HTA Outcome Report

Cost Effectiveness Analysis of Thiamine Supplementation among pregnant and post partum women to prevent infantile beriberi deaths

Carinthia Balabet Nengnong, Bindiya Sara Babu, Roshine Koshy, Tiameren Jamir, Laura Downey, Sandra Albert

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Introduction: The incidence of thiamine deficiency is believed to be particularly high in the northeastern states of Manipur, Meghalaya, and Assam, where the average thiamine intake is much lower than the national average. The lack of a diagnostic test for thiamine deficiency, also referred to as beriberi, poses a challenge in early detection and prevention, resulting in increased morbidity and mortality. Despite increasing evidence linking thiamine deficiency to maternal and infant deaths, there appears to be a lack of awareness and a low index of suspicion among healthcare providers, which hinders effective prevention and management of the problem. Several countries around the world recommend the provision of thiamine supplements for pregnant and postpartum women as a cost-effective means of preventing thiamine deficiency. India does not have a policy regarding thiamine supplementation in pregnancy. Evidence-based policies targeted at those most vulnerable to thiamine deficiency are important to prevent the morbidity and mortality associated with this condition. Thus this study aimed to conduct a cost effectiveness analysis of a thiamine supplementation programme in pregnant and lactating women to assess the cost-effectiveness of implementing this programme in the North East to prevent infantile death due to thiamine deficiency.

Methods: A Systematic Review was conducted in order to assess the effectiveness of thiamine supplementation among pregnant and postpartum women to prevent thiamine deficiency in infants. Expert opinion interviews were conducted in order to fill the gaps in published evidence and understand the prevalence and experience of managing thiamine deficiency cases in the context of Northeast India. A decision-tree was built to model the lifetime costs and outcomes accrued as a consequence of implementing a 12 month thiamine supplementation program in pregnant and post partum women across the North East of India. Both costs and outcomes were calculated for the neonatal population only. The costs for clinical events were taken from the National Cost Database, India. The primary outcome measure was life years gained based on average life expectancy at birth and prevented mortality in order to estimate the incremental cost per life year gained as a consequence of thiamine supplementation.

Results: The literature review revealed a dearth of published evidence related to the incidence and prevalence of thiamine deficiency in pregnant and post partum populations. There were no published studies on cost effectiveness in our population of interest either. Qualitative data obtained from the expert interviews highlighted the complexity of thiamine deficiency and related morbidity and mortality in Northeast India, where clinical suspicion is low and case fatality rate is therefore high despite thiamine treatment efficacy. Some outcome evidence from a recent hospital cohort in Assam provided data for the model.

Results of the cost effectiveness model indicates that a routine of 6 months antenatal and 6 months postnatal Thiamine supplementation via one multivitamin per day containing 10 milligrams of thiamine is likely to be highly cost effective with an ICER of INR 2386 per life year saved at a WTP threshold of INR 1, 72,000 (1 x GDP).

Conclusion: Thiamine deficiency is a serious health issue in the North-Eastern region of India, particularly affecting pregnant and lactating women and their infants. This study has demonstrated that a supplementation programme of a multivitamin tablet that contains at least 10 milligrams of thiamine is a cost effective means to avert deaths due to thiamine deficiency in infants. The findings have important implications for informing policy that can help mitigate the burden of thiamine deficiency in pregnant

and postpartum women and in reducing infantile morbidity and mortality due to beriberi across the Northeast of India.

INTRODUCTION

Thiamine, or vitamin B1, is a water-soluble vitamin for the body and plays an important role in several biological processes (1) . This micronutrient is present in whole grains, legumes and nuts, and meat including beef and pork (1–3). The supply of thiamine in the human body is wholly dependent on dietary intake (1). As thiamine has a short half-life ranging between one to twelve hours, the body is incapable of storing thiamine greater than 30 mg, therefore requiring a regular dietary supply for maintenance of tissue-thiamine levels (2).

Deficiency in thiamine can cause a wide range of disorders, including neurologic, cardiovascular and gastrointestinal, commonly manifested as dry or wet beriberi, and Wernicke's encephalopathy. Dry beriberi is characterized by involvement of nervous system while wet beriberi is characterized by the involvement of cardiac. Wernicke-Korsakoff is an acute neurological condition, also associated with severe alcohol disorder. Alcohol interferes with thiamine transportation, resulting in poor intake of thiamine by the cells (1).

The global prevalence of thiamine deficiency is poorly documented due to lack of data to establish definitive biochemical levels indicative of symptomatic thiamine deficiency (2,4,5). In high-income countries such as the USA, wheat flour, cereals and infant formulae are fortified with thiamine (2). In these countries, thiamine deficiency is mainly documented as the result of alcoholism. However, in low and middle-income countries (LMICs) thiamine deficiency is often documented in relation to dietary practices and nutritional intake. Many LMIC populations rely on polished rice as the staple source for carbohydrates, resulting in the depletion of thiamine and thiamine deficiency (1).

Prevalence of thiamine deficiency-related diseases like beriberi is reported to be as high as 58% to 66% in many poor households in LMICs (6). Thiamine deficiency is primarily documented in poor households, or in high-risk isolated populations such as prisoners, refugees in refugee camps and in conflict settings where there is a lack of diversity in terms of vitamin- rich foods (3,7–10).

Studies have shown that exclusively breastfed infants of thiamine deficient mothers, especially those within three months of age, are at the highest risk of thiamine deficiency and if left untreated, the mortality rate of infants due to thiamine deficiency disorders is almost 100 percent (5,8). In India, Kashmir is endemic to infantile thiamine deficiency (11). A number of studies conducted in Kashmir reported cases of infantile beriberi who were exclusively breastfed by thiamine deficient mothers where the diet mostly consisted of polished rice and chicken soup due to customary postpartum dietary restriction (6) . Fortunately, most of the infants admitted either with pulmonary hypertension or encephalopathy were found to be responsive to thiamine (2). Similarly, another hospital-based study conducted among peri-partum mothers in Kashmir who presented with complaints of weakness and sensory symptoms also reported positive response to thiamine (6).

Recent instances of extreme thiamine deficiency syndromes have been observed amongst people in the northeast region (NER) of India (12–14) . Several suspected and confirmed cases of Thiamine deficiency disorder have been documented in Assam, Mizoram and Tripura (12–14). These infants who died or presented with an illness later confirmed to be thiamine deficiency were mostly from low socio- economic families and exclusively breast fed (12).

AIMS AND OBJECTIVES

Aim

To conduct a cost effectiveness analysis of thiamine supplementation among pregnant and postpartum women in the North East of India in order to assess whether a supplementation program would be a cost-effective approach to reducing infantile beriberi and associated mortality in the region.

Specific Objectives

1. To determine the incremental cost effectiveness of thiamine supplementation as compared to standard care among pregnant and post-partum women to prevent infantile beriberi
   a) To measure life years gained as a measure of effectiveness of thiamine supplementation
   b) To measure the costs of thiamine supplementation as compared to the costs of usual care
   c) To estimate the incremental costs per life years gained of supplementation of high-risk women with thiamine

PICO STATEMENT

Population	Pregnant and Post-partum women
Intervention	Thiamine supplementation
Comparator	Regular diet followed by the population
Outcome	Life years gained in neonates and infants born to supplemented mothers

METHODS

A systematic literature review was carried out to assess the effectiveness of thiamine supplementation of pregnant and post partum mothers of preventing thiamine deficiency in neonates and infants. In addition to the review, interviews were conducted with clinical experts or healthcare professionals from Meghalaya, Assam, Mizoram and Tripura who have extensive experience and knowledge in the field of thiamine deficiency in the Northeast context. This provided insights from those who deal directly with thiamine deficiency cases to contextualise the findings of the systematic review and inform the structure of the cost-effectiveness model.

