**Health Technology Assessment Resource Centre (HTARC)**

**Department of Preventive and Social Medicine, JIPMER, Puducherry**

**HTA REPORT**

**On**

# COST-EFFECTIVENESS ANALYSIS OF RAPID DIAGNOSTIC KITS WITH ANTIMICROBIAL SENSITIVITY AS POINT-OF-CARE TESTING IN UNCOMPLICATED URINARY TRACT INFECTION

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# ABBREVIATIONS

| | |
|---|---|
| **UTI** | Urinary Tract Infection |
| **INR** | Indian Rupee |
| **NHSCDI** | National Health System Cost Database for India |
| **OWSA** | One Way Sensitivity Analysis |
| **PSA** | Probabilistic Sensitivity Analysis |
| **QALY** | Quality-Adjusted Life Years |
| **ICER** | Incremental Cost-effectiveness Ratio |
| **uUTI** | Uncomplicated Urinary Tract Infection |
| **PHC** | Primary Health Centre |
| **DH** | District Hospital |
| **ICMR** | Indian Council of Medical Research |
| **OPD** | Out Patient Department |
| **IPD** | In Patient Department |
| **IV** | Intra Venous |
| **ESBL** | Extended Spectrum Beta Lactamase |

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## EXECUTIVE SUMMARY

Almost 50% of the women population in India experience at least one episode of urinary tract infection (UTI) in their lifetime, with 20-40% of them showing recurrent episodes of UTI. Urine culture is the gold standard method for determination of susceptible antibiotics for the management of UTI. But, a delay of 24 to 48 hours in obtaining urine culture results has presented a long-standing need for more rapid diagnostic methods. The present report presents the cost effectiveness of two rapid antimicrobial susceptibility test kits which are RightBiotic and Rapidogram in management of uncomplicated UTI among adult women compared with the current empirical management. A decision tree was utilized to depict the process of management of urinary tract infection through one of the three approaches. i.e. empirical antibiotic therapy, RightBiotic, Rapidogram aided antibiotic therapy. The model was built with a cohort of adult women aged 18 years and above. The study adopted a societal perspective and accounted for the cost and consequences for a period of one month. The input parameters for the model were derived from secondary sources such as literature, product brochures and National Health System Cost Database for India (NHSCDI). The study derived an incremental cost-effectiveness ratio (ICER) for RightBiotic and Rapidogram. Robustness of the estimates were assessed through sensitivity analysis. The ICER per QALY gain estimated for RightBiotic and Rapidogram were ₹ 36 and ₹ 16, respectively. These ICER values were found to be highly cost effective which is highly influenced by the probability of giving the right antibiotic in the current empirical management. The scenario analysis revealed that the intervention would become cost-ineffective (negative incremental QALY) if the probability of giving the right antibiotic in empirical management is more than 90%. In the real scenario, the probability of giving the right antibiotic is expected to be high in the regions with lower antimicrobial resistance. Although at the national level, the budget impact for implementation of RightBiotic and Rapidogram in all primary health care centers was 2.5% and 1.1%, respectively, on the current India's health budget, implementation of either of these devices in the region with high prevalence of anti-microbial resistance is recommended.

## 1. INTRODUCTION

Urinary tract infections (UTI) is a common infection among all age groups and is a major public health problem. Each year, about 150 million people acquire UTI worldwide with considerably higher incidence among women (12.6%) than men (3%). (1)The global burden of UTI is also rising, with a 16.1% increase in age-standardized incidence between 1990 and 2013 (2,3). In India, the prevalence of UTI ranges between 21.8% and 31.3%. (4)Almost 50% of the women experience at least one episode of UTI in their lifetime, with 20-40% of them showing recurrent episodes of UTI(5).

According to a systematic review and meta-analysis conducted by Faraz et. al. (2021) E. coli, and Klebsiella sp. are the most commonly isolated uropathogens in Indian population, with a prevalence of 49.6% and 12.8%, respectively. Highest resistance patterns of E.coli was found for Ampicillin (74.11%) and followed by Ciprofloxacin (61.32%). Other uncommon uropathogens showed resistance towards Ampicillin (62.98%) and Ceftriaxone (62.7%).(6)

The medical treatment for UTI is largely rendered through primary healthcare facilities located across the country. The current standard for UTI diagnosis is urine microscopy and culture, followed by antibiotic susceptibility testing (AST) of a midstream, clean-catch urine specimen using the Kirby-Bauer method. UTI patients are empirically treated with antibiotics, and guidelines recommend starting antibiotic treatment before urine culture and AST results become available, delayed by about 48 h the initiation of targeted antibacterial therapy (7–9). Due to the continually changing rates of antimicrobial resistance, empiric treatments do not ensure appropriate stewardship and can result in therapeutic failure (9,10,10). Therefore, the empirical antimicrobial regimen of choice should be based on local resistance patterns, as highlighted in various studies from different countries, to effectively prevent the emergence of multi-drug-resistant uropathogen (10–12).

