# Health Technology Assessment for Implementation of cell counters (Haematology Analysers) for diagnosing suspected dengue cases at Primary Health Care settings in Tamil Nadu

2019

## Conducted by


Regional Resource Centre for HTAIn
ICMR-National Institute for Research in Tuberculosis
No.1, Mayor Sathiyamoorthy Road
Chetpet, Chennai – 600 031
INDIA

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**Resource Centre for**

**Health Technology Assessment in India (HTAIn)**

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**Chennai, India**

# Study Team


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|---|---|---|
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## Abbreviation

| | |
|---|---|
| ELISA | Enzyme Linked Immunosorbent Assay |
| QALY | Quality Adjusted Life Year |
| ICER | Incremental Cost Effectiveness Ratio |
| PSA | Probabilistic Sensitivity Analysis |
| DENV | Dengue Virus |
| RNA | Ribonucleic Acid |
| NS1 | Non – Structural Protein 1 |
| DF | Dengue Fever |
| DHF | Dengue Haemorrhagic Fever |
| DSS | Dengue Shock Syndrome |
| IgG | Immunoglobulin G |
| IgM | Immunoglobulin M |
| MAC-ELISA | IgM Antibody Capture Enzyme-Linked Immunosorbent Assay |
| ICT | Immuno-Chromatographic Test |
| TT | Tourniquet Test |
| PCR | Polymerase Chain Reaction |
| NVBDCP | National Vector Borne Disease Control Program |
| IDSP | Integrated Disease Surveillance Program |
| VRDL | Virus Research and Diagnostic Laboratories |
| RDT | Rapid Diagnostic Test |
| NSAIDs | Nonsteroidal Anti-inflammatory Drugs |
| CBC | Complete Blood Count |
| WBC | White Blood Cells |
| PHC | Primary Health Centre |
| WHO | World Health Organization |
| THC | Tertiary Health Centre |

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## ABSTRACT

**Background:** The burden of dengue in India is high due to its high prevalence and high mortality rate. Lack of effective early screening is the major obstacle for reducing the fatality rate of dengue. At present dengue control in Tamil Nadu is being prioritized to strengthen diagnostic services and surveillance. One of the strategy adopted by the Government of Tamil Nadu is to implement blood platelet counter for screening of dengue at PHC settings in Tamil Nadu. Under this strategy the present delay in diagnosing dengue at an earlier stage is prioritized, which could help in reduction of dengue morbidity and mortality.

**Methods:** Decision tree analysis was used to estimate the cost-effectiveness of strategies to screen, detect early and treat dengue in the population. The cost-effectiveness analysis was performed for the proposed and current strategy. The outcomes are expressed in incremental cost-effectiveness ratios (ICERs) per quality-adjusted life years (QALYs). Discount rate of 3% was applied for cost and QALYs.

**Results:** Implementation of haematology analyser at PHC is cost saving. The ICER was estimated to be -41197 for proposed strategy over current strategy. Average incremental net monetary benefit (INMB) for the proposed strategy over control strategy was estimated to be ₹6105504. Sensitivity analysis showed the given parameter namely utility of DHF and DSS dengue patients, indirect cost of fatal cases, life expectancy of the cohort, non-medical cost of non-fatal cases, hospitalisation cost and ambulatory cost of non-fatal cases had higher influence on ICER value. However, with 20% change in these variable values, proposed strategy was still the economically dominant strategy. Probabilistic Sensitivity Analysis (PSA) found that 84% of the resulting ICER value was less costly and more effective. Budget Impact Analysis (BIA) showed the additional budget requirement by the government in the base year for implementation of the proposed screening strategy is ₹574093041. However, increasing cost effectiveness trend was observed on 5 year projection.

**Conclusion:** The proposed screening strategy for dengue at PHC level was found to be less costly and more effective than the current strategy. This was mainly due to the reduction in the number of deaths and severe dengue cases as a result of early detection and management in proposed strategy.



**Keywords.** Dengue; QALY; cost-effectiveness; treatment; screening

# 1. INTRODUCTION

## 1.1. Global burden

Dengue is the most common vector borne infection globally, with an estimated 100 to 400 million infections occurring every year.[1] Dengue is a major public health concern throughout tropical and subtropical regions of the world and South East Asia Region contributing 52% of the disease burden.[2] Dengue infection is increasingly driven by trade, travel, urbanization and climate change.[3] The causative organism for dengue is single positive standard RNA virus of the family Flaviviridae, genus Flavivirus with either one or more of the four closely related serotypes, such as DENV-1, DENV-2, DENV-3 and DENV-4. Dengue fever is a vector borne disease and the infection is transmitted through mosquitoes belonging to two species i.e. *Aedes aegypti* and *Aedes albopictus*.[1] The *Aedes aegypti* mosquitoes breed in artificial containers with water (Ex. cement tanks, overhead tanks, underground tanks, tyres, desert coolers, pitchers, discarded containers, junk materials, etc), whereas, *Aedes albopictus* mosquitoes breeds in natural habitats such as tree holes, plantation etc.[4] So far there is no effective vaccine or medicine available to prevent or cure dengue. It was reported that globally, deaths due to dengue between 2000 to 2015 increased from 960 to 4032.[1] Although, estimates of dengue deaths are less often reported, the most commonly cited number is around 20,000 deaths per year.[5] Symptomatic dengue infections have a broad range of severity and as many as 70% of patients choose not to seek treatment or treat themselves.[6] Even among symptomatic cases, the clinical characteristics of dengue may mimic other disease characteristics, which increases the probability of misdiagnosis.

### 1.2. Burden of dengue in India

India is one of the country with high dengue burden and contributes around 34% of the global burden.[7] Most Indian states have been classified as having frequent or continuous risk of dengue transmission. A meta-analysis of published studies from India estimated, a dengue case fatality ratio of 2.6%.[8] Although dengue is a notifiable disease in India, studies and modelling estimate suggests that the disease is grossly under reported. It has been found that the national vector-borne disease control programme (NVBDCP) has under reported the dengue cases due to the gaps in diagnosis and existing public health surveillance systems.[9,10]

### 1.3. Dengue Control in India

Dengue has an endemic presence in many states of India and leads to increased hospitalization. While dengue was more reported in urban areas in past, currently the distribution has increased in both peri-urban and rural areas.[7,11] Dengue surveillance in India is conducted through a network of more than 600 sentinel hospitals under the NVBDCP, Integrated Disease Surveillance Program (IDSP) and a network of 52 Virus Research and Diagnostic Laboratories (VRDL).[12] The NVBDCP reported more than 100,000 laboratory confirmed cases of dengue in 2016.[13] High dengue disease burden and frequent outbreaks result in an adverse impact on country's economy and strain the health systems. So far case detection, case management, and vector control are the main strategies for prevention and control of dengue virus transmission. A new dengue vaccine is now available and several vaccines are in the process of development.[14]

NVBDCP, Government of India recommends use of enzyme linked immunosorbent assay (ELISA) based antigen detection test (NS1) for diagnosing the cases from first day onwards and antibody detection test immunoglobulin M (IgM) capture ELISA (MAC-ELISA)

for diagnosing the cases after fifth day of onset of disease. A number of rapid diagnostic test (RDT) kits for NS1 antigen and anti-dengue IgM/IgG antibodies are commercially available at present, which produces the results within 15-25 minutes. However, the accuracy of these diagnostic tests is not known since they have not yet been properly validated. RDTs have been independently evaluated, the results showed a high rate of false positive when compared to standard tests. The sensitivity and specificity of RDTs are also found to vary largely.[15,16] Hence, currently, use of RDT is not recommended under the NVBDCP program. Approach to clinical management of dengue fever (DF) may vary from mild, moderate and aggressive states depending on severity of illness. Patients who have fever without any warning signs or complications may be managed with clinical management. Those who have warning signs should be managed with close monitoring for progression to dengue hemorrhage fever (DHF) or dengue shock syndrome (DSS) or severe bleeding. The patients presenting with significant bleeding or involvement of various organs in Grade-III (Circulatory failure manifested by a rapid, weak pulse and narrowing of pulse pressure or hypotension, with the presence of cold, clammy skin and restlessness) and Grade-IV (Profound shock with undetectable blood pressure or pulse) will require aggressive management to reduce morbidity and mortality. Patient may develop more complications during later stage of fever effervescence (the critical phase of dengue) or afebrile phase (who presents without fever but with severe myalgia). Management of dengue fever is based on symptoms and supportive treatment. Patients should be monitored for 24-48 hours in DHF endemic areas until they become afebrile without the use of antipyretics and after haematocrit determinations are stable, platelet count is >50,000/$mm^3$ or improving.[17]

The diagnosis of dengue is usually made clinically. The classic picture is high fever with no localizing source of infection, a petechial rash with thrombocytopenia and relative

leukopenia (low platelet and white blood cell count). Care has to be taken as diagnosis of DHF can mask end stage liver disease and vice versa. If one has persistent fever for more than two days then they should go for a complete blood count (CBC) check-up. If the low platelet count (less than 100,000 per $mm^3$) and white blood cell count (WBCC) are below than their usual range one should go for dengue antigen test.

There is no specific anti-viral drug against dengue infection. Mortality can be minimized by early diagnosis and prompt symptomatic management of the cases. Guidelines for clinical management of DF, DHF, and DSS have been developed. The main components for prevention and control of dengue are: (1) surveillance (disease and entomological surveillance); (2) case management (laboratory diagnosis and clinical management); (3) vector management (environmental management for source reduction, chemical control, personal protection and legislation); (4) outbreak response (epidemic preparedness and media management); (5) capacity building (training, strengthening human resource and operational research); (6) behaviour change communication (social mobilization and information education and communication); (7) inter-sectoral coordination (with ministries of urban development, rural development, panchayati raj, surface transport and education sector); (8) monitoring and supervision (analysis of reports, review, field visit and feedback intensive health education activities through print, electronic and inter personnel media, outdoor publicity as well as an inter-sectoral collaboration with civil society organization, panchayati raj institutions and municipal bodies have been emphasized).