1. SYSTEMATIC LITERATURE REVIEW

A systematic review was conducted to assess the effectiveness of thiamine supplementation in pregnant and postpartum women to prevent infantile beriberi in South East Asian Population. For reporting, the guidelines of the preferred Reporting items for Systematic Reviews and Meta-analysis (PRISMA) statement were adopted. The review was pre-registered in the PROSPERO International prospective register of systematic reviews (2021: CRD42021276658).

1.1 Methods

Electronic searches

The following databases were searched:

1. MEDLINE (PubMed)
2. Cochrane Central Register of Controlled Trials (CENTRAL)
3. Google scholar
4. Web of Science
5. Scopus

Search Strategy: A search strategy was defined for each database using a combination of key terms generated from the PICO framework (Annexure A). A search string was developed using these key terms and the string was adapted accordingly for each of the electronic databases. (Annexure B)

Selection Criteria

Types of studies: The review included randomised controlled trials (RCTs), non-randomised studies and quasi- RCTs, and observational studies that evaluated the effect of thiamine supplementation in pregnant and lactating women for preventing thiamine deficiency in neonates and infants.

Types of participants: Participants included pregnant and postpartum women (irrespective of age, socio economic status, ethnicity, disease, health condition) and infants up to the age of six months.

Types of interventions: Studies in which pregnant and postpartum women received Thiamine supplementation (Vitamin B1) were included, as were observational cohort studies that reported on incidence and clinical outcomes of thiamine deficiency in unsupplemented women to inform the comparator arm of the model.

Primary outcome measures

1. Infantile beriberi incidence among infants born to supplemented and un-supplemented mothers
2. Beriberi deaths among infants born to supplemented and un-supplemented mothers

Secondary Outcome measures

1. Clinical outcomes in confirmed cases of thiamine deficiency

Screening Process

Selection of studies: Two reviewers independently screened titles, abstracts of all potential studies to ensure that they meet the eligibility criteria. When a Title or abstract could be rejected with certainty, full texts of the articles for further evaluation were obtained. The accuracy for the final assessment of the articles was reviewed by the clinical expert. If full text articles were not accessible, attempts were made to contact the respective authors for further details of the study. The reviewers' classified the studies as "include", "exclude" and "unsure. In case of disagreements at any stage of the eligibility assessment process, discussion with a third reviewer was done to resolve the disagreement and come to a general consensus.

Quality Appraisal: The Joanna Briggs Institute (JBI) Critical Appraisal Checklist (15) was employed to assess the quality of all included studies. The quality appraisal was undertaken by two reviewers and uncertainties were addressed through discussion and consensus.

Data extraction and management

Data was extracted in MS Excel using a standard template which was modified to include key parameters of interests. The key parameters extracted for each paper included the following:

1. Study title 2. Authors 3. Year of Publishing, 4. Type of Study, 5. Objectives of the Study, 6. Clinical Symptoms 7. Population, 8. Number of participants, 9. Intervention, 10. Comparison, 11. Outcome, 12. Results

Evidence Synthesis: A narrative synthesis was conducted to describe and interpret key findings related to the effectiveness of thiamine supplementation to prevent thiamine deficiency. No Meta analysis was performed as there was a high level of heterogeneity in terms of study designs and reported outcomes.

1.2 Results

The PRISMA Chart (Fig 1) summarises the systematic screening process. A total of 801 studies were identified across the five databases: 104 studies from PUBMED; 0 studies from COCHRANE; 44 from Google Scholar; 147 from Scopus; and 478 from Web of Sciences. Titles were screened for relevance and 158 studies were included for abstract screening. At abstract screening, 97 studies were assessed as relevant for full record screening. 40 studies were identified as relevant for full-text screening, of which 24 were identified as duplicates and removed, resulting in 16 studies for full text screening. After consultation with clinical experts, 16 studies were included where only 1 study out of the 16, reported the primary outcome and all 16 studies reported the secondary outcomes.