The presence of uropathogenic bacteria in urine is the hallmark of UTI, and urine culture is the gold standard method for the determination of clinically relevant bacteriuria. However, the 24- to 48-h delay in obtaining urine culture results has presented a long-standing need for more rapid diagnostic methods. Presently available rapid point of care methods for detection of bacteriuria, including microscopy and test strips for detecting nitrite, has the limitation of poor sensitivity (8,13–15). A meta-analysis of 34 studies evaluating the accuracy of nitrite test strips across settings and populations found a mean sensitivity of 48% (using a definition of 105 CFU/ml for significant bacteriuria) (16).

For these reasons, a fast and accurate diagnosis, leading to a rational treatment, is essential to achieving a timely and effective therapy. There are various automated antibiotic susceptibility testing (AST) devices. Their use is widespread because of their automation, simplicity, and compactness. Disadvantages of all the above-automated systems are lack of reproducibility, sensitivity, and reliability compared with the existing traditional methods. Also, an inability to test a wide range of clinically relevant bacteria (e.g., S. pneumoniae), antimicrobial agents (e.g., vancomycin), and hetero resistant isolates, as well as a limited panel capacity and the high cost of instruments and consumables, are all significant issues that restrict these systems from frequent analysis (17).

An accurate and rapid point-of-care diagnostic method for the detection of bacteriuria would therefore be a powerful new aid in the diagnosis and appropriate treatment of UTIs. Timely diagnosis of UTI is of utmost importance to avoid the reliance on empirical treatment and improper prescription of antibiotics. This will in turn help in the reduction of antimicrobial resistance in the community as well. The RightBiotics and Rapidogram are two rapid point-of-care antibiotic susceptibility testing devices developed in India. The sensitivity and specificity of the RightBiotic was 95.4% (95% CI- 92.44 to 97.48) and 85.6% (95% CI: 82.10 to 86.11) respectively. The Rapidogram has the sensitivity and specificity 96% and 80%, respectively. The capital cost for RightBiotics is ₹ 4,85,200 and the cost per kit is ₹ 550. Rapidogram costs ₹ 500 per kit and there is no direct capital cost. The major advantage of these two devices is the running time which is 4 to 6 hours whereas the conventional urine culture takes 3 to 4 days get the result. This will facilitate the earlier identification and administration of the appropriate antibiotics. Further, the portability of the devices makes more suitable to get installed even at the primary health care facilities. The present study was therefore designed to assess the cost-effectiveness of various rapid UTI testing and antimicrobial sensitivity devices at the PHC level for testing urinary samples of uncomplicated UTIs. Empirical treatment followed by conventional urine culture and AST using Kirby Bauer disc diffusion method is compared to

Rapidogram and RightBiotic rapid UTI testing alternatives. We have also calculated the costs and consequences of the above three scenarios of uncomplicated UTI diagnosis and management. (Annexure I give the information about the two rapid UTI testing devices/kits used as intervention in this study).

## 2. RESEARCH QUESTION

Whether the use of rapid diagnostics kits with antibiotic susceptibility at point of care testing for uncomplicated urinary tract infection cost-effective among adult women?

## 3. OBJECTIVE

To estimate the incremental cost-effectiveness ratio (ICER) per quality-adjusted life years (QALY) gained with testing of uncomplicated urinary tract infection with rapid diagnostic kits (RightBiotic OR Rapidogram) among adult women compared with the current empirical management.

# 4. METHODOLOGY

## 4.1 Economic Evaluation

### *4.1.1 Frame Work:* PICO

| | | |
|---|---|---|
| P *(Population)* | – | Adult women aged 18 years and above with symptomatic uncomplicated UTI |
| I *(Intervention)* | – | Rapid anti-microbial susceptibility test using<br>I. RightBiotic<br>II. Rapidogram |
| C *(Comparator)* | – | Empirical management of UTI (current scenario) |
| O *(Outcome)* | – | Incremental Cost-Effectiveness Ratio (ICER) per Quality-adjusted life years (QALY) gained |

### *4.1.2 Study Perspective:*

The present study was conducted from a societal perspective. The costs incurred by the provider (health system) and patients (direct & indirect medical costs along with income loss due to illness) for alternative interventions and comparator were included in the economic evaluation.

### *4.1.3 Time Horizon:*

The cost and consequences associated with the alternative interventions and comparator were simulated for one month.

