionately high in carbohydrates increases the metabolic demands for thiamine (6) thus compounding a thiamine deficiency problem. For studies investigating the link between postpartum food taboo adherence and infant thiamine deficiency and beriberi, the results have been mixed. In two case-control studies, maternal adherence to postpartum practices was associated with cases of infantile beriberi (1, 33). However in another study involving hospitalized infants in Vientiane, there was no association found between maternal food taboo adherence and infant biochemical thiamine status (10). There are other factors thought to augment thiamine deficiency in pregnant and lactating women in populations at risk including febrile illness such as malaria (34) and the consumption of foods containing thiaminase – an enzyme which breaks down thiamine. Consumption of thiaminase-containing products such as tea, fermented fish and betel nut has been identified by WHO as a risk factor for thiamine deficiency (6, 18). Current evidence suggests that even with adequate dietary intakes of thiamine, high consumption of thiaminase can lead to blood thiamine deficiency (6) . In a Karen refugee population relatively high prevalence of betel nut chewing and consumption of fish

A mother and her children wait at a health services station in their community.

paste were identified possible causes for persistent thiamine deficiency in lactating women despite weekly thiamine supplementation of 10mg (5). However the degree to which thiaminase plays a role in thiamine deficiency pathogenesis remains to be determined. Indeed in case-control studies in Cambodia (30) and Lao PDR (1) no association between maternal thiaminase consumption and infantile beriberi was found.

While maternal thiamine deficiency is undoubtedly the primary cause of beriberi in the breastfed infant, there may be other factors which play a role in precipitating infantile beriberi. A Cambodian study found that thiamine deficiency was prevalent in both mothers of infants with beriberi and mothers of apparently healthy babies (30). In another Cambodian study, little difference was found between blood thiamine concentrations in infants with beriberi and healthy matched controls (31). It is possible that infection and other co-morbidities may have predisposed the 'cases' to the development of beriberi, however this hypothesis requires further investigation.

Suboptimal infant feeding practices have also been implicated in the perpetuation of infantile beriberi in Lao PDR. While 95.6% of infants are breastfed for at least some time, only 26.4% of those under six months are exclusively breastfed (36). Two studies observed that it was common for Lao women to delay the first breast feed (nationally 29.8% of women put baby to the breast within the first hour of birth (36)) and to discard the colostrum due to the belief that this first milk is not beneficial for the baby (3, 7). The same surveys found that the practice of feeding pre-masticated rice to infants within the first month of life was also widespread in Lao communities. Early introduction of solid food is of concern because it can interfere with the volume of breast milk consumed and may lead to cessation of breastfeeding (2). Suboptimal infant feeding practices have been described as one direct cause of high undernutrition rates in children in Lao PDR (35) however the degree to which these play a role in the development of infantile beriberi remains uncertain. Early introduction to solid food was associated with thiamine blood concentrations in infants diagnosed with beriberi in a Cambodian clinic, however it is worth noting the small sample size for this study. (30) Finally, various parental socioeconomic factors have been associated with infantile beriberi. In the two case-control studies carried out in a Vientiane hospital, the following factors were associated with infantile beriberi; fewer years of maternal schooling (1, 10), fathers being farmers (1, 33) and mother having to perform hard physical labor (1). While the latter factor likely contributes to increased maternal thiamine requirements, the former two may underpin poor access to adequate dietary diversity and foods rich in thiamine.

2.2 The prevention of infantile beriberi in Lao PDR

While treatment for infantile beriberi with parenteral thiamine is effective and inexpensive, without rapid access to this treatment, there is a high case-fatality rate. The three main approaches to addressing micronutrient deficiencies in a population are, "fortification, supplementation and dietary diversification" (40). Thiamine deficiency in a population has been historically addressed mainly through fortification and efforts to improve dietary diversity, however these measures are not necessarily easy to implement in developing countries where widespread poverty and food insecurity are barriers. It has long been recognized that if thiamine deficiency in pregnant and lactating women is adequately addressed, infantile beriberi is likely to be eliminated:

"Prophylactic thiamine fortification of the diet or pharmaceutical supplementation is desirable to avert neonatal death where deficiency is known to exist" (41) in (42).

There are no formal preventive measures for infantile beriberi outlined in the current Lao MNCH strategy 2009-2015(14). Folate and iron supplementation are included in the essential maternal and

newborn package however vitamin B1 supplementation is not (14). Where thiamine supplementation coupled with nutrition education has have been included in routine antenatal and postnatal care through programs implemented by non-governmental organizations (NGOs) there is anecdotal evidence of a reduction in infantile beriberi cases. In Myanmar, national policy recently introduced thiamine supplementation for all pregnant and lactating women however the intervention has not been in place long enough to measure impact.