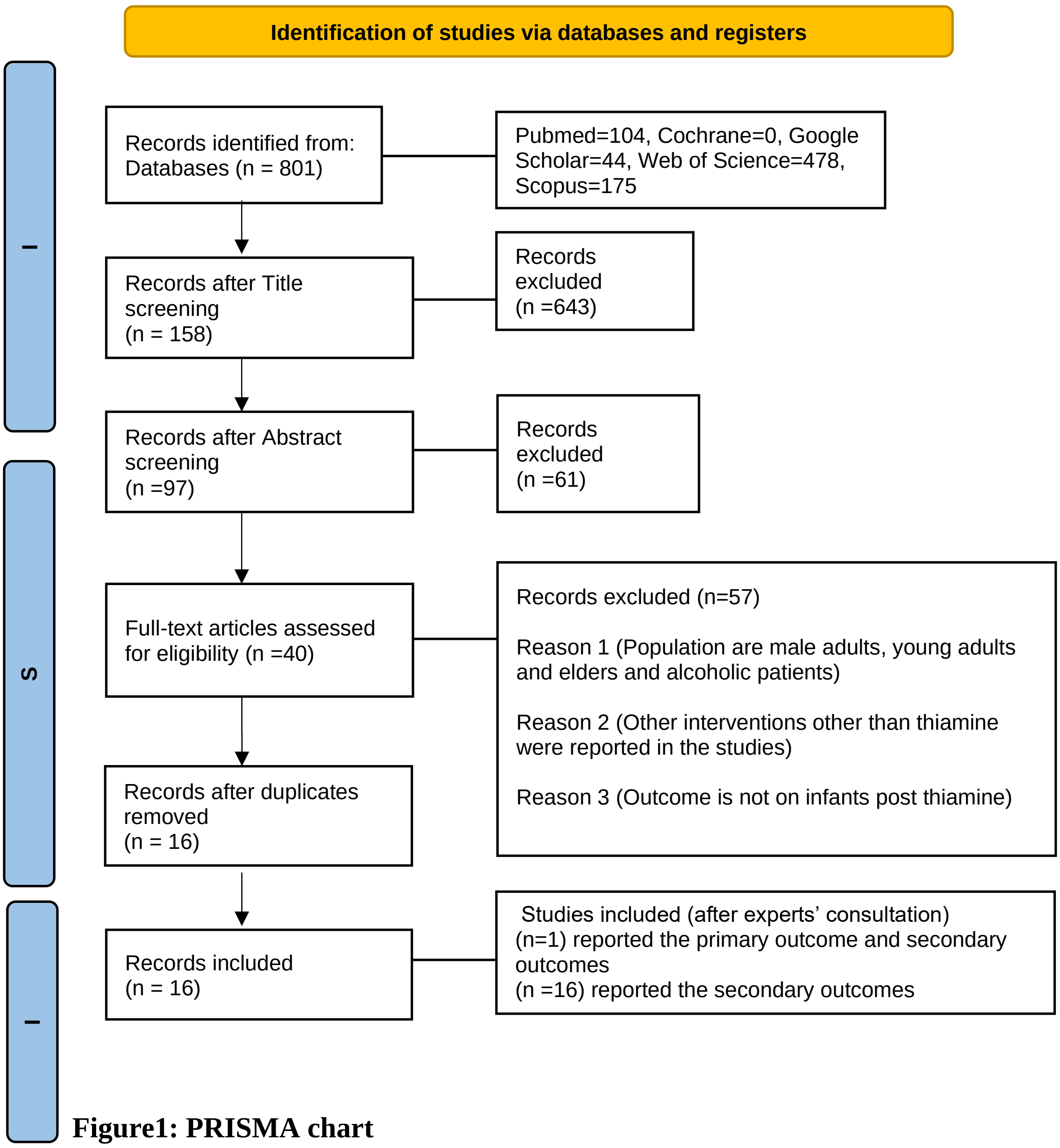


Figure1: PRISMA chart

1.2.1 Description of Included studies

Studies with a thiamine supplementation program were considered for inclusion, as were observational studies that reported on the incidence of beriberi in unsupplemented mothers. A total of 16 potential studies were included which reported four key outcomes: thiamine levels; description of the clinical presentation of thiamine deficiency; efficacy of the thiamine treatment; and reporting infantile beri beri as the cause of death. Out of the 16, 13 were conducted on infants and the studies reported that thiamine administration in infants showed a significant improvement in health outcomes where recovery from clinical symptoms was reported. Three studies were conducted in mothers which assessed the thiamine levels in breast milk where two studies administered thiamine supplementation to mothers and one study focused on comparing different doses of thiamine supplementation among mothers.

Table 1: Studies Reviewed

S No.	Study title	Authors name	Year	Study Type
1	Low-dose thiamine supplementation of lactating Cambodian mothers improves human milk thiamine concentrations: a randomized controlled trial	Gallant et al	2021	RCT
2	Shoshin Beriberi-thiamine responsive pulmonary hypertension in exclusively breastfed infants: A study from northern India	Bhatt et al	2016	Cohort
3	Beri-beri: a major cause of infant mortality in Karen refugees	Luxemburg et al	2003	Cohort
4	Post partum thiamine deficiency in Karen displaced population	Mcgready et al	2001	Cohort
5	Infantile Cardiac Beriberi in Rural North East India	Thankaraj et al	2020	Cross Sectional
6	Thiamine pharmacokinetics in Cambodian Mothers and their breastfed infants	Coats et al	2013	Quasi Experimenta l
7	Thiamine deficiency in tachypnoeic Cambodian infants	Keating et al	2015	Case Control
8	Thiamine deficiency and cardiac dysfunction in Cambodian infants	Porter et al	2014	Case Control
9	The rediscovery of thiamine deficiency disorders at a secondary level mission hospital in Northeast India	Koshy et al	2020	Case Report
10	Thiamine Responsive Acute Pulmonary Hypertension of Early Infancy (TRAPHEI)-A case Series and Clinical Review	Panigrahy et al	2020	Case Series
11	Thiamine-responsive, life-threatening, pulmonary hypertensive crisis with encephalopathy in young infants: A case series	Suryakanty et al	2021	Case Series

12	Case report: Fulminant infantile beriberi: A report of six cases	Samprathy et al	2020	Case Series
13	Thiamine responsive acute life threatening metabolic acidosis in exclusively breastfed infants	Quereshi et al	2015	Case Series
14	Thiamine-responsive acute severe pulmonary hypertension in exclusively breastfeeding infants: A prospective observational study	Satry et al	2021	Case Series
15	Beriberi (Thiamine Deficiency) and High Infant Mortality on Northern Laos	Barennes et al	2015	Case Series
16	Cardiac Beriberi: Often a Missed Diagnosis	Rao et al	2009	Case Series

Of these 16 studies, 1 study (Luxemburg et al (2003)) reported on the primary and secondary outcomes of interest. For the primary outcome, the study estimated the prevalence of beriberi in the study population and revealed that infantile beriberi was identified as the primary cause of death, accounting for 7%- 40% of infant mortality cases. The study reported that in Cohort I, thiamine deficiency was considered responsible for 40% (19/48) of all infant deaths and 7% (6/88) of all infant deaths in Cohort II. In this Cohort, 84 infants presented with infantile beri beri, which resulted in an incidence rate of 75 cases per 1000 with a 95% CI of 60-91 per 1000. For the secondary outcome, the study reported that all infants who were diagnosed with infantile beriberi had received intramuscular thiamine injections with the dosage of 50 mg, the response to this treatment was described as dramatic, with most babies showing signs of recovery within 6 hours after receiving the thiamine injection with majority of these infants (93%, 78/84) were treated successfully.

The 16 studies reported the clinical outcomes in confirmed cases of thiamine deficiency. One case study/report (Koshy 2020) reported the different presentations of thiamine deficiency disorders in infants and reported a dramatic recovery post supplementation. The seven case series by Panigrahy et al (2020), Suryakanty et al (2021),Samprathy et al (2020), Quereshi et al (2015), Sastry et al (2021), Barennes et al(2015) and Rao et al (2009) highlighted the importance of early recognition and treatment of thiamine deficiency, as it can lead to severe complications such as acute pulmonary hypertension in infants. Also, thiamine supplementation has shown significant therapeutic benefits in these cases. Three cohort studies (Bhatt et al. (2016), Luxemburg et al. (2003) and Mcgready et al. (2001) revealed that thiamine administration was effective in the recovery and resolution of pulmonary hypertension. One cross sectional study by Thankaraj et al. (2020) revealed that thiamine supplementation proved to be effective in resolving the symptoms of beriberi in affected infants. This indicates that timely administration of thiamine can treat and reverse the condition, leading to a positive outcome and potentially saving the lives of affected infants. Two case control studies Keating et al (2015) and Porter et al (2014) highlights the impact of thiamine deficiency on cardiac function and tachypnoea in infants and reported the potential benefits of thiamine treatment in reversing the abnormalities associated with the deficiency. One quasi-experimental study conducted by Coats et al. (2013) focused on characterizing thiamine pharmacokinetics in Cambodian mothers and their breastfed infants. One RCT by Gallant et al (2021) was reported which estimated the dose at which additional maternal intake of oral thiamine no longer significantly increased milk thiamine concentrations in the infants.

Effectiveness of thiamine intervention for confirmed thiamine deficiency

The case report (Koshy 2020), seven case series by Panigrahy et al (2020), Suryakanty et al (2021),Samprathy et al (2020), Quereshi et al (2015), Sastry et al (2021), Barennes et al(2015) and Rao et al (2009), the three cohort studies (Bhatt et al. (2016), Luxemburg et al. (2003) and Mcgready et al. (2001) and the cross sectional study by Thankaraj et al. (2020) uniformly reported that treatment with high-dose thiamine is highly effective in alleviating symptoms and preventing fatality in those with confirmed thiamine deficiency.

1.2.2. Quality appraisal

The Joanna Briggs Institute (JBI) Critical Appraisal Checklist was employed to appraise each study for quality and risk of bias and assign scores accordingly (Annexure C). The scores were converted to percentage ranges to aid quality classification labelling. Based on this, the ranges of the scores given were: <50=Low, 51-80=Moderate and 81-100=High. The Cohort, Case control and cross sectional studies which were moderate in quality did not report on confounding factors such as diet and socio economic status and were marked down in quality rating as a result. In the quasi experimental study, there was no control group identified and inadequate information on the follow up of treatment. In the case series and case report, there was no detailed information on the population demographics nor the setting. There was no statistical analysis undertaken in these case series and no adverse events were reported or described in the case report

2. **EXPERT OPINION INTERVIEWS**

Expert opinion interviews were conducted in four states of the Northeast Region of India with the aim to explore various aspects related to detection, management, morbidity, mortality, and population incidence of thiamine deficiency in this context.