## 4.2 Current Scenario / Comparator

Patients with symptomatic uncomplicated UTI were managed with empirical antibiotics. The proportion of the population with persistent UTI even after receiving empirically-chosen antibiotics was switched to the second choice of empirical antibiotics. Over time, patients who develop complications (pyelonephritis) were forwarded to tertiary care hospitals for management of disease either as inpatient or outpatient.

## 4.3 Study Intervention

The present study proposed the implementation of two rapid antibiotic susceptibility test devices, which are RightBiotic and Rapidogram, as the first-line diagnosis of symptomatic uncomplicated UTI. In the intervention, the patients with symptomatic-uncomplicated UTI were tested for antibiotic susceptibility using RightBiotic and Rapidogram. Based on the susceptibility pattern, patients who received appropriate antibiotics got cured before the onset of complications. As per the diagnostic accuracy of Rightbiotic and Rapidogram, the proportion of the cohort who received the wrong antibiotics was tested again using RightBiotic and Rapidogram before the second line prescription of antibiotics.

### 4.4 Model Overview

Decision analytical model was used to model the progression and management of symptomatic uncomplicated UTI. The decision tree model was built with three arms which were empirical treatment, as a comparator, and the intervention arms as RightBiotic and Rapidogram. The cohort of the target population i.e., women aged 18 years and above with symptomatic-uncomplicated UTI entered the model in either the empirical management, RightBiotic- or Rapidogram- aided management arm. The cohort in each arm attained the cure at the end of the model. However, based on the choice of correct (susceptible) antibiotics, the duration of attaining cure, the severity of the diseases and the development of complications varied across the arms.

Across the three arms of the model, it was assumed that patients receiving correct antibiotics get 100% cure for that episode. Similarly, the proportion of the cohort who received the wrong antibiotics, a cure rate of 0% was assumed. As a result, all of the patients who were given the wrong antibiotics had a persistent UTI and were given a second round of empirical antibiotics. Choice of the correct antibiotic in the first line of empirical management was based on the anti-microbial resistance status of the microorganism persisting in a community. It was assumed that the chance of receiving the correct antibiotic as a second-line empirical treatment was 20% higher than the first-line empirical treatment.

In the intervention arm, the choice of correct antibiotics was based on the sensitivity and specificity of the RightBiotic and Rapidogram. The respective tests were performed two times. First, the entire initial cohort was tested for antibiotic susceptibility using RightBiotic or Rapidogram. The test was performed for the second time for the proportion of the cohort who received the wrong antibiotics and presented with persistent UTI. In both intervention and comparator, the cohort with complications was proportionated based on the type of management (hospitalization and outpatient) required for the treating complications. It was assumed that all the patients underwent ultra-sonogram during hospitalization.