The following section synthesizes the current global evidence for the prevention of infantile beriberi and discusses the feasibility of various interventions in Lao PDR.

2.2.1 Maternal supplementation

Inadequate maternal dietary intake of thiamine during pregnancy (43) and the lactation period (30) have been correlated with reduced breast milk thiamine concentrations in several populations. Where intake is inadequate, vitamin B1 supplementation of pregnant women is a viable way of preventing deficiency in the mother-infant dyad.

Table 1 summaries the available evidence for the effectiveness of maternal thiamine supplementation on either maternal thiamine blood or breast milk concentrations and/or infant blood concentrations. While none of these studies were conducted in Lao PDR, similar populations in terms of diet and customs were used. There were no identified studies evaluating the effectiveness of maternal supplementation on infantile beriberi as an outcome measure, however the findings of several trials in thiamine deficient lactating women have documented that breast milk concentrations rapidly increase following maternal supplementation (12, 44). Breast milk concentrations are good indicators of the thiamine status of both mother and infant (19) and should translate into risk of infantile beriberi in the exclusively breastfed infant (45) . In addition, while the data remains unpublished, a cross-sectional survey in 2008 undertaken to evaluate the maternal vitamin B1 supplementation program in Myanmar found that a low proportion of women who were supplemented with thiamine suffered deficiency (2.7%) compared with those who were unsupplemented (6.7%).

There is a need for the "implementation of an evidence-based supplementation regime in affected populations" (19) however there are no current global guidelines for optimal supplementation in stable "endemic" populations. In emergency settings, if dietary intake of thiamine is inadequate, WHO recommends blanket supplementation of pregnant and lactating women (6). Preceding this recommendation, in a refugee camp in Thailand, only pregnant women with symptoms of beriberi were provided with supplementation (100mg daily) while lactating women received 10mg per week. Under this regime, breast milk thiamine deficiency remained prevalent ; up to 58% of postpartum women had inadequate thiamine levels in their breast milk at three-months-postpartum (5). This suggests that subclinical thiamine deficiency was prevalent in this population and implies that maternal clinical symptoms may not be reliable markers of risk for infantile

Table 1. Studies investigating preventive strategies for thiamine deficiency

Study design	Study population (n)	Year	Investigation	Key Findings
Coats et al. Thiamine pharmacokinetics in Cambodian mothers and their breastfed infants (12)				
Non-randomized experimental trial	16 healthy Cambodian mothers and their exclusively breastfed infants (infant aged between 1 and 7 months). Controls: 16 healthy American nursing mothers and infants.	2013	The effectiveness of thiamine supplementation (daily oral dose of 100mg for 5 days) on maternal and infant thiamine status	Median thiamine status of Cambodian mothers was below the adult reference range (measured by plasma and TDP concentrations). Maternal supplementation following 5 days improved maternal median thiamine levels to within normal limits. Infant median level remained below the reference range.
Vimokesant SL et al. Effects of betel nut and fermented fish on the thiamine status of northeastern Thais (46)				
Non-randomized experimental trial	Healthy adults from a Thai village aged 18 to 50 years of age. Group I: 30 participants who consumed raw fish and chewed betel nut . Group II: 21 participants who consumed raw fish but did not chew betel nut	1975	The effect of thiaminase found in fermented fish and betel nut on blood thiamine status and how this is modified by thiamine supplementation	Withdrawal from consumption of thiaminase-containing products resulted in increases in blood thiamine levels. Supplementation (10mg per day) was sufficient to counteract the effect of the raw fish on blood thiamine levels but not the betel nut.
McGready R et al. Postpartum thiamine deficiency in a Karen displaced population (5)				
Cohort study	Pregnant women in a Karen displayed population (Thailand) were followed from 30 weeks gestation to 3 months postpartum (n=50). Group I: supplemented with 100 mg thiamine daily due to beriberi symptoms (n=25) Group II: un-supplemented and asymptomatic (n=25)	2007	To evaluate the effectiveness of the thiamine supplementation program and investigate the correlation between symptoms of deficiency and biochemical thiamine	There was no significant difference in birth weight between the two groups. Visual alertness in neonates was significantly greater in the supplemented group. At 3 months postpartum breast milk concentrations did not differ between groups. Clinical signs do not correlate with biochemical thiamine deficiency.
Stuetz W et al. Thiamine diphosphate in whole blood, thiamine and thiamine monophosphate in breast-milk in a refugee population (13)				
Retrospective cohort study	Postpartum breastfeeding women in the Maela refugee camp, Thailand (Karen ethnic group refugees) n= 636	2012	The effectiveness of thiamine supplementation (daily oral dose of 100mg) and 10mg for lactating women on breast milk concentrations	The high dose supplementation regime was effective in normalizing breast milk concentrations of thiamine
Stuetz W et al. Micronutrient status in lactating mothers before and after introduction of fortified flour: cross-sectional surveys in Maela refugee camp (47)				
Sequential cross-sectional	Breastfeeding women (3 months postpartum) in the Maela refugee camp, Thailand (Karen ethnic group refugees) Group I: Pre-introduction of fortified flour (n= 86) Group II: 4-5 months post introduction of fortified flour (n= 99)	2012	To evaluated the impact of the introduction of thiamine fortified flour as part of the ration on blood and breast milk thiamine concentrations	Thiamine deficiency was rarely detected in either group due to the existing supplementation program. Breast milk concentrations were significantly higher in the post-fortified flour group.