2.1 Methods

A total of seventeen experts in total were selected where eight were from Meghalaya, one from Mizoram, one from Tripura and seven from Assam. (Table 2) The interviews were conducted both face to face and through telephone and the duration was approximately one hour each. All interviews were conducted in English by two researchers between January to March 2023.

Table 2: Expert Opinion Interviews

Meghalaya	Assam	Mizoram	Tripura
1. Nazareth Hospital Shillong 2. Dr. H.G. Roberts Hospital, Shillong 3. NEIGRIHMS (North Eastern Indira Gandhi Regional Institute of Health & Medical Sciences), Shillong 4. Children's Hospital Shillong 5. Ganesh Das Hospital Shillong 6. Jengjal Sub-Divisional Hospital, West Garo Hills	Makunda Christian Leprosy & General Hospital Assam	Synod Hospital, Mizoram	Agartala Government Medical College

Note: Makunda Christian Leprosy and General Hospital, Karimganj, Assam and Jengjal Sub-Divisional Hospital, West Garo Hills are the two hospitals included in the sample which documents and manages thiamine deficiency cases

Interviews were conducted using an interview topic guide with open ended questions (Annexure D). Interview probes were adapted as per the responses of the participants and interviews were carried out face-to-face, and audio recorded with informed consent. Transcription was done by the interviewer and a follow up interaction/s with the experts was done for clarification or additional information when required.

2.1.1 Ethical considerations

Participant Information Sheet and Informed Consent Forms were prepared which describes the purpose and ethical concerns pertaining to the study and were provided to the respondents.

Verbal and written consent was taken from the participants before conducting the interviews. Consent was also taken for recording the interviews. Ethical approval for the study was granted by the Indian Institute of Public Health Shillong-Institutional Ethics Committee (IIPHS-IEC) at Indian Institute of Public Health, Shillong.

2.1.2 Analysis of data

Interviews were transcribed and analysed using a thematic approach. Transcripts were read repeatedly, and codes and categories were developed for analysis.

2.2 Results

A total of seventeen experts were selected for the expert opinion interviews which aimed to explore various aspects related to thiamine deficiency in the region.

The key areas identified from the interviews are: 1. Prevalence of Thiamine Deficiency - its frequency, occurrence rates, and any patterns they have observed in their clinical experience 2. Clinical Manifestations 3. Challenges in Diagnosis 4. Factors Contributing to Thiamine Deficiency and 5. Existing Interventions. The interviews concluded with expert recommendations on how to address thiamine deficiency effectively.

1. Prevalence of Thiamine Deficiency: Experts discussed the frequency and occurrence rates of thiamine deficiency that they have observed in their clinical experience. The deficiency was prevalent among patients coming from low socio-economic backgrounds and the mean age of infants affected by thiamine deficiency was noted to be around 3-4 months.

2. Clinical Manifestations: The experts spoke about the clinical manifestations which includes cardiac manifestations and neurological effects which could be probable thiamine deficiency. This was observed to have a sudden onset in the infants where the deficiency develops rapidly leading to clinical symptoms in a short period. The cardiac form of infantile beri beri has 100% case fatality which is seen in less than six months of age if left untreated.

3. Challenges in Diagnosis: The main crux of the interviews delved into the challenges faced by clinicians in diagnosing this deficiency. These challenges attributed to the lack of easily available diagnostic tests and its expensive nature, then leading the hospitals to rely on clinical suspicion for diagnosis. However, the dramatic improvements seen after thiamine administration were used as a diagnostic tool for infantile beriberi, helping to confirm the role of thiamine deficiency in the observed symptoms. There is also a challenge to procure thiamine injections and thiamine tablets and had to use B complex supplements which have a lower content of thiamine.

4. Factors Contributing to Thiamine Deficiency: The experts discussed about the dietary habits and socioeconomic conditions which were identified as potential contributors to thiamine deficiency. These included chewing of betel nut, consumption of “Nakam” (fermented fish), and consumption of polished rice.

5.Existing Interventions: Experts shared information about the existing thiamine supplementation interventions at their hospitals or healthcare facilities. Thiamine is supplemented to infants and adults with suspected thiamine deficiency based on clinical criteria and for prevention, mothers are supplemented for at least the last 3 months of pregnancy and until their lactation period is over.

6. A lack of local recognition and experience of diagnosing and treating thiamine deficiency: Healthcare professionals in the city of Shillong reported that they do not routinely consider thiamine deficiency when patients present with symptoms that could be associated with thiamine deficiency. It was also noted that when patients present with thiamine deficiency symptoms, other conditions that share similar symptoms are diagnosed, sometimes inaccurately. This leads to cases of true thiamine deficiency being misdiagnosed, further contributing to the lack of documented cases and clinical recognition of thiamine deficiency.

Based on the Makunda hospital data, it was found that there were no infant deaths reported in the cohort group of 489 mothers in Makunda Hospital who received Vitamin B supplementation and 4 deaths were reported in the unsupplemented mother's groups of 499. Preliminary data received from an ongoing study by National Institute of Nutrition (NIN) reports thiamine deficiency for pregnant women is currently 44% and lactating women is 33%, indicating a much higher prevalence than previously suspected.

In conclusion, the experts interviewed, and especially those based in rural areas where thiamine deficiency was thought to be endemic, emphasised the need for awareness and prevention to address the issue of thiamine deficiency effectively. Experts raised the need for extensive research studies to be conducted to determine the true burden of the deficiency in the region, and effective preventative and management strategies to contain this burden.

3. COST EFFECTIVENESS MODEL

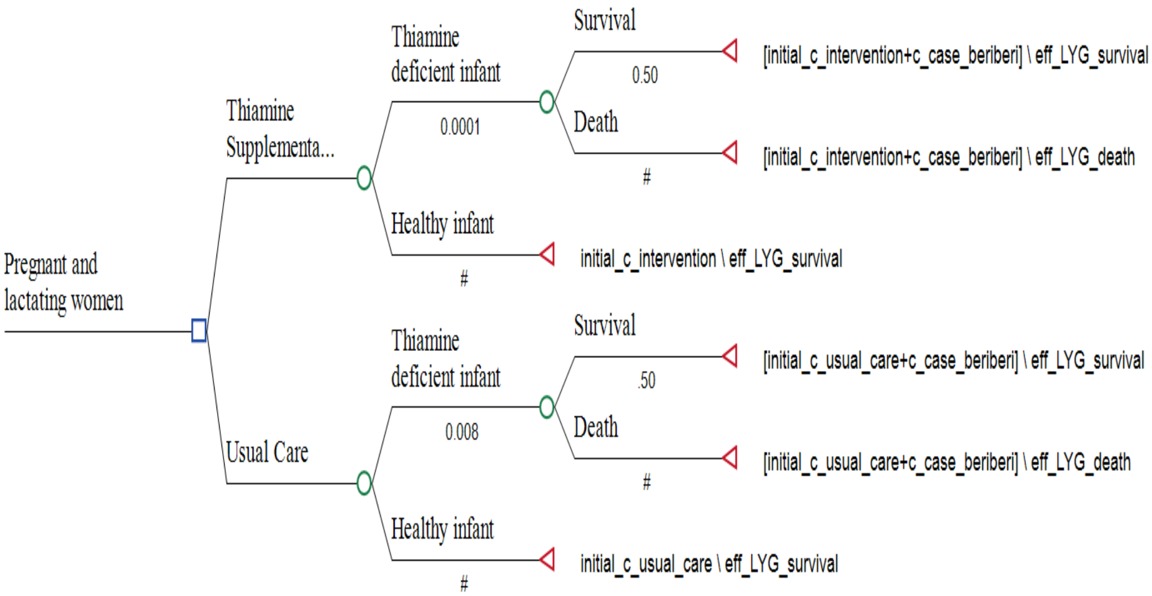
3.1 Methods

A decision tree model was constructed in Microsoft Excel and later imported into TreeAge, to assess the costs and outcomes of the two treatment strategies: Thiamine supplementation (multi B vitamin, 10 mg daily for 12 months) and standard treatment (usual care with no supplement and thiamine from regular diet).The population of interest for the model were pregnant and lactating women.