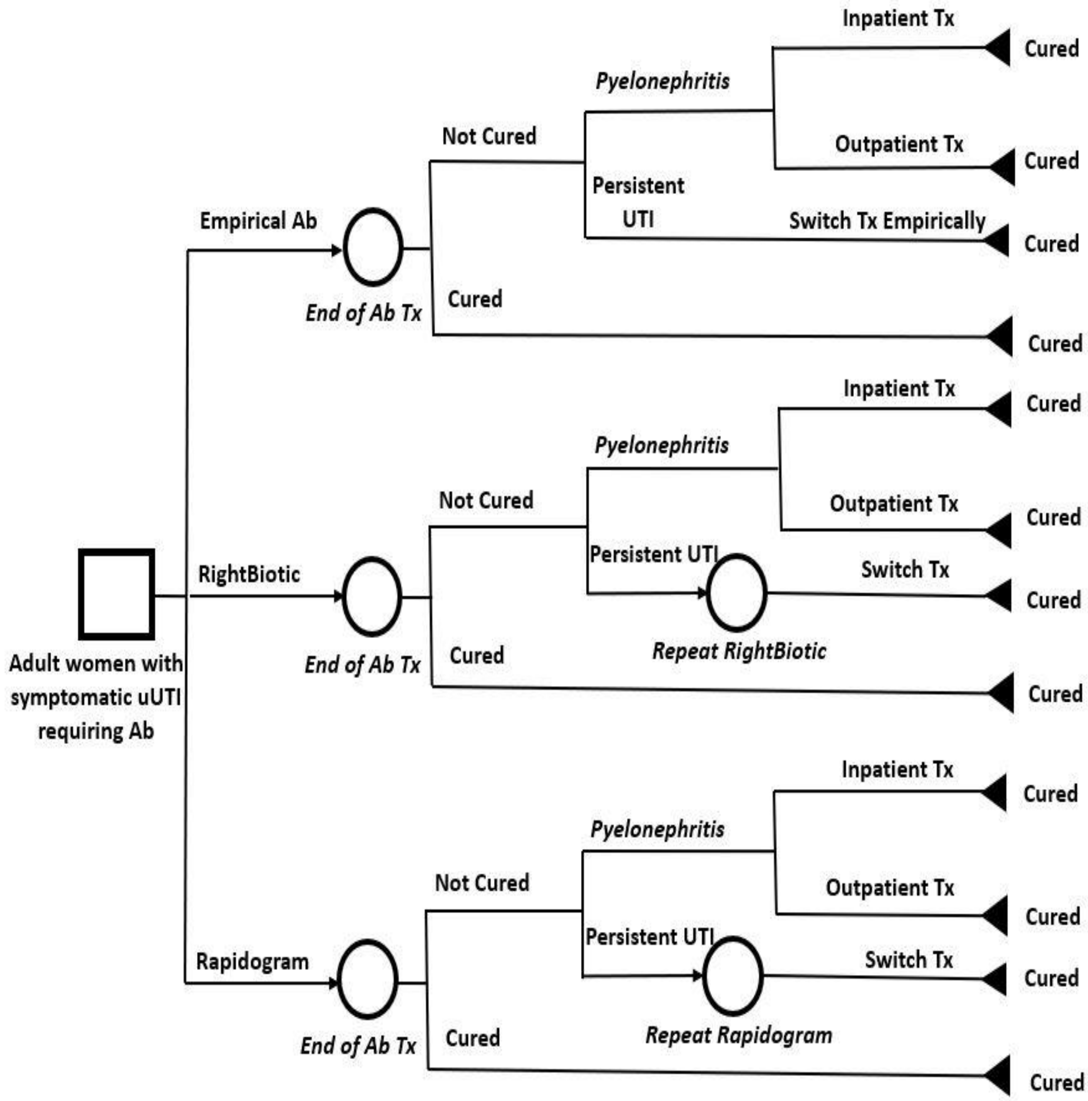



**Figure 1** Schematic diagram of decision tree. Ab-Antibiotics; Tx-Treatment; UTI-Urinary Tract Infection;

Cost per outpatient department (OPD) visit in PHC and cost per OPD visit in district hospital were estimated from the national health system costing database. For empirical treatment of uncomplicated UTI, either one of the recommended antibiotics like Tab. Co-trimoxazole, Tab. Nitrofurantoin or Inj. Amikacin was assumed to be given as first-line treatment as per Treatment Guidelines for Antimicrobial Use in Common Syndromes 2019 by the Indian Council of Medical Research (ICMR) (Guidelines Ref. 23) (Table A1). The cost of oral and intravenous (IV) antibiotics used for treating uncomplicated UTI and pyelonephritis were obtained from the national health system costing database. Strategies for treating acute pyelonephritis in OPD and the inpatient department (IPD) were obtained from the ICMR treatment guidelines. It is assumed that patients who develop pyelonephritis were referred from PHC to the district hospital for further management. It is also assumed that all of them will undergo urine analysis, urine culture susceptibility test and ultrasonogram as diagnostic procedures. For acute pyelonephritis patients treated in OPD, it was assumed that the patients were given IV antibiotics for the first 3 days, after which they were changed to oral antibiotics based on the urine culture and susceptibility report (Table A2). For treating the acute pyelonephritis patients requiring hospitalization, it was assumed that patients receive empirical IV antibiotics for the first 3 days after it was changed to susceptible IV antibiotics based on culture report if required. Inj. Ertapenem, a sub-type of Carbapenem category of antibiotics had also been considered in costing, in case of community-acquired extended spectrum beta-lactamase (ESBL) producing E coli could be a causative organism. The average duration of hospital stay was assumed to be 10 days. The cost of acute pyelonephritis treatment in IPD was given in Table A3. All the costs were adjusted as per the current inflation rate.