### 1.4. Diagnosis of Dengue

The clinical diagnosis of dengue is complex due to non-specific symptoms and symptoms similar to other infections. Dengue infection is characterized into three phases, i.e., febrile

phase, critical phase and convalescent phase. Dengue viral infection is defined as either symptomatic or non-symptomatic. The symptomatic infection is categorized into four classifications, such as undifferentiated fever, DF, DHF and DSS.[18] Currently World Health Organization recommends tourniquet test to diagnose dengue during the first 2-7 days of the initial, acute, febrile phase.[19] The clinical diagnosis of dengue may be confirmed by laboratory testing by the measurement of an antibody response IgM or IgG and by ELISA considered to be the diagnostic gold standard.[20] Newer diagnostic tests also includes reverse transcriptase polymerase chain reaction (PCR) or direct antigen detection (non-structural protein 1). While these tests are likely to offer an improvement in diagnostic accuracy, the cost and current limitation of not detecting all serotypes limits their application.

### 1.5. Burden of dengue in Tamil Nadu

The epidemiology of dengue is complex, which involves interaction between host (man and mosquito), agent (virus) and the environment (abiotic and biotic factors). Since the last two decades, twenty nine states and six union territories in India have been reported to have dengue cases.[21] Most severe dengue fever outbreaks occurred during 1996 and 2006 in India which reported positive cases of 16,517 and 12,317 with fatality rate of 3.3% and 1.5% respectively.[22] The burden of dengue in India especially Tamil Nadu is high due to its high prevalence and high mortality rate. A recent study reported that case fatality rate of dengue among general population is 56.9%.[8] This was higher than that of the fatality rate of laboratory confirmed dengue patients which is 2.6%.[8] Lack of effective early screening is the major obstacle for reducing the fatality rate of dengue. Hence, implementation of screening facilities at the primary health care (PHC) level will help identify dengue cases earlier and will avoid morbidity and mortality. Thrombocytopenia which is sudden reduction of platelet in blood, one of the chief characteristic of DHF which leads to mortality. Therefore, screening of dengue suspects

by monitoring their blood platelet level will be promising in identifying the dengue virus infection at the earliest, which will prevent the disease progression and death.

### 1.6. Economic Burden

Dengue is a serious global health endemic problem in developing country, affecting millions of people every year and causing disability and death. Cost of the disease includes direct medical expenses and also indirect costs incurred from impaired quality of life and the loss of work productivity. An inter-state study in India assessed that the median cost of treatment per hospitalized dengue patient was $432 and the average total economic burden was estimated to be $27 million.[23] Another study in India showed total average cost for dengue treatment per household in government and private facilities to be around ₹668 and ₹14,288 respectively, which implies the costs in private hospitals for dengue treatment are higher than the costs in government hospitals by 95%.[24] It was reported that total direct annual medical cost in India in ambulatory settings was $99 million and hospitalized cases comprising of $449 million.[25] A systematic review conducted in India reported that an estimate average direct cost per case of dengue ranged between $24 and $161 and the indirect cost was around $25 whereas the average cost of hospitalization ranged between $186 and $432. The cost of dengue treatment in the private health sector was two to four times higher than that in the public sector hospitals. It was also estimated that the average total economic burden due to dengue in India was $27 million.[8] The overall economic burden of dengue would be even higher if the cost borne by individual patients is combined with the societal level cost of dengue prevention, vector control, disease control, and dengue surveillance as well as the cost of research and development.

### 1.7. Rationale for the study

One of the major hindrance in the control and management of dengue infection is the lack of timely and point-of-care diagnosis. The complex clinical presentation of dengue symptoms and lack of rapid screening and diagnostic tests results in delay in diagnosis and leads to rapid disease progression and mortality. At present dengue control in Tamil Nadu is being prioritized to strengthen diagnostic services and surveillance. One of the strategy adopted by the Government of Tamil Nadu is to implement blood platelet counter for screening of dengue at PHC settings in Tamil Nadu. Under this strategy the present delay in diagnosing dengue at an earlier stage is prioritized which could help in reduction of dengue morbidity and mortality.

### 1.8. Research Questions

To find out whether using hematology analyzer at primary health care facilities is a cost-effective strategy for dengue screening?

### 1.9. Objective

- To estimate the quality adjusted life years (QALYs) gained as a result of screening dengue suspects at primary health care facilities by monitoring platelet level.
- To estimate the incremental cost incurred as a result of screening dengue suspects at primary health care facilities by monitoring platelet level.
- To estimate the incremental cost effectiveness ratio (ICER) as a result of screening dengue suspects at primary health care facilities by monitoring platelet level.

## 2. METHODOLOGY

### 2.3 Study Population

Our study population represents a hypothetical cohort of 1000 individual with fever suspected for dengue. The population is considered representative of Tamil Nadu State, with a total population of 82,439,997 based on census 2011 projected population, which is economically well-developed and urbanised. Between 2013 to October 2020 a total of 48551 dengue cases and 102 deaths were reported in Tamil Nadu[26].

### 2.2 Study setting

The NVBDCP is implemented in Tamil Nadu as a vertical program under the National Health Mission (NHM). Under NVBDCP, thirty sentinel surveillance hospitals for dengue are established as part of the public sector that can offer access to quality assured testing. The present program in the state ensure the availability of dengue diagnostic services at district level and further aims to expand till sub-district level at PHC level in a phased manner.

### 2.3 Study Design

This study is a model based estimation of incremental costs and QALYs gained by introduction of screening intervention for dengue at PHC level in comparison to current strategy for dengue screening in Tamil Nadu, India.

### 2.4 Study Perspective

The cost-effectiveness modelling is conducted primarily from societal perspective, which includes cost incurred by the health system and costs incurred by the individual with symptoms suggestive of dengue who access diagnostic services at public health facilities.

### 2.5 Comparator and time horizon

The present model compares the costs and outcomes of decentralized screening strategies for dengue at PHC facilities with the current practice implemented in tertiary level. A single episode of dengue infection with life time horizon is considered for the effectiveness and cost estimation. Global discount rate of 3% was incorporated for both the cost and consequences. This model characterizes the health state of the population and the population was followed till cure or death. In addition, life years gained, death averted and quality of life of patients were also taken into consideration.

### 2.6 Model assumption

This economic evaluation model was conceptualized based on the natural history of dengue infection followed by ambulatory or hospitalization based treatment and care. The present model considered two different scenarios, which included the current screening strategy used for dengue diagnosis under the NVBDCP at THC level. The intervention scenario considered a strategy in which dengue screening will be performed at the PHC level. This strategy is considered as decentralized strategy, in which a point-of-care screening is provided for those who access PHC services for fever. Both the scenarios involve a confirmatory Enzyme Linked Immunosorbent Assay (ELISA) test for dengue. The cost inputs and outcomes of the two screening strategies were modelled using a decision tree. The specific assumptions used for model were:

i. Two repeat dengue screening test (Platelet count) each at 2 days interval with ELISA test for those with >100000 platelet count in proposed strategy (Proposed strategy by Government of Tamil Nadu)

ii. One repeat dengue screening test (Platelet count) at 2 days interval with ELISA test for those with >100000 platelet count in current strategy is considered for dengue diagnosis. (NVBDCP and expert opinion)

iii. 50% reduction in severe dengue cases (DHF and DSS) due to early diagnosis in proposed strategy. (Based on expert opinion)

iv. No loss-to-follow up in screening, diagnosing and treatment cascade (Considered in both strategies as there is no available data on loss to follow up details)

### 2.7 Model structure

The present study utilised an economic model to calculate ICER for the current and proposed dengue screening strategy. The ICER is calculated from the cost and QALYs of the two different strategies for dengue diagnosis. The strategies considered for dengue diagnosis is summarized in Table-1.

**Table 1. Different screening strategies for dengue screening**

| Strategies | Level of implementation | Diagnostic Tool | Population | Frequency of screening | Referral |
|---|---|---|---|---|---|
| **Proposed Strategy** | Primary Health Care (PHC) | Complete Blood Count (CBC) for platelet level | Persons with febrile illness and warning signs | Repeat CBC at 2nd & 4th days, If Platelet count >100000 | Tertiary for ELISA, If ELISA positive repeat CBC twice a day & hospitalize |
| **Comparator** | Tertiary Health Care (THC) | CBC & Enzyme Linked Immuno-Sorbent Assay (ELISA) | Persons with febrile illness and warning signs | Repeat CBC once for self-reporting patients at 2 days interval, If Platelet count >100000 | If ELISA positive repeat CBC twice a day & hospitalize |

## 2.8 Current Strategy

Patient with 2-5 days of febrile illness having two or more of the following symptoms- head ache, retro orbital pain, myalgia, arthralgia, rash and hemorrhagic manifestation are considered as dengue suspects. The suspects approaching the PHC facility were referred to tertiary hospitals for diagnosis. At the tertiary care hospital the symptoms are managed along with dengue diagnosis. Dengue diagnosis in tertiary care hospital is done by testing platelet count ($<100000/mm^3$) for screening and ELISA test for conformation. During treatment the patient will be subjected to continuous monitoring for the reduction in the blood platelet count at tertiary health care facilities.

## 2.9 Proposed Strategy

For early diagnosis of dengue, it is proposed to screen the dengue suspects at PHC level using hematology analyzer. Platelet count is assessed and those with less than $100000/mm^3$ will be referred to the tertiary health care facility for further management. In dengue suspects with more than $100000/mm^3$, platelet count will be re-assessed at two days interval. A Maximum of two times repeat platelet count will be undertaken to rule out dengue.