3.1.1 Model structure

The decision tree health state diagram is illustrated in Figure 1

Fig.1. Decision Tree where Pregnant and Postpartum mothers were supplemented andoutcomes were measured in infants



The first chance node in the tree illustrates two alternate pathways - Thiamine supplementation and usual care. These two pathways are further divided into Thiamine deficiency and healthy infants for both supplemented and un-supplemented arms. Terminal nodes (i.e. endpoints of the model) are survival in full health and death.

3.1.2 Data

A number of data sources were used to populate the model. Given the paucity of relevant peer-reviewed literature, the majority of parameters were populated using information obtained from clinical interviews (see Section 2), the medical records database of Makunda Hospital, Assam, where health services are provided to people coming from Mizoram, different parts of Assam, Tripura and Meghalaya, and the preliminary results of an as unpublished results from a hospital based pregnancy cohort where pregnant mothers who have accessed regular antenatal care in Makunda (which supplements thiamine as part of routine antenatal and post-natal care) are followed up till one year after delivery along with their infants. No infants with thiamine deficiency were detected in supplemented mothers in this cohort.

<u>Probability values</u>

The probability values for the tree are approximations from the medical records database of

Makunda Hospital and the preliminary results of the pregnancy cohort. To avoid extreme data points in the model and division by 0 to derive incremental effectiveness, it was assumed that the probability of thiamine deficient infants who were born to multivitamin supplemented mothers is 0.0001 and the probability of non-Thiamine deficient infants born to supplemented mothers is 0.999.

The poor detection of thiamine deficiency in the community has implications for estimating true incidence and probability values in our population of interest. The probability of thiamine deficient infants who were born to un-supplemented high risk mothers was set at 0.008, as was reported in the literature (Barennes, 2015) and verified as feasible by local experts. The corresponding probability of non-Thiamine deficient infants born to un-supplemented mothers was thus set at 0.092.

The probability of Thiamine deficient infants who live is assumed to be 0.50 with the corresponding probability of Thiamine deficient infants who die from beriberi to also be 0.50. It is important to note that these probability values reflect approximation for real-world experience of beriberi survival and death in the North east of India. This is because much of the beriberi in the high-risk Northeastern population goes undetected, leading to infantile death, not as a consequence of poor treatment, but as a consequence of poor detection in the community and the near certainty of death in undetected cases.

Cost data

Cost parameters and data are provided in table 3 below:

Cost Parameters	
Intervention Costs	
Unit Cost of one pack of Multi-B tablets	43
Unit Cost of ANC Visit	403
Number of Becosule packs required for intervention	12
Number of ANC visits required for intervention	4
Total cost of intervention	2128
Usual Care costs	
unit cost ANC visit	403
Number of ANC visits assumed for usual care	3
Total costs of usual care	1209
Case costs	
Unit cost of OPD for beriberi presentation	403
Unit cost intensive thiamine treatment	360
Unit cost NICU Admission Charges per day	5109
Unit cost Discharge Medicine for home management	360
Unit cost follow-up appointment	403
Number of OPD visits per case	1
Number of intensive thiamine treatment courses per case	1
Average number of days in NICU per case	7
Number of follow-up appointments per case	2
Total cost per case of thiamine deficient neonate	37692

Table 1 Cost parameters and values

* Cost data was sourced from the Indian national Cost database and from Makunda hospital records

Clinical expert interviews were conducted to inform the intervention cost data within the model. The experts from Makunda Hospital prescribe one multi B vitamin capsule for 9 months (six months pregnancy and three months postpartum). The cost of the multi B vitamin capsule is taken from IndiaMart and listed in the supplementary materials. The cost of the intensive Thiamine intervention is taken from Makunda hospital records. The costs for ANC visits, OPD visits and NICU admission charges are taken from the Indian National Cost Database. The National Cost Database did not have the NICU cost per day so it is assumed to be the same as the ICU charges for the purpose of this model.

Outcome

The primary outcome measure was defined as life years saved derived from a baseline of average life expectancy of a healthy person in India of 70.8 years of life, according to the latest World Health Organization estimates from 2019

Base-Case Analysis

Based on best practice guidelines set by the WHO and the HTAIn reference case, one time gross domestic product per capita of India in 2023 is used as the cost-effectiveness willingness to pay (WTP) threshold. An incremental cost effectiveness ratio (ICER) below the WTP threshold was considered cost-effective.

3.1.3 Key model assumptions

Full adherence to the daily thiamine supplement regimen was assumed, based on adherence rates reported in the Makunda pregnancy cohort. Slightly higher ANC attendance in the intervention arm was also assumed whereby the routine care in the supplementation arm was structured to include 4 ANC visits per pregnant woman, as was observed in the Makunda cohort, and the usual care arm was structured to incorporate 3 ANC visits, as was reported as standard during pregnancy in those availing ANC through the Meghalaya Health Insurance Scheme (17). An assumption was made that any infant who developed beriberi with a case fatality of 100% would do so in the first 6 months of life as is reported in the literature (3). Those infants who develop beriberi were assumed to either be treated and survive in full health with no lasting morbidity, as clinical experts informed was the case, or to die of complications directly associated with this deficiency. The high mortality rate of beriberi is largely due to lack of clinical and community recognition of the symptoms of this condition, and the delay in detection and treatment. In order to adequately capture cost per case of beriberi in this model, each case is costed from the health system perspective where outpatient assessment, inpatient admission, high-dose thiamine treatment is administered, and follow-up care is provided. In reality, the probability of survival post treatment for detected infantile beriberi is close to 100% according to clinical experts and the published literature. However, both clinical experts and the published literature also indicate that due to the gross lack of awareness and recognition of beriberi, that case fatality is also close to 100% and those who are detected and treated successfully form a minority. In order to account for this dichotomy within the model, the probability of death post active infantile beriberi is set at 50%, which is likely to be an underestimate. However, the cost per case of beriberi also includes hospital-level detection, treatment, and management costs, when we know that majority of cases will go undetected and untreated and therefore incur no financial costs to the health system. Setting the probability of death/survival at 50% and assuming a standard cost per case of beriberi that includes hospital-level costs is intended to balance this low detection and high mortality with a need to capture the healthcare costs associated with cases of beriberi and not have zero health system costs assigned to active beriberi cases within the model.

3.2 Results

Population

The population of interest for this model was defined as all pregnant women in North East India in a given calendar year.