**Table 1** Model input parameters

| **Parameters** | **Base case** | **Lower limit** | **Upper limit** | **Distribution** | **References** |
|---|---|---|---|---|---|
| Prob of giving right Antibiotic | 0.496 | 0.397 | 0.595 | Beta | Manshahia PS et al (18) |
| Cure with right Antibiotic | 1.000 | 0.800 | 1.000 | Beta | Assumption |
| Probability of developing Pyelonephritis | 0.040 | 0.032 | 0.048 | Beta | Sadler et al (19) |
| Hospitalization due to Pyelonephritis | 0.200 | 0.160 | 0.240 | Beta | Sadler et al (19) |
| RightBiotic_Sensitivity | 0.954 | 0.924 | 0.975 | Beta | Estimated |
| RightBiotic _Specificity | 0.856 | 0.821 | 0.861 | Beta | Estimated |
| Rapidogram_Sensitivity | 0.960 | 0.768 | 1.000 | Beta | Estimated |
| Rapidogram_Specificity | 0.800 | 0.640 | 0.960 | Beta | Estimated |
| Utility_Pre_Treatment | 0.600 | 0.480 | 0.720 | Beta | Ernst et al (20) |
| Utility_Post_Treatment | 0.850 | 0.680 | 1.020 | Beta | Ernst et al (20) |
| Utility_Day0_Responding | 0.681 | 0.545 | 0.817 | Beta | Ernst et al (20) |
| Utility_Day3_Responding | 0.772 | 0.618 | 0.926 | Beta | Ernst et al (20) |
| Utility_Day7_Responding | 0.820 | 0.656 | 0.984 | Beta | Ernst et al (20) |

| | | | | | |
|---|---|---|---|---|---|
| Utility_Day14_Responding | 0.828 | 0.662 | 0.994 | Beta | Ernst et al (20) |
| Utility_Day28_Responding | 0.814 | 0.651 | 0.977 | Beta | Ernst et al (20) |
| Utility_Day0_Not_Responding | 0.670 | 0.536 | 0.804 | Beta | Ernst et al (20) |
| Utility_Day3_Not_Responding | 0.714 | 0.571 | 0.857 | Beta | Ernst et al (20) |
| Utility_Day7 _Not_Responding | 0.707 | 0.566 | 0.848 | Beta | Ernst et al (20) |
| Utility_Day14_Not_Responding | 0.755 | 0.604 | 0.906 | Beta | Ernst et al (20) |
| Utility_Day28_Not_Responding | 0.792 | 0.634 | 0.950 | Beta | Ernst et al (20) |
| Disutility_Day 0 | 0.012 | 0.009 | 0.014 | Beta | Ernst et al (20) |
| Disutility_Day3 | 0.063 | 0.051 | 0.076 | Beta | Ernst et al (20) |
| Disutility_Day7 | 0.072 | 0.058 | 0.086 | Beta | Ernst et al (20) |
| Disutility_Day14 | 0.046 | 0.037 | 0.055 | Beta | Ernst et al (20) |
| Disutility_Day28 | 0.043 | 0.035 | 0.052 | Beta | Ernst et al (20) |
| Utility_Pyelonephritis | 0.580 | 0.448 | 0.672 | Beta | Bermingham et al (21) |
| Cost_OPD in PHC | 971 | 524 | 1885 | Gamma | NHSCDI |
| Cost_UTI Antibiotic | 59 | 47 | 70 | Gamma | NHSCDI |
| Cost_Acute Pyelonephritis OPD | 9347 | 5608 | 13086 | Gamma | Estimated |
| Cost_Acute Pyelonephritis IPD | 61420 | 36852 | 85988 | Gamma | Estimated |
| Cost_RightBiotic | 800 | 640 | 960 | Gamma | Estimated |
| Cost_Rapidogram | 750 | 600 | 900 | Gamma | Estimated |
| Cost_OOPE_PHC_Visit | 407 | 326 | 488 | Gamma | Estimated |
| Cost_OOPE_DH_Visit_OPD | 773 | 618 | 928 | Gamma | Estimated |
| Cost_OOPE_DH_Hospitalization | 25071 | 5888 | 39408 | Gamma | Estimated |

*OPD- Outpatient Department; PHC-Primary Health Centre; DH- District Hospital;*

### 4.5 QALY Estimation

Using the formula given below, the overall health gain in the form of QALY from the utilities and life-years expectancies at each arm and its associated health states were estimated.

$$\text{QALY} = \text{Utility} \times \text{Life Expectancies}$$

### 4.6 ICER Estimation

The present economic model aimed to estimate the Incremental Cost-Effectiveness Ratio (ICER)per QALY gained as follows:

$$\text{Incremental Cost} = \text{Total Cost (Monthly) of Intervention} - \text{Total Cost (Monthly) of Comparator}$$

$$\text{Incremental Cost} = \text{Total QALY in Intervention} - \text{Total QALY in Comparator}$$

$$\text{Incremental Cost-effectiveness Ratio} = \text{Incremental Cost / Incremental QALY}$$

**4.7 Sensitivity Analysis**

The robustness of the model and parameters used in the model were assessed through one-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA). Both analyses were carried out in MS excel. PSA was done using macros through visual basic coding for simulating the results (over 1000 times) obtained from the Monte Carlo method. The results of OSWA and PSAwere represented in the tornado graph and cost-effective plane, respectively.