beriberi, an observation that supports the argument that all pregnant and lactating women in at risk populations should receive vitamin B1 supplementation. Indeed in the same refugee camp, after the supplementation program had been changed to include daily supplementation (100mg) for all pregnant and postpartum women together with increased rations for this group, mean breast milk thiamine level was considered to be "in the upper range reported for well nourished women" (13). The study concluded that in terms of breast milk concentrations, the change in supplementation regime appeared to be highly effective in the Karen population (13).

Optimal duration of maternal supplementation has not been quantified (10). However the fact that vitamin B1 stores are depleted within a few weeks of a diet lacking in thiamine, supplementation should theoretically be sustained while the infant is at risk of beriberi. In a Cambodian study, lactating women with median thiamine blood concentration well below the normal adult reference range were supplemented with a daily dose of 100mg for five days which was successful in normalizing blood concentrations of thiamine in the mothers but not in the infants(12) . The authors suggested that a longer treatment course was needed in order to benefit the breastfeeding infant. In Myanmar routine thiamine supplementation is commenced at eight months gestation and continued through to three-months-postpartum (15).

The dosage regime recommended by WHO (in an emergency situation) for thiamine supplementation of lactating women at risk of mild deficiency is 10mg daily for a week then 3-5 mg for at least 6 weeks (6). For stable populations, there are no guidelines in terms of dosage and this would depend on the frequency of supplementation and the local determinants of thiamine deficiency. One study in Thailand investigating effects of thiaminase consumption on blood thiamine levels reported that supplementation (10mg/d) was effective in compensating for the effect of tea consumption but not of betel nut (46). However, in the Karen refugee population also in Thailand, researchers found that any effects of thiaminase consumption on maternal thiamine status appeared to be 'eclipsed' by the high dose (100mg/d for all pregnant women) supplementation regime(13). The findings of these two studies suggest that for populations with high consumption of thiaminase-containing foods, higher thiamine doses may be required. Given excess Vitamin B1 is excreted by the kidneys there is no recommended upper limit for supplementation dosage (42).

There is little documented in the literature around ideal delivery mechanisms for supplemental thiamine for pregnant and lactating women. Thiamine has been included as one of 10 essential micronutrients recommended by WHO and UNICEF to be included in a multi-micronutrient supplement in this high risk group in developing countries (48); the joint report states that "it's more feasible to provide micronutrients in one supplement than in multiple" (48). However in a 2006 Cochrane systematic review on multi-micronutrient supplementation in pregnant women there was insufficient evidence to warrant a global policy change to replace the current WHO recommendation supporting iron and folate supplementation only (38).

The most convenient platform for the delivery of thiamine supplementation for pregnant and lactating women is through existing ANC and postnatal programs. In Lao PDR, this option would be ideal in regions in which ANC attendance is high; for example in one urban population studied, ANC coverage was 91% (2) however in rural areas where ANC attendance is generally lower (52%) (36), other options to increase supplementation coverage would need to be considered. Coverage of antenatal and postnatal care was noted as broadly insufficient in the MoH MNCH strategy report (14). It is interesting to note that reports from 'Save the Children' of high incidence of infantile beriberi in the Luang Prabang province, ANC coverage was only 50.6% (36).

2.2.2 Maternal nutrition education

There were no studies identified in this literature search investigating the effect of nutrition education interventions for pregnant and lactating women on maternal thiamine status or infantile beriberi incidence. However in the beriberi literature, authors frequently suggest that nutrition education to increase dietary diversity to include thiamine-rich foods and to decrease consumption of thiaminase-containing products for the prevention of thiamine deficiency should be part of the ANC package in affected populations (1, 3, 16). Further investigation is necessary to determine which foods rich in thiamine would be acceptable despite postpartum food taboos and therefore feasible choices for promotion in Lao PDR .Where 'Save the Children' have implemented vitamin B1 supplementation, this has been coupled with nutrition education interventions, however the relative contribution of the education component in the reduction of infantile beriberi incidence is unknown.