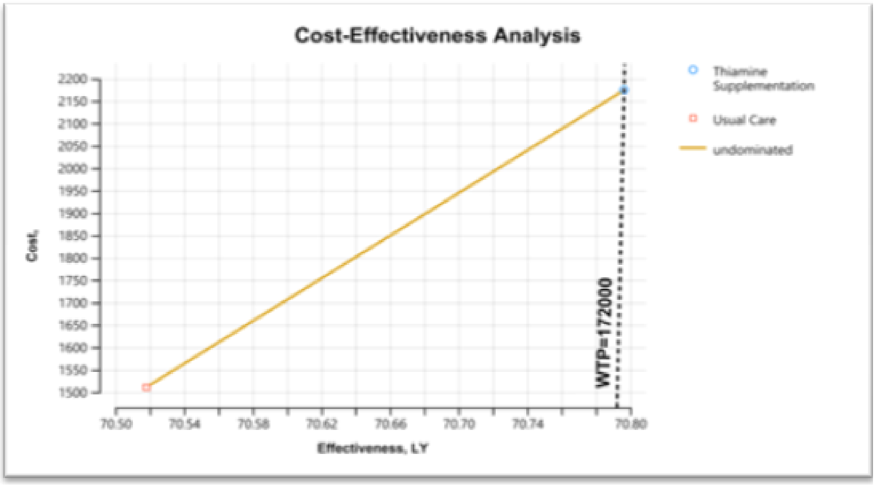
Base-Case Analysis

In the base-case, a regimen of 6 months antenatal and 6 months postnatal Thiamine supplementation of one Multivitamin per day was found to be highly cost effective at an ICER of INR 2386 per life year saved at a WTP threshold of INR 1, 72,000, as outlined in table 2 and represented pictorially in the cost effectiveness plan in figure 2.

Table 4. The Base-Case Results

Category	**Strategy**	**Cost**	**Incre. Cost**	**Effectiveness**	**Incremental Effectiveness**	**ICER**
Undominated	No Supplementation	1510.5		70.5		
Undominated	Thiamine Supplementation	2174.7	664.2	70.9	0.27	2386.2

Fig. 2 The Cost-Effectiveness Plane



Sensitivity Analysis

A deterministic sensitivity analysis was used to alter the primary parameter value of cost for the thiamine intervention and assess its impact on the ICER value. The intervention remained highly cost effective even when cost was inflated to 10x the base-case amount with an ICER of 72580.

4. Budget Impact Analysis

A budget impact analysis was conducted to calculate the approximate budget impact of implementing the intervention across the entire North East, based on multiplying the cost of multivitamin (the brand used as a prototype for the purpose of calculation is Becosules which has 10 mg Thiamine), the number of months of supplementation (6 months antenatal and 6 months postnatal), and the size of population of interest in each state. The number of pregnant women in Assam, Meghalaya, Mizoram and Tripura were taken from HMIS database for the year 2022. This is outlined in Table 5.

Table 5 Budget Impact Analysis

Name of Selected States	Total Number of Pregnant Women (2022)	Estimated Cost per State
Assam	920010	474725160
Meghalaya	80070	41316120
Mizoram	19110	9860760
Tripura	58560	30216960

To calculate the number of infantile beriberi cases that could be prevented in each state as a consequence of intervention implementation, the number of live births per state taken from HMIS database for the year 2022were multiplied by the estimated base-case probability of pregnant and lactating mothers who give birth to infants with beriberi which is 0.008.. This is outlined in Table 6 below.

Table 6 Infantile Berberi Cases Averted per State (2022)

Name of State	Number of Live Births Per State (2022)	Estimated Cases per State
Assam	739920	5919.36
Meghalaya	76330	610.64
Mizoram	17760	142.08
Tripura	52010	416.08

Results summary / Discussion

The literature review revealed a dearth of published evidence related to the incidence and prevalence of thiamine deficiency in pregnant and post-partum women. There were no published studies on cost effectiveness analysis in our population of interest either. In the systematic review, of the 801 studies screened only16 potential studies of interest were identified. But of these only one study from Cambodia reported on the primary outcome of interest; Infantile beriberi incidence and deaths among infants born to supplemented and un-supplemented mothers. All the 16 studies provided information only on clinical outcomes in confirmed cases of thiamine deficiency; these were not the primary outcome of interest in this CEA study.

Expert opinion interviews from four states in NER, were conducted in order to fill the gaps in published evidence and understand the experience of managing thiamine cases in the context of the northeast region of India. Qualitative data obtained from the expert interviews highlighted the complexity of thiamine deficiency and related morbidity and mortality in Northeast India, where clinical suspicion is low and case fatality rate is therefore high despite thiamine treatment efficacy in deficient states. Experts, particularly those doctors practicing in the rural areas reported that they do see cases. They said that thiamine deficiency in infants leads to cardiac and neurological symptoms with a 100% fatality rate if untreated. Diagnosis is challenging due to the lack of affordable tests, and thiamine administration often serves as a diagnostic tool. Possible contributing factors include, low socio-economic status, dietary habits and customary practices.

Considering the paucity of effectiveness data from India, some outcome evidence from a recent hospital cohort in Assam, NER provided data for the model. Based on the hospital (Makunda) data, it was found that there were no infant deaths reported in the cohort group of 489 mothers in who received Vitamin B supplementation and 4 deaths were reported in the un-supplemented mother's groups of 499 (control group). In addition, preliminary unpublished data (communication received by participating hospital) from an ongoing study by NIN reports thiamine deficiency for pregnant women to be 44% and in lactating women is 33%, indicating a much higher prevalence than previously suspected.

The primary outcome measure was defined as life years saved as a consequence of prevented infantile beriberi derived from a baseline of average life expectancy of a healthy person in India of 70.8 years of life and for the base-case analysis. One time gross domestic product per capita of India in 2023, 172000 rupees was used as the cost-effectiveness willingness to pay (WTP) threshold. A health system costing perspective was used and a one year time period was taken for the purpose of the study.

Results of the cost effectiveness model indicates that a routine of 6 months antenatal and 6 months postnatal Thiamine supplementation via one multivitamin per day containing 10 milligrams of thiamine is likely to be highly cost effective with an ICER of INR 2386 per life year saved at a WTP threshold of INR 1, 72,000 (1 x GDP).

The intervention is likely to be much more cost-effective than estimated in this study when accrued benefits to both infants and their mothers are taken into account; as this study took into account only benefits to infants.

Study Limitations

There are a number of limitations to this study that should be recognized. Firstly, there was a dearth of published data in relation to population prevalence of thiamine deficiency and associated probability of death in infants due to thiamine deficiency. Comprehensive cost studies were not able to be undertaken due to the lack of real-world data on thiamine supplementation provision for pregnant and lactating women in Northeast India. In the absence of this data, expert clinical opinion was used to inform a number of parameter values. Should the proposed thiamine supplementation intervention be implemented in the population of interest, a real-world longitudinal study of cost and clinical outcomes is recommended to monitor and evaluate its effectiveness in eliminating death due to beriberi in infants and their mothers in the Northeast.

CONCLUSION AND POLICY IMPLICATIONS

This model indicates that thiamine supplementation for pregnant and postpartum women in Northeast India is a highly cost-effective intervention to prevent infantile deaths due to beriberi with an ICER of INR 2386 per Life Years Gained at a WTP threshold of INR 1, 72,000

This is driven by the relatively high risk of thiamine deficiency in infants in this population (0.8 %) and the high rate of mortality from thiamine deficiency in infants in the Northeast. Thiamine supplementation is a cheap intervention and preliminary data from a hospital cohort indicates a high acceptability and efficacy rate by pregnant and lactating women adhering to this daily regimen.

There are important equity factors for this population that should also be considered in the context of policy, where thiamine deficiency is highly correlated with low socioeconomic status and under-nutrition, and is more common in women as compared to men due to the interaction of complex social and biological factors.