**4.8 Scenario Analysis**

Scenario analysis on the probability of choice of right antibiotics in the empirical arm was carried out to assess change in the incremental cost and QALY of RightBiotic and Rapidogram. The AMR status in a community decides the susceptibility of antibiotics chosen empirically. Hence the probability of receiving the right antibiotics under the empirical management of uncomplicated UTI is varied across the settings.

**4.9 Budget Impact Analysis**

Budget impact analysis was conducted at the national and state (Tamil Nadu) levels for the implementation of RightBiotic and Rapidogram in all PHCs. The cost of implementation was determined for the first and second years. The first year’s cost included devices cost (capital cost) as well as recurring cost. The recurring cost comprised manpower cost and reagent cost. Unlike first year, the second year budget included recurrent costs and no capital costs. The device cost and man power costs were relative to the number of PHC whereas the recurring cost was proportional to the number of tests.

# 5 RESULTS

## 5.1 Base Case Results

The results shown in tables 2.1 & 2.2 are for testing with rapid diagnostic kits among adult women with uncomplicated urinary tract infections. The total cost incurred was ₹ 215 for empirical treatment, ₹ 224 for RightBiotic and ₹ 219 for Rapidogram. The total QALY for empirical treatment, RightBiotic and Rapidogram were 3.406, 3.665 and 3.662, respectively. The incremental cost and QALY for RightBiotic and Rapidogram were ₹ 9.29/₹ 3.98 and 0.259/0.256, respectively, compared with no testing. ICER/QALY gained with RightBiotic and Rapidogram were ₹ 35.87 and ₹ 15.55, respectively. Table 1.2 presents the corresponding net monetary benefit (NMB) associated with both RightBiotic and Rapidogram. Assuming the threshold value (λ) as one-time GDP per capita income of ₹ 1, 45,679 in 2022, the NMB for RightBiotic and Rapidogram were found to be ₹ 37,715 and ₹ 37,281, respectively.

## 5.2 Sensitivity Analyses

### 5.2.1 One-way sensitivity analysis

Variations in the ICER concerning the higher and lower base case parameter values are presented in figures 2 and 3. In RightBiotic, “Probability of giving right antibiotics” and “Cure with right Antibiotics” had the highest variations in the ICER when assessed with the respective lower and higher range values. Other parameters that influenced ICER values were “Cost of OPD visit in PHC”, “Cost and sensitivity of Rightbiotic”, and “Probability of giving second right antibiotics” and so on, as given in the figure. Likewise, in Rapidogram, “Diagnostic accuracy of Rapidogram”, “Cure with right Antibiotics” and “Probability of giving right antibiotics” had the highest influence on the ICERs. The influence of other parameters on the ICER is presented in the figure.