## 2.10 Decision Tree Model

Decision model planned for this study is constructed based on the natural progression of dengue and its diagnostic cascade (Figure-1).[27,28,29,30] The proposed strategy is decentralized as compared to the standard diagnostic strategy under the NVBCDP. Both strategies were modelled as two parallel trees using probabilities associated with the dengue diagnosis, treatment and outcome. Patient diagnosed with dengue in each strategy were further classified based on the disease severity in to three disease states which includes Dengue fever (DF), Dengue Haemorrhagic fever (DHF) and Dengue Shock Syndrome (DSS). In each disease state

the considered outcomes are survival after hospitalization, survival after ambulatory treatment and death. Microsoft excel spread sheet and Tree-Age software (Licensed version 2020 R 1.0) is used for analysis.

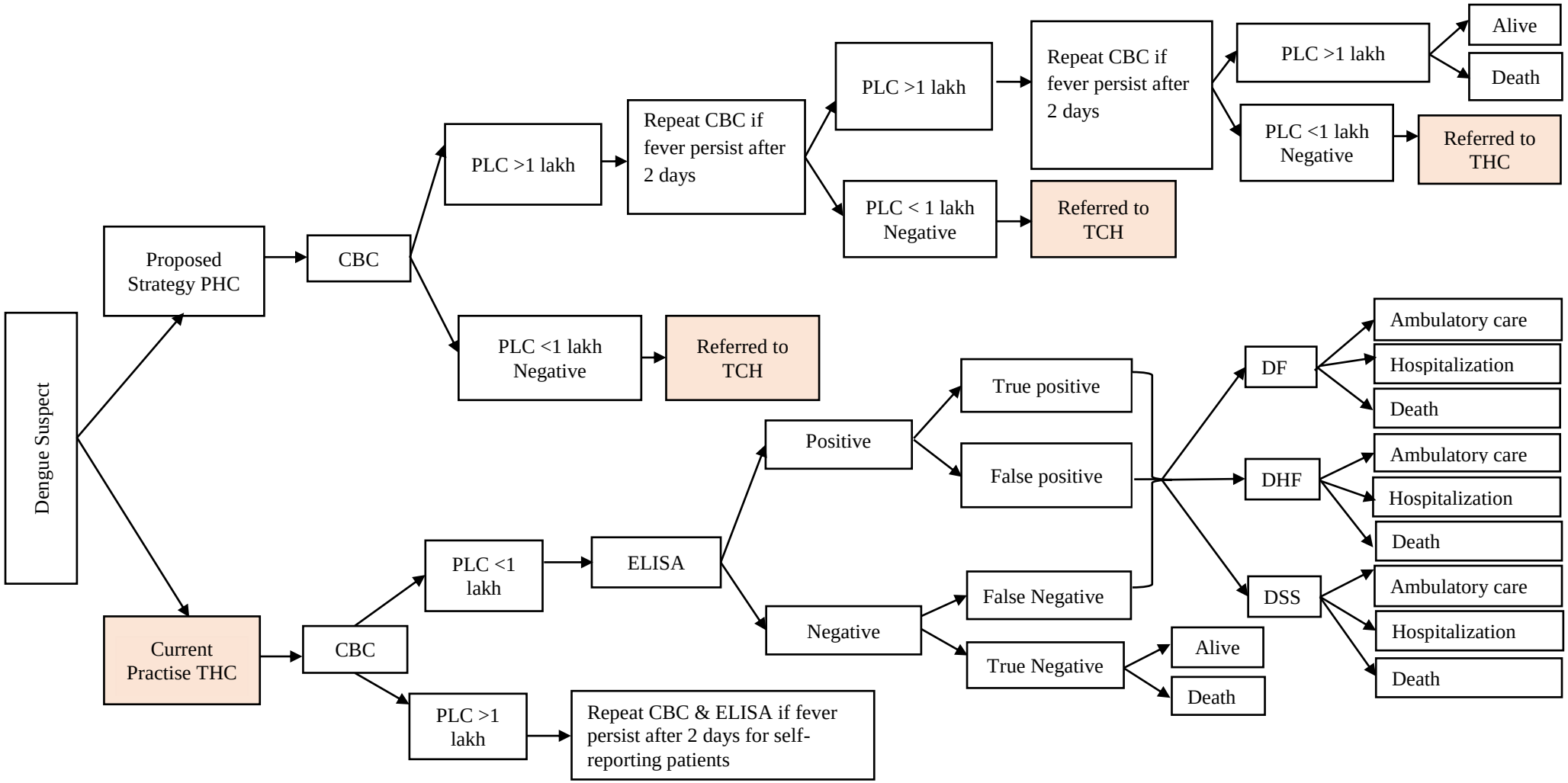
### 2.11 Model input parameters

The key input parameters for the model includes: demographic,[8] prevalence of dengue,[8] prevalence dengue suspects[31], sensitivity and specificity of ELISA, health state probability of DF, DHF and DSS[32], death due to dengue[8], all-cause mortality[33], probability of cure[34], quality of life score for different health states[35], health system and patient cost incurred for dengue diagnosis and treatment[32, 36]. All these information were extracted from the published literature and NVBDCP reports. Table-2 presents the input parameter values used in the analysis with 20% upper and lower limits along with their distribution.

### 2.12 Cost Data

Cost data was used from a meta-analysis report of the published studies from India. The average cost of dengue non-fatal and dengue fatal cases estimated in the report includes health system cost, patient out-of-pocket expenditure and productivity loss. Information on health system costs such as per CBC test cost and ELISA test cost is obtained from Central Government Health Scheme (CGHS 2014) rates published by Government of India. All the costs abstracted were adjusted for the year 2019. Total cost incurred for a dengue patient in a single disease episode is calculated separately in each strategy.

**Figure 1**. **Decision tree for dengue screening at primary level as compared to tertiary care level**



### 2.13 Effectiveness Data

Health outcomes is determined in terms of number of suspects diagnosed with dengue infection and related quality of life scores. Quality of life utility values for each stage of dengue infection for DF, DHF and DSS taken from recently published study.[35] Since, the utility score for each stage of dengue infection was not available for India; we used contextually relevant data from an Asian country. Treatment outcome in terms of cured and mortality is taken from the published meta-analysis based on the Indian studies.[8]

### 2.14 Other data

Life expectancy was taken from the India's life table published based on Sample Registration System (SRS) data. Start age of cohort in the model was 22 years, which was based on the mean age of dengue patients during the time of diagnosis. Mean age of dengue infection and prevalence of dengue data were used form the recent published Indian specific meta-analysis on dengue infection in India.

**Table 2. Input parameters used for model based cost-effectiveness analysis of dengue screening at PHC level**

| | Parameters | To model | Lower | Upper | Distribution | Source |
|---|---|---|---|---|---|---|
| **Demographic values** | Average age of dengue suspect | 22 | NA | NA | NA | 8 |
| | Life Expectancy for average age of dengue suspect | 53 | 42.4 | 63.6 | Normal | Life Table |
| | Cohort population | 1000 | NA | NA | NA | Assumption |
| **Prevalence** | Sero prevalence of dengue | 0.383 | NA | NA | NA | 8 |
| **Mortality** | Probability of All-cause mortality for the average age of dengue suspect | 0.006 | 0.005 | 0.007 | Beta | Life Table |
| | Probability of death due to dengue in current strategy | 0.026 | NA | NA | NA | 8 |

| | Parameters | To model | Lower | Upper | Distribution | Source |
|---|---|---|---|---|---|---|
| | Probability of death due to dengue in early screening | 0.010 | NA | NA | NA | 1 |
| | Probability of death due to DF | 0 | 0 | 0 | NA | Assumption |
| | Probability of death due to DHF in current strategy | 0.010 | 0.008 | 0.012 | Beta | Estimated |
| | Probability of death due to DSS in proposed strategy | 0.015 | 0.012 | 0.018 | Beta | Estimated |
| | Relative risk of mortality due to DHF in proposed strategy | 0.380 | 0.300 | 0.460 | Beta | Estimated |
| | Relative risk of mortality due to DSS in proposed strategy | 0.380 | 0.300 | 0.0460 | Beta | Estimated |
| **CBC test** | Probability of <100000 platelet count in presence of warning signs | 0.710 | 0.568 | 0.852 | Beta | 31 |
| | Probability of CBC test positive | 0.399 | 0.319 | 0.478 | Beta | Estimated |
| **ELISA test** | Sensitivity | 0.77 | NA | NA | NA | 7 |
| | Specificity | 0.94 | NA | NA | NA | 7 |
| | True positive | 0.888 | 0.704 | 1 | Beta | Estimated |
| | True negative | 0.868 | 0.694 | 1 | Beta | Estimated |
| **Disease state Probability** | Lab confirmed to be DF in current strategy | 0.77 | 0.616 | 0.924 | Beta | 8 |
| | Lab confirmed to be DHF in current strategy | 0.18 | 0.144 | 0.216 | Beta | 8 |
| | Lab confirmed to be DHF in proposed strategy | 0.09 | 0.072 | 0.108 | Beta | Assumption |
| | Lab confirmed to be DSS in current strategy | 0.05 | 0.04 | 0.06 | Beta | 8 |
| | Lab confirmed to be DSS in proposed strategy | 0.025 | 0.02 | 0.03 | Beta | Assumption |
| | Outpatients among patients with DF | 0.68 | 0.544 | 0.816 | Beta | 32 |
| | Outpatient among patients with DHF | 0.26 | 0.208 | 0.312 | Beta | 32 |
| | Outpatient among patients with DSS | 0 | 0 | 0 | NA | 32 |
| **Utility value** | Utility for death | 0 | 0 | 0 | NA | By Definition |
| | Utility for Undifferentiated fever | 0.91 | 0.728 | 1 | Beta | Assumption |

| | Parameters | To model | Lower | Upper | Distribution | Source |
|---|---|---|---|---|---|---|
| | Utility for DF | 0.91 | 0.728 | 1 | Beta | Assumption |
| | Utility for DHF | 0.66 | 0.528 | 0.792 | Beta | 34 |
| | Utility for DSS | 0.41 | 0.328 | 0.492 | Beta | Assumption |
| **Diagnostic Cost** | Cost of CBC per test (in INR) | 153.65 | 122.92 | 184.38 | Gamma | CGHS |
| | Cost of ELISA per test (in INR) | 314.85 | 251.88 | 377.82 | Gamma | CGHS |
| **Treatment** | Cost of ambulatory not fatal disease per case (in INR) | 2896.78 | 2317.42 | 3476.13 | Gamma | 34 |
| | Cost of hospitalized not fatal disease per episode (in INR) | 21816.20 | 17452.96 | 26179.44 | Gamma | 34 |
| | Non-Medical cost per non-fatal case in current strategy (in INR) | 1260.20 | 1008.16 | 1512.24 | Gamma | 34 |
| | Non-Medical cost per non-fatal case in proposed strategy | 630.10 | 504.08 | 756.12 | Gamma | Assumption |
| | Direct fatal cost per case | 5186.11 | 4148.88 | 6223.33 | Gamma | 34 |
| | Indirect fatal cost per case | 2730021.97 | 2184017.56 | 3276026.35 | Gamma | 34 |
| **Willingness to pay threshold** | Willingness to pay threshold (GDP per capita) (in INR) | 135966 | - | - | NA | 50 |