The intervention is likely to be much more cost-effective than estimated in this study when accrued benefits to both infants and their mothers are taken into account. Investment in implementing thiamine supplementation for pregnant and lactating mothers in the North East is recommended based on this study

ANNEXURE A: Key search terms

POPULATION	INTERVENTION	OUTCOME	MESH TERMS
Postpartum	Thiamine	Infant death*	**Population**
postpartum period	Aneur*	Infant mortality	Postpartum period
Postnatal	Vitamin B1	Newborn death*	Lactation
Perinatal	Thiamin*	Beriberi death*	Breast feeding
Peripartum	Thiamine Monophostate	Sudden infant death*	Pregnant Women
Lactat*	Nutrition		Pregnancy
Breastfed*	Micronutrients	Quality-adjusted life Years	**INTERVENTION**
Exclusive Breast Feeding	Vitamin B Complex	Disabilty-adjusted life Years	Thiamine
Pregnant Women	Thiamine intake	DALY	Beriberi
Pregnancy	Vitamin B1 Intake	QALY	Vitamin B complex
Mothers	Aneurine intake		
Women	Thiamine supplement*	Life-years gained	Thiamine Deficiency
Infant*	Thiamin supplement*	Beriberi	Micronutrients
Newborn	Vitamin B1 supplement*	Beri-beri	Thiamine Monophostate
Breastfed infant	Micronutrient supplement*	Beri beri	
Toddler		Infantile beriberi	
Bab*		Infantile cardiac beriberi	
Neonat*		Acute beriberi	
Infant, newborn		Infantile encephalitic beriberi	
Thiamine Deficien*			
Vitamin B1 deficien*			
Aneurin deficien*			
Aneurine deficien*			
Micronutrient Deficien*			

ANNEXURE B: Search Strings

Figure 1: Pubmed search string

((((("postpartum period"[MeSH Terms] OR ("lactation"[MeSH Terms] OR "Breast feeding"[MeSH Terms]) OR "Breast feeding"[MeSH Terms] OR "pregnancy"[MeSH Terms] OR "Pregnant women"[MeSH Terms] OR ("Breast feeding"[MeSH Terms] OR ("breast"[All Fields] AND "feeding"[All Fields]) OR "Breast feeding"[All Fields] OR "breastfeeding"[All Fields] OR "breastfeedings"[All Fields] OR "breastfeeders"[All Fields]) OR ("postnatal"[All Fields] OR "postnatally"[All Fields]) OR ("perinatal"[All Fields] OR "perinatally"[All Fields] OR "perinatals"[All Fields]) OR ("peripartum period"[MeSH Terms] OR ("peripartum"[All Fields] AND "period"[All Fields]) OR "peripartum period"[All Fields] OR "peripartum"[All Fields]) OR "Breast fed"[All Fields] OR "Exclusive breast feeding"[All Fields] OR "Exclusive breastfeeding"[All Fields] OR ("mother s"[All Fields] OR "mothered"[All Fields] OR "mothers"[MeSH Terms] OR "mothers"[All Fields] OR "mother"[All Fields] OR "mothering"[All Fields]) OR ("womans"[All Fields] OR "women"[MeSH Terms] OR "women"[All Fields] OR "woman"[All Fields] OR "women s"[All Fields] OR "womens"[All Fields])) AND ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "newborn"[All Fields] OR "newborns"[All Fields] OR "newborn s"[All Fields])) OR "Breastfed infant"[All Fields] OR ("toddler"[All Fields] OR "toddler s"[All Fields] OR "toddlers"[All Fields]) OR ("baby s"[All Fields] OR "babys"[All Fields] OR "infant"[MeSH Terms] OR "infant"[All Fields] OR "babies"[All Fields]) OR ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonatal"[All Fields] OR "neonate"[All Fields] OR "neonates"[All Fields] OR "neonatality"[All Fields] OR "neonatals"[All Fields] OR "neonate s"[All Fields])) AND "thiamine deficiency"[MeSH Terms]) OR "thiamine deficient"[All Fields] OR "Vitamin B1 deficiency"[All Fields] OR "Vitamin B1 Deficient"[All Fields] OR "Aneurin Deficiency"[All Fields] OR "Micronutrient deficient"[All Fields] OR "micronutrient deficiency"[All Fields]) AND ("thiamine"[MeSH Terms] OR "Vitamin B Complex"[MeSH Terms] OR "Micronutrients"[MeSH Terms] OR "thiamine monophosphate"[MeSH Terms] OR "Vitamin B1"[All Fields] OR ("thiamine"[MeSH Terms] OR "thiamine"[All Fields] OR "thiamin"[All Fields] OR "thiamines"[All Fields]) OR ("nutrition s"[All Fields] OR "nutritional status"[MeSH Terms] OR ("nutritional"[All Fields] AND "status"[All Fields]) OR "nutritional status"[All Fields] OR "nutrition"[All Fields] OR "nutritional sciences"[MeSH Terms] OR ("nutritional"[All Fields] AND "sciences"[All Fields]) OR "nutritional sciences"[All Fields] OR "nutritional"[All Fields] OR "nutritionals"[All Fields] OR "nutritions"[All Fields] OR "nutritive"[All Fields]) OR "Thiamine intake"[All Fields] OR "Vitamin B1 intake"[All Fields] OR "thiamine supplement"[All Fields] OR "Micronutrient supplement"[All Fields]) AND ("beriberi"[MeSH Terms] OR "infant"[MeSH Terms] OR "infant, newborn"[MeSH Terms] OR "infant death"[MeSH Terms] OR "infant mortality"[MeSH Terms] OR "quality adjusted life years"[MeSH Terms] OR "Sudden infant death"[MeSH Terms] OR "newborn death"[All Fields] OR "Disability adjusted life years"[All Fields] OR "DALY"[All Fields] OR ("quality adjusted life years"[MeSH Terms] OR ("quality adjusted"[All Fields] AND "life"[All Fields] AND "years"[All Fields]) OR "quality adjusted life years"[All Fields] OR "qaly"[All Fields]) OR "Life years gained"[All Fields] OR "beri beri"[All Fields] OR ("beriberi"[MeSH Terms]

OR "beriberi"[All Fields] OR ("beri"[All Fields] AND "beri"[All Fields]) OR "beri beri"[All Fields]) OR "infantile beriberi"[All Fields] OR "infantile cardiac beriberi"[All Fields] OR "acute beriberi"[All Fields] OR "Infantile encephalitic beriberi"[All Fields])

Figure 2: Scopus Search String

((((((((((((ALL=(Perinatal)) OR ALL=("Pregnant women")) OR ALL=("Exclusive Breastfeeding")) OR ALL=(mothers)) OR ALL=(women)) AND ALL=(newborn)) OR ALL=("Breastfed infant")) AND ALL=(Thiamine)) OR ALL=("Vitamin B complex")) OR ALL=("Vitamin B1")) OR ALL=("Thiamine intake")) AND ALL=("Infantile beriberi")) OR ALL=("Infantile cardiac beriberi"))

Figure 3: Web of Sciences String

((((((((TS=(women)) OR TS=(mothers)) OR TS=(infants)) OR TS=(postpartum)) AND ALL=(Thiamine)) OR ALL=("thiamine deficiency")) OR ALL=("thiamine supplementation")) AND ALL=("infantile beriberi")) OR ALL=(beriberi)

ANNEXURE C: Rating on the Quality of Studies

S No.	Authors name	Year	Study Type	Score	Total	Percentage
1	Gallant et al	2021	RCT	12	13	92
2	Bhatt et al	2016	Cohort	10	11	91
3	Luxemberg et al	2003	Cohort	11	11	100
4	Mcgready et al	2001	Cohort	8	11	73
5	Thankaraj et al	2020	Cross Sectional	6	8	75
6	Coats et al	2013	Quasi Experimental	7	9	78
7	Keating et al	2015	Case Control	10	10	100
8	Porter et al	2014	Case Control	8	10	80
9	Koshy et al	2020	Case Report	6	8	75
10	Panigrahy et al	2020	Case Series	8	10	80
11	Suryakanty et al	2021	Case Series	9	10	90
12	Samprathy et al	2020	Case Series	7	10	70
13	Quereshi et al	2015	Case Series	9	10	90
14	Satry et al	2021	Case Series	10	10	100
15	Barennes et al	2015	Case Series	10	10	100
16	Rao et al	2009	Case Series	9	10	90