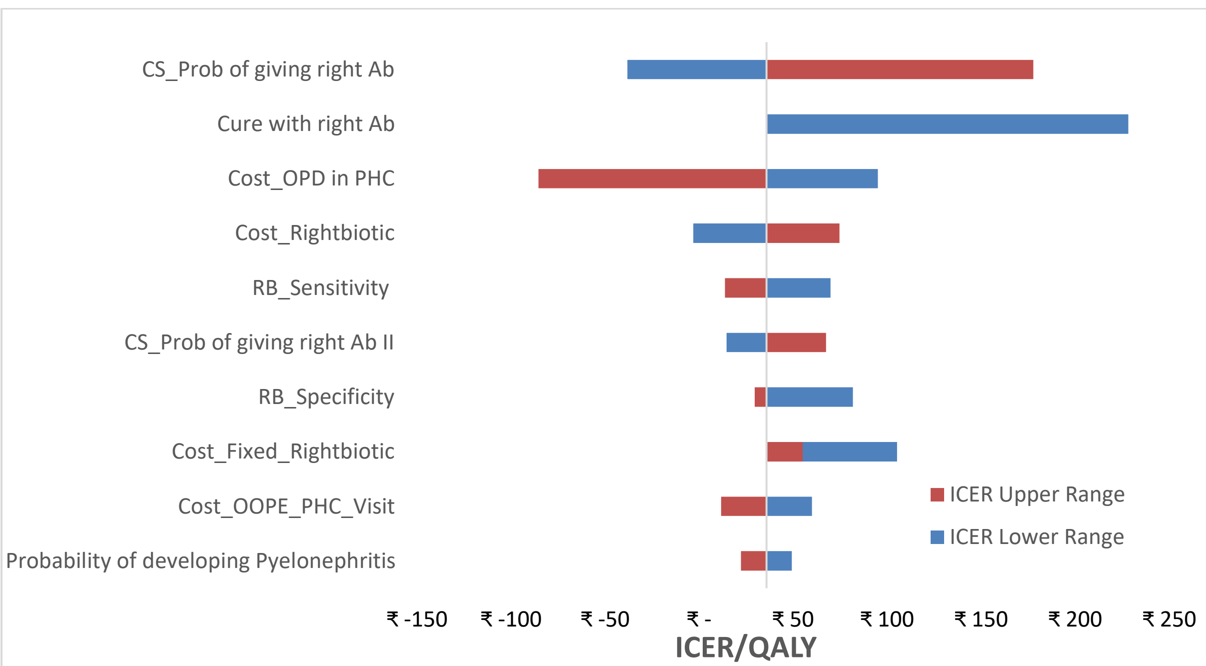
**Table 2.1 Base Case Results (N=1)**

| | Empirical Treatment | RightBiotic | Rapidogram |
|---|---|---|---|
| *Total cost* | ₹ 215 | ₹ 224 | ₹ 219 |
| *Total QALYs* | 3.406 | 3.665 | 3.662 |
| *Incremental cost* | - | ₹ 9.29 | ₹ 3.98 |
| *Incremental QALYs* | - | 0.259 | 0.256 |
| ICER/QALY gained | - | ₹ 35.87 | ₹ 15.55 |

**Table 2.2 Net Monetary Benefits associated with use of rapid diagnostics kits (N=1)**

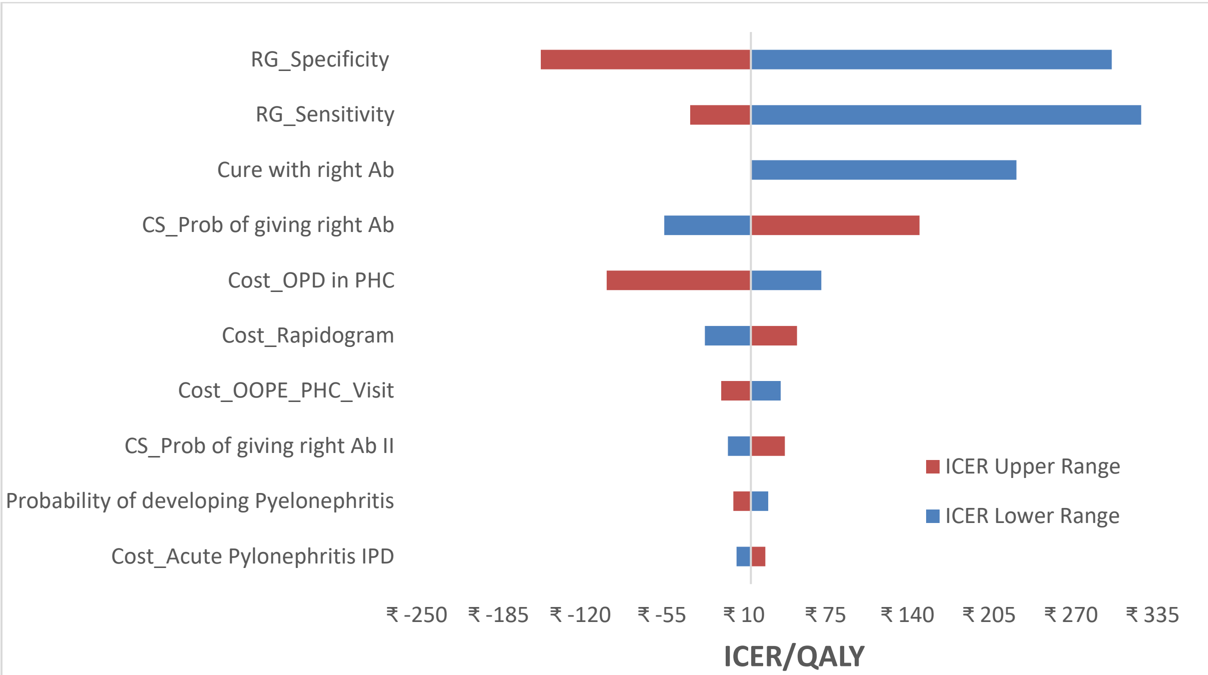
| | Incremental cost | Incremental benefit | Net Monetary Benefit |
|---|---|---|---|
| RightBiotic | ₹ 9.29 | ₹ 37,725 | ₹ 37,715 |
| Rapidogram | ₹ 3.98 | ₹ 37,285 | ₹ 37,281 |

*Note: Assuming threshold (λ) = ₹ 1, 45,679*




*CS-Current scenario; RB-RightBiotic; OPD-Out patient department; Ab-Antibiotics*