## 2.15 Model outcomes

The outcomes of the model are expressed in terms of QALYs, life years gained and overall cost incurred per patient in both, intervention and comparator scenario. Model also compared incremental cost with incremental QALYs to obtain ICER. Further, ICER was compared with a threshold of one-time Gross Domestic Product (GDP) per capita of India to determine its cost-effectiveness[37]. We also calculated net monetary benefit (NMB) and additional budget required for implementing hematology analyzers for screening dengue suspects at PHC level.

## 2.16 Base case analysis

Cohort size of 1000 individuals entered the decision analytic model for the estimation of incremental costs and QALYs gained by introduction of new strategy for dengue screening. Results were also expressed in terms of QALYs gained, life years gained, deaths averted and cost per cure.

## 2.17 Calibration and sensitivity analysis

The robustness of model results was tested through a sensitivity analysis by varying input parameters between 20% above or below the estimated values. Tree Age software was used to perform Monte Carlo simulations (1000 times) and assess 95% confidential intervals for the estimated parameters: quality of life score associated with different health state and cost associated with ambulatory and hospitalization care. The sources of uncertainty especially parameter uncertainties which would influence ICER was evaluated by one-way sensitivity analysis (OWSA). Uncertainty in outcome variables and their effect on ICER is tested by Tornado diagram. The robustness of the model was further evaluated by probabilistic sensitivity analysis (PSA) which gives 1000 different cost and effectiveness for each strategy. The resulting incremental cost effectiveness is plotted in a scatter plot. The results were presented on a cost-effectiveness acceptability curve (CEAC), which indicated the models probabilistic response to a cost-effectiveness threshold.

## 2.18 Budget impact analysis

Cost of haematology analyzer, reagent cost, training cost and maintenance cost is considered for estimating implementation cost. Unit cost for implementing the screening strategy at PHC level and estimated population coverage was used to calculate the additional budget requirement for implementing haematology analyzers for screening suspected dengue cases at

PHC level by Government of Tamil Nadu. Assuming increasing coverage of dengue suspects in PHC over years; cost, QALY and ICER values were estimated. Projection was made for five years with 10%, 30%, 50%, 70% and 80% coverage in comparison with the base year.

# 3 RESULTS

## 3.1 Model Descriptive analysis

The average age of the cohort was 22 years for both male and female gender. The results of descriptive analysis from the model is given in Table-3. The proposed decentralized screening strategy detected 24 additional dengue cases when compared to current strategy. Severe dengue cases were less in proposed strategy as compared to the current strategy (DHF- 15 vs 24, DSS- 4 vs 7). The hospitalization for dengue was more in proposed strategy as compared to the current strategy (12.05% vs 11.12%). A total of four and three deaths were estimated from current and proposed strategy respectively

**Table 3: Results of Model Descriptive Analysis**

| **Parameters n (%)** | **Proposed strategy N= 500** | **Current Strategy N= 500** |
|---|---|---|
| Test positive | 130 (26) | 106 (21) |
| DF | 146 (29) | 103 (21) |
| DHF | 15 (3) | 24 (5) |
| DSS | 4 (0.82) | 7 (1.34) |
| Hospitalized care | 60 (12.05) | 56 (11.12) |
| Out-patient care | 103 (20.60) | 77 (15.38) |
| Death | 3 (0.65) | 4 (0.79) |

### 3.2 Base case Result

#### 3.2.1 Costs

The cost per test for CBC and ELISA was ₹153.65 and ₹314.85 respectively. The summary of various cost estimated in dengue screening strategies is given in Table-4. The total health system cost for the cohort estimated in proposed and current strategy were ₹1910131 and ₹1696177 respectively. It contributes 17.45% and 14.67% to the total cost estimation in proposed and current strategy. The patient out-of-pocket expenditure and productivity loss was estimated to be ₹9030056 and ₹9859103. The productivity loss due to premature death contributes higher to the total cost in the proposed and current strategy (81.57% vs 83.87%).

**Table 4: Summary of costs estimated in dengue screening strategies**

| Cost type | Total Cost in INR | |
|---|---|---|
| | **Proposed strategy** | **Current Strategy** |
| **Health system cost** | | |
| a. Ambulatory care cost (Medical) for non-fatal cases | 297807 | 221723 |
| b. Hospitalization care cost (Medical) for non-fatal cases | 1319351 | 1230295 |
| c. Investigation cost | 273997 | 223556 |
| d. Medical cost for death patients | 18977 | 20602 |
| **Total health system cost** | **1910131** | **1696177** |
| **Patient cost** | | |
| a. Non-medical cost for non-fatal cases | 102884 | 167525 |
| b. Indirect cost for death patients | 8927172 | 9691578 |
| **Total patient cost** | **9030056** | **9859103** |

The base case analysis estimated that under the current strategy the undiscounted cost incurred per person for diagnosis and treatment of dengue was ₹23564 and under the proposed screening strategy it was ₹22372. Using global discounting rate of 3% for 53 years of remaining life expectancy, the estimated discounted cost per person was ₹4919 and ₹4670 under the current and proposed strategy respectively (Table-5).

**Table 5: Base case results for dengue screening strategies**

| Parameters | Proposed Strategy | Current Strategy |
|---|---|---|
| Total Cost | | |
| a. Undiscounted | 11186000 | 11782000 |
| b. Discounted | 2335000 | 2458000 |
| Total Life Years | | |
| a. Undiscounted | 26327 | 26312 |
| b. Discounted | 5496 | 5493 |
| Total Quality Adjusted Life Years (QALY) | 23665 | 23455 |
| a. Undiscounted | 4940 | 4896 |
| b. Discounted | | |

### 3.2.2 Health outcome

The estimated undiscounted life years per person from the current and proposed strategies was 53 and 52.65 respectively. Similarly, the estimated undiscounted QALY per person from the current and proposed strategies was 46.91 and 47.33 respectively (Table-5).

### 3.2.3. Incremental costs and effectiveness

The proposed strategy was cost saving and the incremental cost saved over current strategy was estimated to be ₹-1192 per person. The total undiscounted incremental life years gained was 14.4 and discounted was 3.02. The total undiscounted incremental QALY gained was 210 and discounted was 43.83. The summary of the outcomes presented in Table-6.

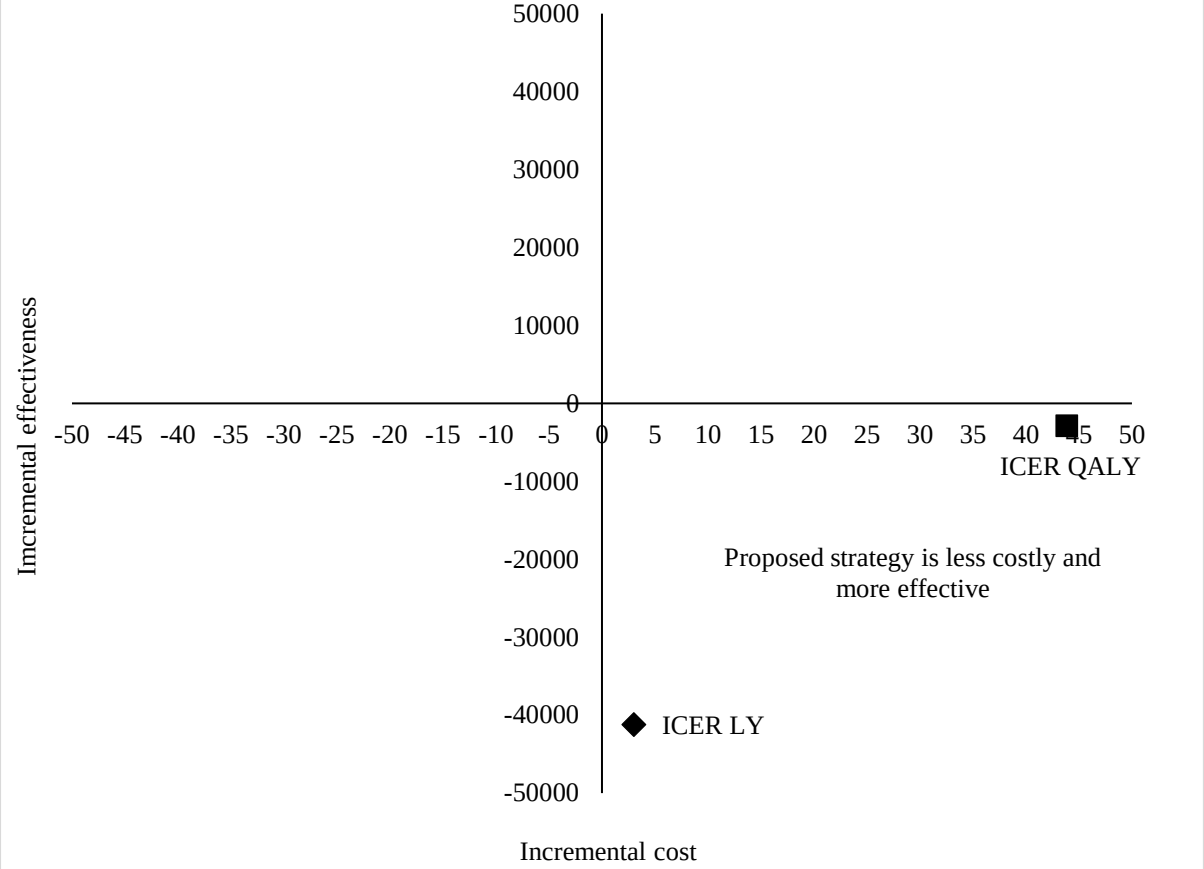
**Table 6: Model Outcome summary table for dengue screening at PHC**