ANNEXURE D- Interview Guide

Respondent Details

Name (optional):

Age: **Gender:**

Profession:

a. Qualification
b. Position:
c. Total years of experience
d. Location (Address/District/Block)
e. Hospital/Health Centre name:

1. **The prevalence of thiamine deficiency in their practice**
    - Do you see cases of thiamine deficiency in your practice?
    - If yes, how do they present?
    - What is the Local prevalence or local incidence of beriberi?
    - In children –
    - In mothers-
    - In others –
    - What are the manifestations of thiamine deficiency that you come across (wet beriberi, dry beriberi, **any other disorder (probe the nature of ailments)** etc)
2. **Criteria they use in making a diagnosis of thiamine deficiency**
    - When did you first start suspecting thiamine deficiency as a potential diagnosis? Were there some triggering incident?
    - What challenges do you face in making a clear diagnosis?
    - Can you give me an idea of how often you see such cases?
    - In the past one year how many would you have seen?
    - After you started seeing cases did you make any changes to your practice pattern? Such as routing supplementation> do explain….
3. Can you describe the general profile of patients coming to your centre with respect to thiamine deficiency?
    - Socio-economic background
    - Location- from other districts?
    - Age group of the patients
    - Common health complaints
4. Treatment approaches and challenges they face in managing Thiamine Deficiency

- What are the clinical symptoms/representations that you recommend thiamine as the treatment?
- Is tablet or IV administered? When is it administered?
- Is supplementation the first type of intervention provided or did you give some other treatment when thiamine deficiency cases are suspected?
- What according to you are the challenges when it comes to managing thiamine deficiency cases?
- Can you share any recommendations that you have towards the management of thiamine deficiency?

5. When you find a patient with thiamine deficiency showing symptoms/manifestations how will you rate their health status in below two scenarios
6. Are the deaths reported at the hospital in the last one year related to thiamine deficiency/beriberi?
7. Does thiamine supplement prevent death or just reduce likelihood?
8. What is the current Practice? Is it given to mothers or infants? Is it B1 alone or with other interventions?
9. The supplementation given to infants? Is it preventing or treating infants? Are all infants given this supplementation irrespective of having symptoms or not?
10. Do you see the Cross benefit that supplementing mother will prevent TD/infantile beri beri in infants?
11. Is it feasible for all neonates to be given thiamine? Would all mothers accept? Is there any risk?
12. Based on what you have seen with regard to thiamine deficiency what preventive measures would you suggest to prevent the deficiency in the given population? Elaborate.
13. Any other observation and recommendations on offer by the Clinical expert.

COST

- Complications due to beriberi and associated management (e.g. hospitalization, seen by specialists, medications required, etc – all interactions that are associated with a cost!)
- What is the cost of the thiamine intervention itself?
- In the absence of direct quality of life estimates for beriberi, are there other clinical conditions which the clinicians see as similar in terms of decreased quality of life and risk of death, such as deficiency in another vitamin? Or perhaps malnutrition more generally?

REFERENCES

1. Martel JL, Kerndt CC, Doshi H, Franklin DS. Vitamin B1 (Thiamine) [Internet]. StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482360/

2. Whitfield KC, Smith G, Chamnan C, Karakochuk CD, Sophonneary P, Kuong K, et al. High prevalence of thiamine (vitamin B1) deficiency in early childhood among a nationally representative sample of Cambodian women of childbearing age and their children. Tickell KD, editor. PLoS Negl Trop Dis. 2017 Sep 5;11(9):e0005814.

3. World Health Organisation. Thiamine deficiency and its prevention and control in major emergencies [Internet]. World Health Organisation; 1999 [cited 2021 May 10] p. 1–52. Available from: https://www.who.int/nutrition/publications/en/thiamine_in_emergencies_eng.pdf

4. Nazir M, Lone R, Charoo BA. Infantile Thiamine Deficiency: New Insights into an Old Disease. Indian Pediatr. 2019 Aug;56(8):673–81.

5. Johnson CR, Fischer PR, Thacher TD, Topazian MD, Bourassa MW, Combs GF. Thiamin deficiency in low- and middle-income countries: Disorders, prevalences, previous interventions and current recommendations. Nutr Health. 2019 Jun;25(2):127–51.

6. Hilal Ahmad S, Ahmad SB, Jan A. Thiamine deficiency related peripheral neuropathy in peripartum women of Kashmir, India: a hospital based study. Int J Adv Med. 2019 May 24;6(3):662.

7. Ahoua L, Etienne W, Fermon F, Godain G, Brown V, Kadjo K, et al. Outbreak of Beriberi in a Prison in Côte D'Ivoire. Food Nutr Bull. 2007 Sep;28(3):283–90.

8. Luxemburger C, White NJ, Ter Kuile F, Singh HM, Allier-Frachon I, Ohn M, et al. Beri-beri: the major cause of infant mortality in Karen refugees. Trans R Soc Trop Med Hyg. 2003 Mar;97(2):251–5.

9. Tiamkao S, Boonsong A, Saepeung K, Kasemsap N, Apiwattanakul M, Suanprasert N, et al. An Outbreak of Peripheral Neuropathy in a Prison. Case Rep Neurol. 2019 Feb 26;11(1):53–60.

10. Watson JT, El Bushra H, Lebo EJ, Bwire G, Kiyengo J, Emukule G, et al. Outbreak of Beriberi among African Union Troops in Mogadishu, Somalia. Morgan D, editor. PLoS ONE. 2011 Dec 21;6(12):e28345.

11. Bhat JI, Rather HA, Ahangar AA, Qureshi UA, Dar P, Ahmed QI, et al. Shoshin beriberi-thiamine responsive pulmonary hypertension in exclusively breastfed infants: A study from northern India. Indian Heart J. 2017 Jan;69(1):24–7.

12. Malsawma J. Infantile Beri Beri: The Mizoram Experience. Indian Pediatr. 2020 Apr 15;57:376–7.

13. Koshy RM, Thankaraj S, Ismavel VA, Solomi CV. The rediscovery of thiamine deficiency disorders at a secondary level mission hospital in Northeast India. Ann N Y Acad Sci. 2021 Aug;1498(1):96–107.

14. Shajin Thangkaraj, Roshine Koshy, Vijayanand Ismavel. Infantile Cardiac Beri beri in Rural Northeast India. Indian Pediatr. 2020 Sep 15;57:859–60.

15. JBI [Internet]. JBI- Critical Appraisal Tools. Available from: https://jbi.global/critical-appraisal-tools

16. Johnson LE. Merk Manual Consumer Version. Thiamine Deficiency. Available from: https://www.merckmanuals.com/home/disorders-of-nutrition/vitamins/thiamin-deficiency#:~:text=Thiamin%20deficiency%20(causing%20beriberi%20and,people%20with%20alcohol%20use%20disorder

17. Dutta EK, Kumar S, Venkatachalam S, Downey LE, Albert S. An analysis of government-sponsored health insurance enrolment and claims data from Meghalaya: Insights into the provision of health care in North East India. Sharma GA, editor. PLOS ONE. 2022 Jun 3;17(6):e0268858.