The national nutrition policy, 2008 noted a "lack of success in community –based nutrition education due to inappropriate training materials (and) barriers in language and traditional food cultures hampering behavioral changes". However a recent impact evaluation of an MCH program in rural Lao PDR demonstrated that with targeted community delivered education programs, harmful infant feeding practices can be reduced; the prevalence of the practice of feeding pre-masticated rice to infants in the first month of life was decreased from 75% to 22% between baseline and end-line surveys (7). In addition, an increase in the proportion of women who fed their babies colostrum increased substantially following program completion (7). More qualitative evidence from the northern highlands of Lao PDR suggested that women were open to receive information about how to better care for their child which is promising in terms of likely success of behavior change strategies(3).

2.2.3 Increasing the thiamine content of rice

In populations for which the staple rice is parboiled prior to it being milled– a process which forces the thiamine from the husk into the grain of rice and reduces it's loss during milling and washing - infantile beriberi is rare (11). In particular, low incidence of beriberi in India has been linked to the widespread practices of parboiling (6). Parboiled rice is also reportedly produced in Bangladesh, Sri-Lanka, Thailand and Myanmar however the change in color and taste of parboiled rice compared to other forms of milled rice may make it unacceptable in other Asian countries (11) while altering long-held traditional food habits may be very challenging (6).

Food fortification to address micronutrient deficiencies at a population level has been identified by the World Bank as one of the "most cost-effective of all health interventions"(40). Historical evidence for the effectiveness of food fortification with thiamine in the prevention of beriberi is strong (18). Since the widespread fortification of cereals in industrialized countries during the 1940s, infantile beriberi has been rarely seen (18).

Thiamine enriched rice was first commercially produced in the United States (U.S) in the 1940's. At a similar time, widespread production of fortified rice began in the Philippines with significant successes in reducing the incidence of beriberi. Such a public health issue was beriberi in the Philippines prior to fortification, rice manufacturers were obliged under law to enrich all rice with thiamine however reportedly, not all complied (11).

There is an absence in the literature of any recent accounts of positive impacts of thiamine fortification on the thiamine status of populations for which deficiency is endemic. One study conducted in the 1970s in rural Thai villages found no significant impact of rice fortification

on nutrition outcomes (49). However, more recently, in the Maela refugee camp, breast milk concentrations of thiamine in postpartum women were significantly higher after the introduction of thiamine-fortified flour as part of the ration, however thiamine concentrations were already within normal limits due to an established daily thiamine supplementation program (47). In non-refugee populations, flour consumption is not common, especially in rural Laos.

Thiamine is rated as low risk in terms of fortification (18) and rice fortification holds promise in terms of public health impact if scaled up in developing countries. However the widespread production and implementation of rice fortification programs in such countries have been hampered by several constraints. One technical limitation relates to the nutrition stability of one type of fortified rice in which much of the added vitamin is lost during washing and cooking (11). A newer technique which applies a vitamin premix to the rice grains is more likely to be successful in addressing thiamine deficiency as the micronutrients are protected from loss during washing due to a water-resistant coating. However there have been few reports around the successes or failures of use of the premix fortified rice in developing countries settings. There was no evidence found that fortified rice is available in Lao PDR, nor any indicative relative costing of whether fortified rice would be affordable for at-risk populations.

Several publications have identified a set of conditions necessary for successful implementation of fortification programs; these include the availability of quality data on food consumption patterns, political will, existing infrastructure for regulatory and marketing systems and consumer acceptability(11, 40). Lack of government commitment to enforce the conditions necessary for rice fortification to be successful was a significant issue in attempts to introduce the measure in many Asian countries in the 1940s-1950s (50).
In Lao PDR, there is little available evidence on rice consumption or purchasing patterns. Given "78% of the... population (in Lao PDR) are rural subsistence farmers" (3) and poverty is widespread, fortified rice programs are unlikely to reach the people who need it the most. Further constraints in Lao PDR to successful introduction of fortified rice could be the lack of central rice processing and legal and regulatory systems to ensure quality control (40). While, the World Food Programme (WFP) country strategy states that the introduction of fortified rice to Lao PDR is possible(51), feasibility studies are necessary to determine likely success.