| Outcome | Value |
|---|---|
| Incremental cost | |
| a. Undiscounted | -596000 |
| b. Discounted | -124415 |
| Life Years (LY) Gained | |
| a. Undiscounted | 14.4 |
| b. Discounted | 3.02 |
| Quality Adjusted Life Years (QALY) gained | |
| a. Undiscounted | 210 |
| b. Discounted | 43.83 |
| Incremental Cost Effectiveness Ratio (ICER - using LY) | |
| a. Undiscounted | -41388.88 |
| b. Discounted | -41197.01 |
| Incremental Cost Effectiveness Ratio (ICER- using QALY) | |
| a. Undiscounted | -2838.90 |
| b. Discounted | -2838.58 |
| Total death averted | 0.27 |

### 3.2.4 Incremental costs-effectiveness ratio

The ICER value calculated using discounted life years and discounted QALY was -41197.10 and -2383.58 respectively (Table-6). The incremental cost effectiveness plane plotted indicates that the proposed dengue screening strategy is more effective and less expensive compared with the current strategy (Figure-2).

**Figure 2: The cost-effectiveness plane for dengue screening at primary care level as compared to tertiary care level**




ICE LY- Incremental Cost Effectiveness using Life Years

ICER QALY- Incremental Effectiveness using Quality Adjusted Life Years

### 3.2.5. Out-of-pocket expenditure

With respect to out-of-pocket expenditure, the current screening strategy incurs ₹64641 additional cost when compared to the proposed strategy. The proposed intervention with increased case detection had higher number of patients than the current strategy. However, due to reduced travel distance and reduced number of visits to tertiary care saved ₹129 per person.

### 3.2.6. Net Monetary Benefit (NMB)

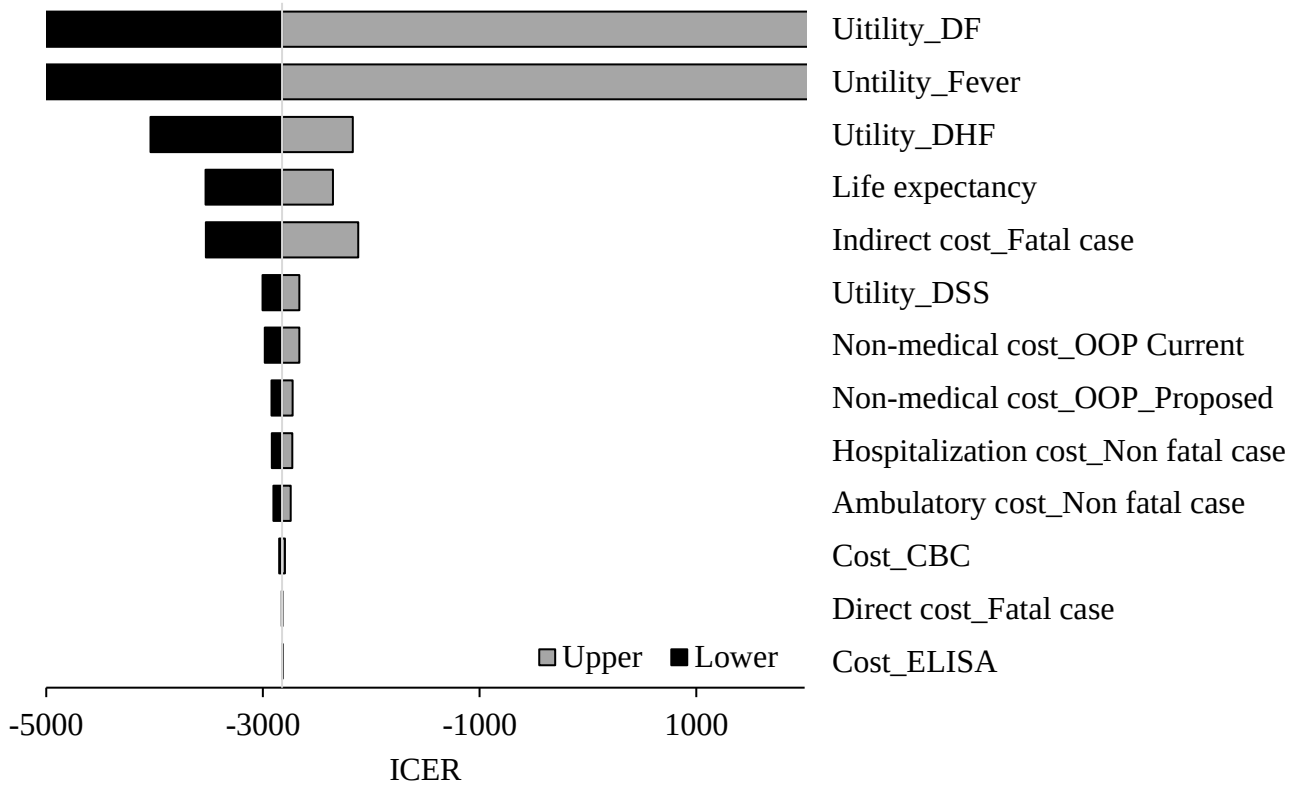
The NMB estimated using willingness to pay, for the proposed strategy is ₹669337040 and that of the current strategy is ₹663231536. This resulted an Incremental Net Monetary Benefit

(INMB) of ₹6105504 for the proposed strategy, suggesting that the proposed strategy is highly acceptable for achieving net benefit.

### 3.3. One-way sensitivity analysis (OWSA)

Uncertainty in outcome variables and their effect on ICER was tested using OWSA and presented in Tornado diagram. OWSA was carried out assuming 20% change in these variables. The parameters, utility of DHF and DSS dengue patients, indirect cost of fatal cases, life expectancy of the cohort, non-medical cost of non-fatal cases, hospitalization cost and ambulatory cost of non-fatal cases had higher influence on ICER value (Figure-3).

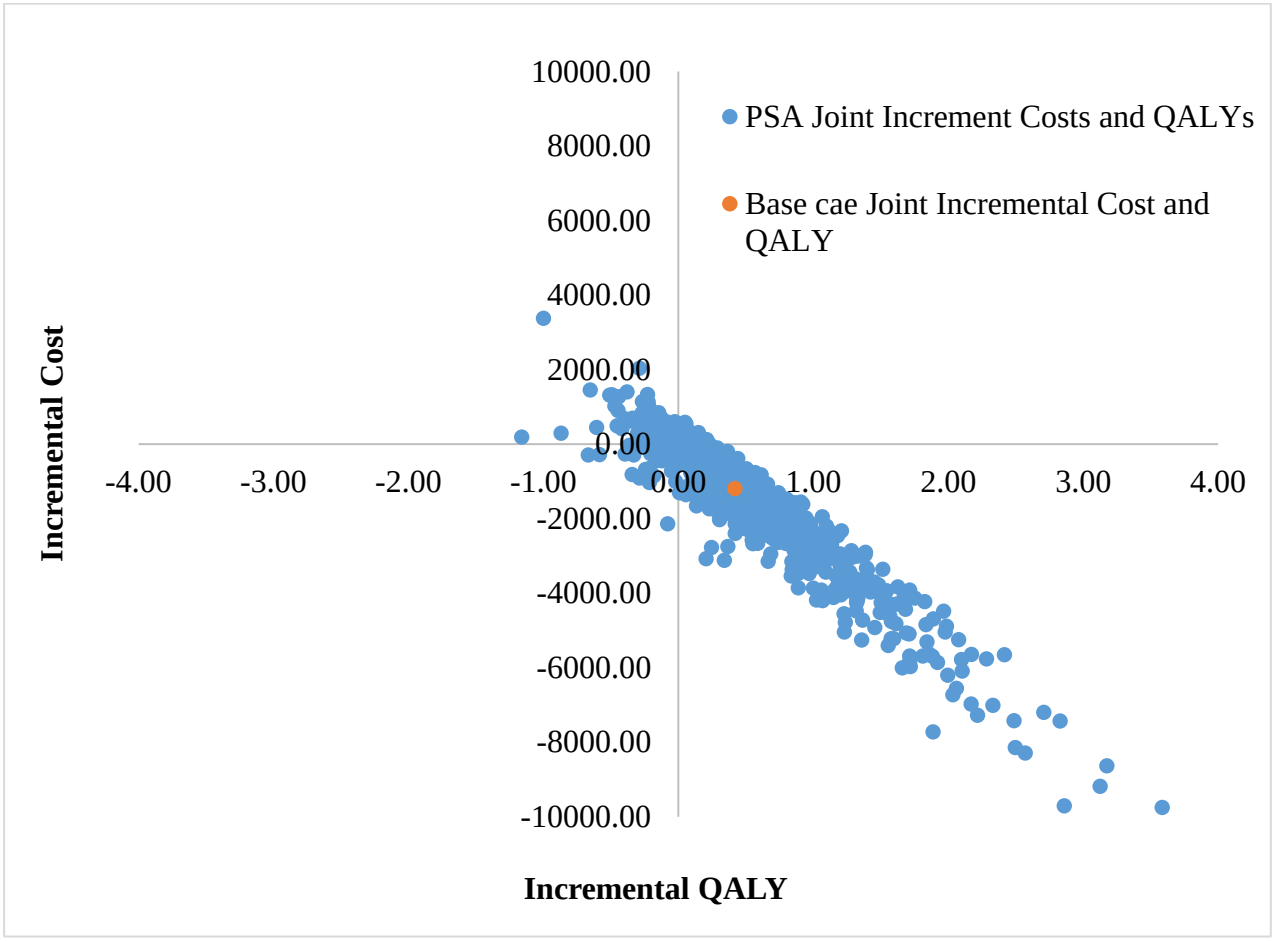
**Figure 3: Tornado plot illustrating the effect of individual parameters on incremental cost-effectiveness ratio (ICER)**



### 3.4. Probability sensitivity analysis (PSA)

PSA was performed using Monte-Carlo simulation to identify the impact of joint uncertainty of all the input parameters on ICER value. Distribution was assigned to each variable and 1000 iterations were performed. Joint incremental cost and effectiveness using QALY was less costly and more effective for approximately 84% of the iteration values (Figure-4).

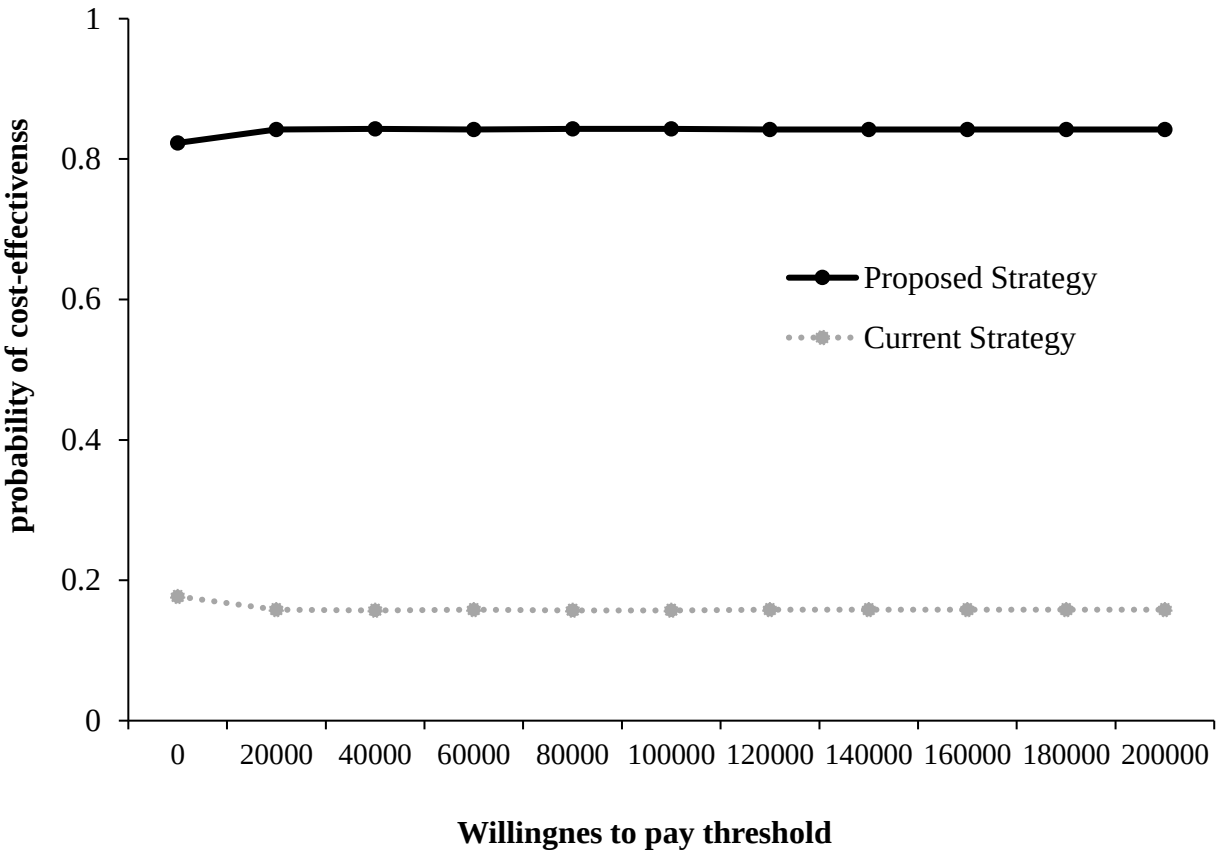
**Figure 4. Incremental cost effectiveness scatterplot in Probabilistic Sensitivity Analysis**




#### 3.4.1. Cost-effectiveness acceptability curve

The cost-effectiveness acceptability curve highlights that 0.8 probability of being economically dominant strategy as compared to current strategy at different cost effectiveness threshold values (Figure-5).

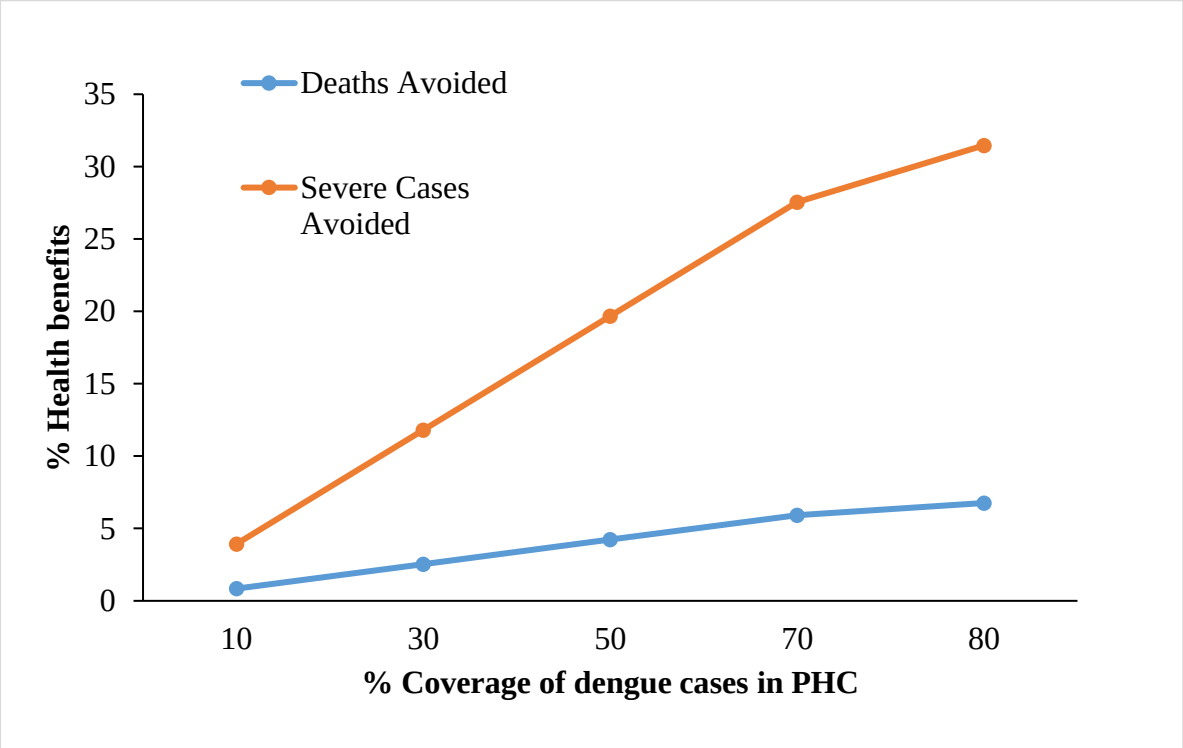
**Figure 5. Cost Effectiveness Acceptability curve**




### 3.5. Budget Impact Analysis (BIA)

BIA was done in consideration of the population of Tamil Nadu state where the study was conducted. Based on 2011 census data the projected population of Tamil Nadu for the year 2019 is 82,439,997. Considering 14.8% prevalence of dengue acute febrile illness in Tamil Nadu and 0.38% of sero-positive prevalence, 46365 dengue cases was estimated for base year. The additional budget of ₹574093041 is required for the government to implement the proposed screening strategy at the base year. With increase in proposed strategy coverage, health benefits such as death averted and severe dengue cases averted (DHF and DSS) increased (Figure-6).