Home fortification programs to address micronutrient deficiencies in infants and children in Lao PDR have had a positive effect on the iron status of children (52) however the feasibility of home fortification for pregnant and lactating women is currently unknown.

III. CONCLUSIONS AND RECOMMENDATIONS

Despite more than 100 years of recognition of the public health implications of thiamine deficiency and its causes, it remains prevalent in some populations, in particular in pregnant and lactating women (16, 19). The implications of prevalent thiamine deficiency go beyond infantile beriberi to include many maternal morbidities and possibly longer term cognitive and physical developmental issues for the child exposed (21). Infantile beriberi is recognized in Lao PDR and treatment is available however despite emerging evidence of the risk factors for and prevention of the disease there are no formal central preventive strategies in place.

Text Box 2: Research priorities in Lao PDR

- **Further documentation of the prevalence of thiamine deficiency in pregnant and lactation women and incidence of infantile beriberi(34). If data is unavailable geographical and age-specific trends in infant mortality rates are useful indicators.**
- **The optimal supplementation regime for pregnant and lactating women (30)**
- **Further investigation into the ethnic, cultural and socioeconomic determinants of thiamine deficiency (3) and the acceptability and accessibility of various thiamine-rich foods in order to inform region-specific nutrition promotion**
- **The relative contribution of consumption of different types of rice such as hand-pounded vs machine-milled rice and rice preparation methods (33)**
- **Feasibility studies for rice fortification including rice purchasing patterns, marketing systems and social acceptability (40)**
- **The impact of maternal supplementation and education trials on maternal and infant thiamine status**
- **The longer-term effects of thiamine deficiency on exposed children (16)**

Infantile beriberi is a preventable disease; however research on best practice for thiamine deficiency and beriberi prevention is currently limited. As one author points out, "even a single case of beriberi in a population reflects a public health problem and calls for a full nutritional assessment"(6). This literature review has identified several priority areas for further research around prevention strategies for infantile beriberi in Lao PDR.

The evidence for the prevention of infantile beriberi is not well developed; this is likely due largely to the fact that the disease is primarily confined to parts of South-East Asia and in vulnerable groups such as refugees (37). For Lao PDR, the studies reviewed best support maternal supplementation and nutrition counselling as the most feasible and effective prevention strategy. Authors have stressed the urgent need for maternal supplementation in affected populations such as Lao PDR (1, 16). Several quality studies have demonstrated that maternal supplementation with thiamine rapidly increases breast milk concentrations (12, 13) which should, if sustained translate into improved thiamine status of the exclusively breastfed infant. Indeed reports from 'Save the Children' program managers suggest that where vitamin B1 supplementation is routinely provided at ANC and post-natal clinics, infantile beriberi is rare.

The available evidence suggests that supplementation should cross all pregnant and lactating women in populations in which thiamine deficiency is endemic and biochemical thiamine status is not readily able to be determined. The duration of treatment should continue while the infant remains at risk and the dosage should be context specific. Several cultural factors such as thiamine-depleting rice preparation techniques, postpartum food avoidance and suboptimal infant feeding practices are common in Lao PDR and have been linked with infantile beriberi. There is also some evidence that thiaminase-containing foods play a role in the thiamine deficiency in populations in which consumption of such products is high. These factors could be addressed as part of a nutritional counselling package for pregnant and lactating women; nutrition education coupled with supplementation could potentially be very effective in reducing the incidence of infantile beriberi. Suggestions for the prevention of infantile beriberi in Lao PDR based on the evidence reviewed are outlined in Text Box 3. The ultimate solution, as historical evidence shows, will likely come from national economic advancements and the alleviation of extreme poverty both of which should lead to increased dietary diversification. Rice fortification is also a promising longer-term answer to the thiamine deficiency issue in Lao PDR, however there is not sufficient evidence that this is feasible in the short-term. There is an immediate need for targeted action in Lao PDR; this in the form of maternal supplementation and nutritional counselling is warranted in order to avert further deaths from infantile beriberi.

Text Box 3: Opportunities for the prevention of infantile beriberi in Lao PDR. It is suggested that:

- **Lao PDR adopt a similar approach to Myanmar - targeted supplementation of all pregnant and lactating women-which is best delivered through routine ANC and postpartum packages.**
- **Where ANC coverage is low, options for community delivery of thiamine supplementation are explored.**
- **Supplementation be coupled with nutrition education aimed at increasing consumption of thiamine-rich foods and a reduction in the consumption of thiaminase-containing products and modifying postpartum food avoidance and suboptimal infant feeding practices.**
- **Other options for longer term solutions to the beriberi problem be carefully considered including the potential introduction of fortified rice.**

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