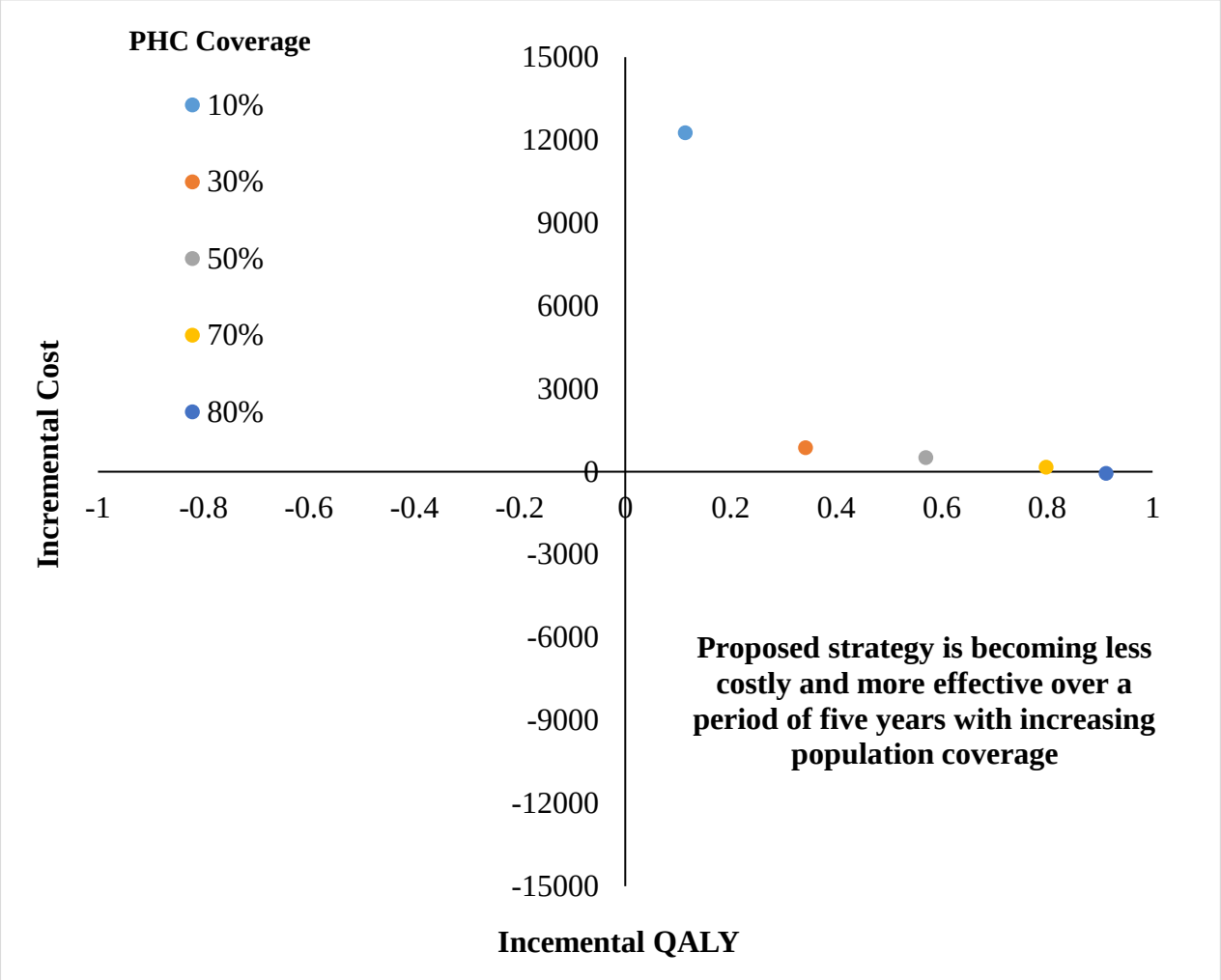
**Figure 6. Health benefit based on population coverage for five years**




### 3.5.1. ICER vs variations in access for dengue screening

We have estimated the ICER based on variations in PHC access for dengue screening over a period of five years. Assuming 10%, 30%, 50%, 70% and 80% increase in PHC access, it was found that health benefits gained in terms of QALYs increased (Figure-7). Without implementation cost, the proposed strategy is found to be cost saving and effective even at 10% coverage in PHC as compared to current strategy. However, cost were high in the implementation phase which gradually decreased over years. The proposed strategy was becoming less costly and more effective over a period of five years with increasing population coverage after implementation.

**Figure-7. Incremental cost effectiveness based on population coverage for five years**




## 4 DISCUSSION

In this study, we assessed the economic impact of using haematology analyser at PHC level for dengue screening as a new screening strategy. We used decision tree mathematical model for this evaluation for comparing the intervention with the current practice. The key finding from our evaluation highlights that implementation of dengue screening at PHC level could lead to incremental gain in QALYs and life years and reduction in out-of-pocket expenditure.

Systematic review conducted on mortality and morbidity due to dengue have shown that significant disability adjusted life years were experienced by the patient during the acute and hospitalisation phase of infection.[38] This review also had highlighted significant drop in quality of life of dengue patients during the hospitalisation and recovery period.[38] Studies concerning the quality of life of dengue patients are scarce and there are paucity of estimates on incremental QALYs gained by dengue interventions.[39] In this background, our findings on the incremental gain of QALYs projected for lifetime of dengue patient's, emphasis that interventions aimed at early stage of diagnosis and acute phase of dengue could lead to long term health gains.

A systematic review conducted on the economic benefits of rapid diagnostic test for dengue in India and other part of the world, found that rapid diagnostic test for dengue was cost-effective in endemic settings. It was also identified that rapid test was less advantageous to symptomatic treatment and management. The review emphasised on the background burden of the setting to be determinant of cost-effectiveness and highlighted the limitations of generalising cost-effectiveness evidences.[40] Through our study, which was conducted within a high dengue burden state in India, we arrived at a cost-effectiveness strategy which is specific for high burden setting.

A study in south India on comparative evaluation of validity and cost-benefit analysis of rapid diagnostic test reported that in dengue outbreak, RDT alone is not reliable but its easily available tool which can be used in acute phase of dengue infection in resource limited settings.[41] Our economic evaluation within the same setting identified that implementation of dengue screening test at PHC level is cost-effective with additional gains of QALYs and

reduction in mortality. This was especially strongly associated with the level of access to diagnostic services at PHC level.

The cost-effectiveness finding of the proposed screening strategy in the present evaluation needs to be interpreted in the context of decentralisation of diagnostic service at PHC level. Studies conducted on decentralised screening of infectious disease have highlighted the economic benefits associated with such strategies.[42,43,44,45] The importance of Thrombocytopenia in predicting dengue has been increasingly recognised in research literature as an valid screening tool. The application of haematology analysers at hospital based settings using small samples have established its usefulness.[46,47] However the implementation of such useful screening strategy has not been studied for its suitability in large community settings with high dengue burden. To assess the suitability of haematology analysers we used an appropriate economic modelling study which could simulate a cohort of patients and study their cost and clinical outcomes in a long term perspective after implementation of this intervention. In the absence of any large scale primary evaluation studies, we utilise the advantage of economic modelling to provide an important evidence for the policy makers to implement evidence based interventions.

The decentralised nature of our proposed screening strategy was identified as a cost-saving intervention for both health system and patients. The out-of-pocket expenditure experienced by patient was found to be decreased due to the proposed intervention. The cost saving strategy could be due to early diagnosis followed by early treatment resulting in prevention of acute and prolonged illness due to delayed diagnosis. Our sensitivity analysis highlights that the three factors namely, QALYs of patients with DF, QALYs of patients with DHF and the cost of death due to dengue had higher influence on ICER value. This could be

understood that there is a possible impact of dengue infections on the quality of life of individuals in long run. The decentralised diagnostic strategy could improve early diagnosis and might result in incremental gain of quality of life score.[39,48] Thus variation in quality of life holds more influence on ICER.

Delayed diagnosis of dengue could potentially lead to hospitalisation and increased bed days and thus increase the expenditure for both health system and on the patient.[49] Our study identifies the reduction in severity of dengue cases including DHF and DSS. This again could be attributed to the decentralized nature of proposed dengue screening strategy. Considering implementation cost, the proposed screening strategy was still cost-effective. However, we did not account for the other collateral benefits of the equipment used for dengue screening at PHC level as identified in table below. This was based on the current implementation plan of the state government which did not deliberate the use of the equipment for any other purpose. On account of which the proposed strategy cost may be further reduced.

**Table 7. Other benefits of Haematology Analyser at Primary Health Care Level**

| Disease | Hematology Analysis |
|---|---|
| Typhoid and other non-specific fevers[50] | Lymphocyte Count (<40%)<br>Platelet count (150001/mm³-450000/mm³) |
| Malaria [51] | Hemoglobin (9.8 g/dl)<br>Platelet count (50000/mm³-100000 /mm³)<br>Lymphocyte Count (<40%) |
| Japanese Encephalitis[52] | Platelet count (<50000/mm³) |
| Antenatal Care | Hemoglobin (Monitoring Normal Range) |
| Neonatal Sepsis [53] | Hematological scoring system (Score > 5) |

**Limitations of the study**

This economic evaluation model was conducted using published data. Also economic cost for Human Resource (HR) was not considered in this study. Further evaluation of this model is planned post pandemic using primary data from the field including economic cost for HR, as this strategy has been partly implemented. Utility score for TB parameter which we have included in the analysis was adopted from different setting and may have resulted in over or under estimation of the benefits and ICER. However, this limitation was addressed through sensitivity analysis technique.

## 5 CONCLUSION

The present model suggests that the dengue screening at PHC level in TN is cost saving and effective when compared to the current practice. This strategy also reduces severe dengue cases and deaths. The implementation of dengue screening strategy may effectively address the dengue disease burden in the state with cost saving benefit to the NVBDCP in TN. However, it is recommended to take economic cost of human resource and collateral benefits of the equipment into consideration before scaling up of the screening strategy.

**eTable.** CHEERS checklist—Items to include when reporting economic evaluations of health interventions

| Section/item | Item No | Recommendation | Reported on page No/ line No |
|---|---|---|---|
| **Title and abstract** | | | |
| Title | 1 | Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared. | Page-1 |
| Abstract | 2 | Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions. | Page-8 |
| **Introduction** | | | |
| Background and objectives | 3 | Provide an explicit statement of the broader context for the study. | Page-9-13 |
| | | Present the study question and its relevance for health policy or practice decisions. | Page-13 |
| **Methods** | | | |
| Target population and subgroups | 4 | Describe characteristics of the base case population and subgroups analysed, including why they were chosen. | Page-14 |
| Setting and location | 5 | State relevant aspects of the system(s) in which the decision(s) need(s) to be made. | Page-14 |
| Study perspective | 6 | Describe the perspective of the study and relate this to the costs being evaluated. | Page-14 |
| Comparators | 7 | Describe the interventions or strategies being compared and state why they were chosen. | Page-14 |
| Time horizon | 8 | State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate. | Page-14 |
| Discount rate | 9 | Report the choice of discount rate(s) used for costs and outcomes and say why appropriate. | Page-14 |
| Choice of health outcomes | 10 | Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed. | Page-15 |

| Section/item | Item No | Recommendation | Reported on page No/ line No |
|---|---|---|---|
| Measurement of effectiveness | 11a | *Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data. | Not Applicable |
| | 11b | *Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data. | Not Applicable |
| Measurement and valuation of preference based outcomes | 12 | If applicable, describe the population and methods used to elicit preferences for outcomes. | Not Applicable |
| Estimating resources and costs | 13a | *Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | Not Applicable |
| | 13b | *Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | Page-16-19 & Table-2 |
| Currency, price date, and conversion | 14 | Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate. | Page-17 |
| Choice of model | 15 | Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended. | Page-16 & Figure-1 |
| Assumptions | 16 | Describe all structural or other assumptions underpinning the decision-analytical model. | Page-14-15 |

| Section/item | Item No | Recommendation | Reported on page No/ line No |
|---|---|---|---|
| Analytical methods | 17 | Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty. | Page-21 |
| **Results** | | | |
| Study parameters | 18 | Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended. | Page-22 |
| Incremental costs and outcomes | 19 | For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios. | Page-24-25 |
| Characterising uncertainty | 20a | *Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective). | Not Applicable |
| | 20b | *Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions. | Page-26-27 |
| Characterising heterogeneity | 21 | If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information. | Not Applicable |

| Section/item | Item No | Recommendation | Reported on page No/ line No |
|---|---|---|---|
| Study findings, limitations, generalisability, and current knowledge | 22 | Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge. | Page-32 |
| | | | |
| Source of funding | 23 | Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support. | - |
| Conflicts of interest | 24 | Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations. | - |

## Annexure I- Technical Notes

### Defintions

### Dengue suspects

Patient with 2-5 days of febrile illness having two or more of the following symptoms of head ache, retro orbital pain, myalgia, arthralgia, rash and haemorrhagic manifestation are considered as dengue suspects.

### Dengue confirmed (Seropositive)

The clinical diagnosis of dengue may be confirmed by laboratory testing by the measurement of an antibody response IgM or IgG and diagnosis by ELISA is considered to be the diagnostic gold standard.

### Health system cost

Health system cost refers to the cost incurred by the provider. The health system in this study is a public health facility which provides medical services at subsidised rate or free of cost. Thus all medical cost were assumed to be incurred only by the public health facility. This includes Human Resource, Infrastructure, Equipment, Investigation, Treatment and Medication cost.

### Diagnostic test cost

The test cost incurred per person for dengue diagnosis. In this study screening for dengue was done using Complete blood count (CBC) and confirmation is done for those with <100000 Platelet count by Enzyme Linked Immune Sorbent Assay (ELISA). The per test cost for CBC

and ELISA was taken from Central Government Health Scheme (CGHS) investigation rate for public health facility.

**Patient cost**

Non-Medical cost from Hariharan D, et al., study was taken for patient cost.[54] This includes travel cost, food cost, other out of pocket expenditure for non medical goods or services and indirect cost (productivity loss)

**Indirect costs**

Indirect costs refer to the loss of income resulting from the work absenteesim, interruption of normal or preferred activities of patient and household members. The study which is reffered for indirect cost considers 18.8 years average productive life years lost for death patient.[55]

**Time Horizon**

When designing a comparative outcomes or a cost-effectiveness analysis, the time horizon defining the duration of time for outcomes assessment considered. The time horizon must be long enough to capture the intended and unintended benefits and harms of the intervention.[56] This study considers life time horizon to capture all cost and effectiveness.

**Decision Tree**

Decision tree is the most powerful and popular tool for classification and prediction. A Decision tree is a flowchart like tree structure, where each internal node denotes a test on an attribute, each branch represents an outcome of the test, and each leaf node (terminal node) holds a class label.

**Cost-effectiveness analysis**

Cost-effectiveness analysis (CEA) is a way to examine both the costs and health outcomes of one or more interventions. It compares an intervention to another intervention (or the status quo) by estimating how much it costs to gain a unit of a health outcome, like a life year gained or a death prevented.

**Incremental cost efectiveness ratio**

The incremental cost effectiveness ratio (ICER) between the current dengue diagnosed strategy at tertiary level with the new intervention of dengue diagnosis strategy at PHC. The difference between the strategies was calculated and compared with the difference in the number of QALYs gained.

$$\text{ICER} = \frac{\text{Cost of the proposed dengue diagnosis strategy (PHC)} - \text{Cost of the current dengue Diagnosis strategy (THC)}}{\text{QALY of the proposed dengue diagnosis strategy (PHC)} - \text{QALY of the current Dengue diagnosis strategy (THC)}}$$

**Net Monetary Benefit**

Net Monetary benefit (NHB) is a summary statistic that represents the value of an intervention in monetary terms considering a willingness to pay threshold for a unit of benefit. This study considers per capita GDP as willingness to pay threshold

NMB= Cost – (QALY * Willingness to pay Threshold)

Incremental NMB (INMB) measures the difference in NMB between alternative interventions, a positive incremental NMB indicating that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold.

INMB= NMB (Proposed Strategy) – NMB (Current Strategy)

**Quality Adjusted Life Year**

The Quality-Adjusted Life Year (QALY) is a standardized measure of disease burden which combines both survival and health-related quality of life into a single index. The QALY is primarily used in cost-effectiveness analyses to guide decisions regarding the distribution of limited health care resources among competing health programs or interventions for a population of interest, but has also been used to aid decisions regarding clinical management and individual patient care.

QALY= Utility * Expected Life years

**One-way sensitivity analysis**

Univariate/one way sensitivity analysis (OSA) is to assess the impact that changes in a certain input (parameter) will have on the output results of an economic evaluation. This will help to assess the robustness of the result to that parameter. It is helpful for decision makers to have insights into the relationship between specific input parameters and the model outputs.

**Probabilistic sensitivity analysis**

Probabilistic sensitivity analysis (PSA) demonstrates the parameter uncertainty in a decision problem. The technique involves sampling parameters from their respective distributions (rather than simply using mean/median parameter values). This technique used in economic modelling that allows the modeller to quantify the level of confidence in the output of the analysis, in relation to uncertainty in the model inputs.

**Cost–effectiveness threshold**

Cost–effectiveness threshold is the ceiling ICER beyond which interventions are no longer considered cost effective, reflecting the maximum value decision makers attach to health

benefits. Three general approaches have been used to provide clear guidance to policy makers: (i) thresholds based on per capita national incomes; (ii) benchmark interventions and (iii) league tables. In recent years, the most common approach has involved the use of thresholds based on GDP. Under this approach which has been promoted by the World Health Organization's Choosing interventions that are cost–effective (WHO-CHOICE) an intervention that costs less than three times the national annual GDP per capita is considered cost–effective, whereas one that costs less than once the national annual GDP per capita is considered highly cost–effective.[57] We followed GDP as threshold value.

**Calculations**

**1. CBC test**

| **Parameter** | **Formula** |
|---|---|
| Test Positive | Number of cohort population x Probability of True test positive |
| Probability of true positive with CBC (<100000 PLC) | (Prevalence of Dengue x Probability of <100000 PLC) ) + ((1-Prevalence of Dengue) x (1-Probability of <100000 PLC) x Probability of <100000 PLC) |

**2. ELISA test**

| **Parameter** | **Formula** |
|---|---|
| Test Positive | Number of cohort population with <100000 platelet count x Probability of ELISA test positive |
| Probability of ELISA test positive | (Prevalence of Dengue x Test sensitivity) + ((1-Prevalence of Dengue) x (1-Test specificity)) |
| True Positive (Positive Predictive value) | (Test sensitivity x Prevalence of Dengue) / |

| | |
|---|---|
| | (Test sensitivity x Prevalence of Dengue) + ((1-Test specificity) x (1-Prevalence of Dengue)) |
| True Negative (Negative Predictive value) | ((1-Prevalence of Dengue) x Test specificity) / (Test specificity x (1-Prevalence of Dengue)) + ((1-Test sensitivity) x Prevalence of Dengue) |

**3. Mortality due to dengue**

| **Parameter** | **Formula** |
|---|---|
| Probability of mortality due to DHF | (Probability of mortality due to dengue * % of population coverage) |
| Probability of mortality due to DSS | (Probability of mortality due to dengue * % of population coverage) |
| Relative risk of mortality due to DHF or DSS in proposed strategy | Probability of mortality due to DHF or DSS in proposed strategy/ Probability of mortality due to DHF or DSS in current strategy |

**4. Discount factor calculation**

The discount factor is multiplied with life years (LY), quality adjusted life years (QALY) and cost to obtain discounted LY, QALY and cost.

$$\text{Discount factor} = \left[\frac{1}{1+\text{Discount rate}}\right] \text{ ^ (Expected remaining life years)}$$

Discounted Life Years (LY) = LY * Discount factor

Discounted Quality adjusted life Years (QALY) = QALY * Discount factor

Discounted Cost = Cost * Discount factor

## 5. Cost estimation

Costs were obtained from meta-analysis report, this did not include diagnostic test cost. Thus, diagnostic test cost was added in cost calculation. Cost for undifferentiated fever cases who tested negative for dengue (True negative) includes only diagnostic test cost as other costs were unavailable.

## 6. Budget Impact Analysis

### a. Implementation cost

Cost of haematology analyzer, cost of reagent, training cost and maintenance cost is considered for implementation cost estimation. Haematology analyzer and reagent (that can be used for 3000 samples) cost of three different brands is taken from Government e-marketing (GEM) website and average cost is taken for analysis. Considering installation of one haematology analyzer every PHC in Tamil Nadu (n=1421), total capital cost is calculated. Three CBC test per person per year is reflected for reagent cost calculation for the total population covered in the proposed strategy. Every year 10% of the total capital cost is considered for maintenance. Assuming ₹2000 for training one staff, total training cost is calculated for providing training to two staff per PHC.

### b. Budget Impact

Gain in total health benefits (in terms of QALY and severe cases avoided) every year due to proposed strategy when compared with the base year is assessed. It is then plotted in line graph for trend analysis.

Incremental Health Benefit (Year x) = Total health benefit (Year x) – Total health benefit (Base Year).

ICER value is calculated for each year in comparison with base year and ICER plane is drawn for assessing change in the incremental cost-effectiveness over the years.

Minimum population coverage at which the proposed strategy is cost-effective is estimated.

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