**Figure 2** One-way sensitivity analysis for RightBiotic




*CS-Current scenario; RG-Rapidogram; OPD-Out patient department; IPD- In patient department Ab-Antibiotics*

**Figure 3** One-way sensitivity analysis for Rapidogram

### 5.2.2 Probabilistic sensitivity analysis (PSA)

The PSA with thousand iterations of the cost-effectiveness model showed clustering of ICERs around the base case results in both the intervention indicating less uncertainty on the estimates. The differences in the incremental costs and incremental outcomes between the two interventions in comparison to the current scenario are presented in the cost-effectiveness plane given in figure 4. Based on the position of incremental costs and QALYs on the right quadrants of the cost-effectiveness (CE) plane, both the interventions were found to be cost-effective. The results obtained from 1000 simulations fell on both the northeast and southeast quadrants of the CE plane.

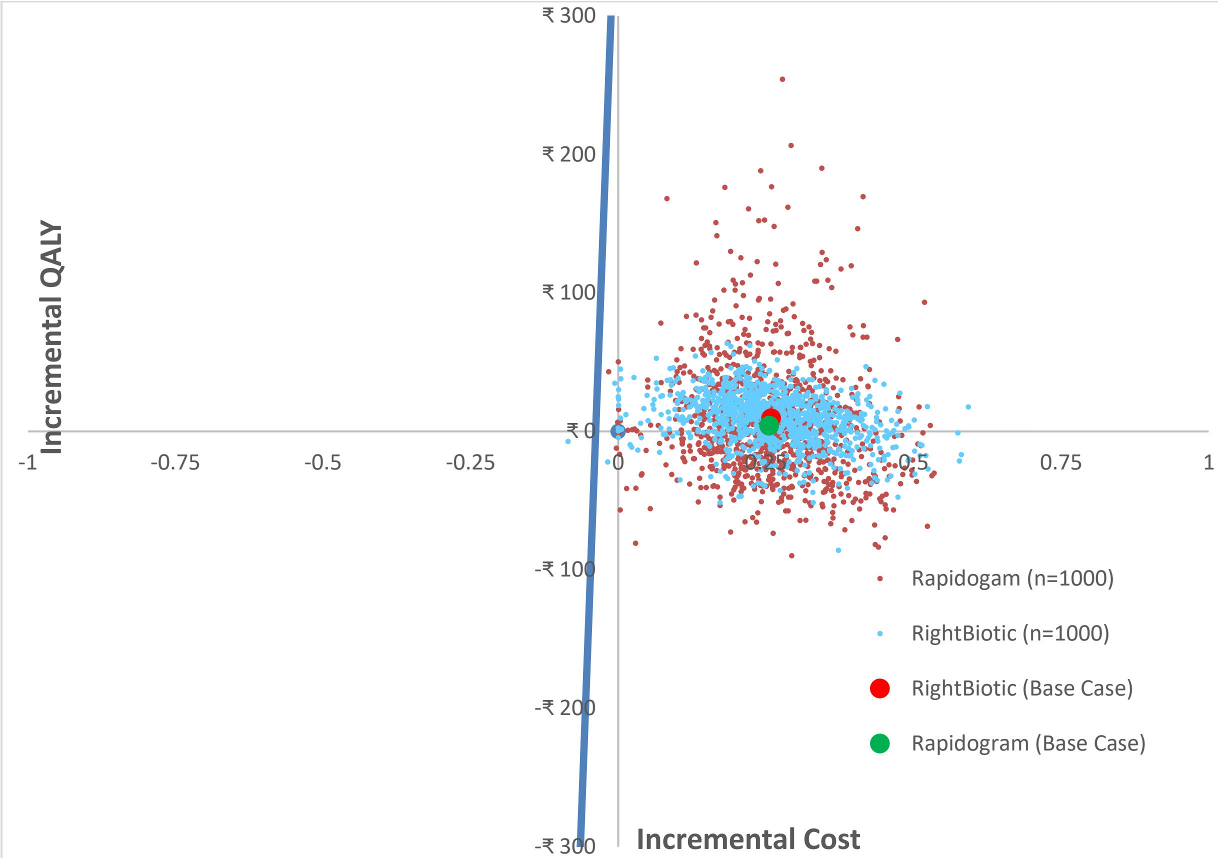



**Figure 4** Probabilistic sensitivity analysis

### 5.3 Cost-Effectiveness Acceptability Curve

Compared to the empirical treatment, the ICER estimates of RightBiotic and Rapidogram were lower than one-time per capita GDP, which was assumed to be the willingness-to-pay threshold for India. According to the assumed willingness to pay, the probability that RightBiotic and Rapidogram to be cost-effective is 100% (Figure 5)

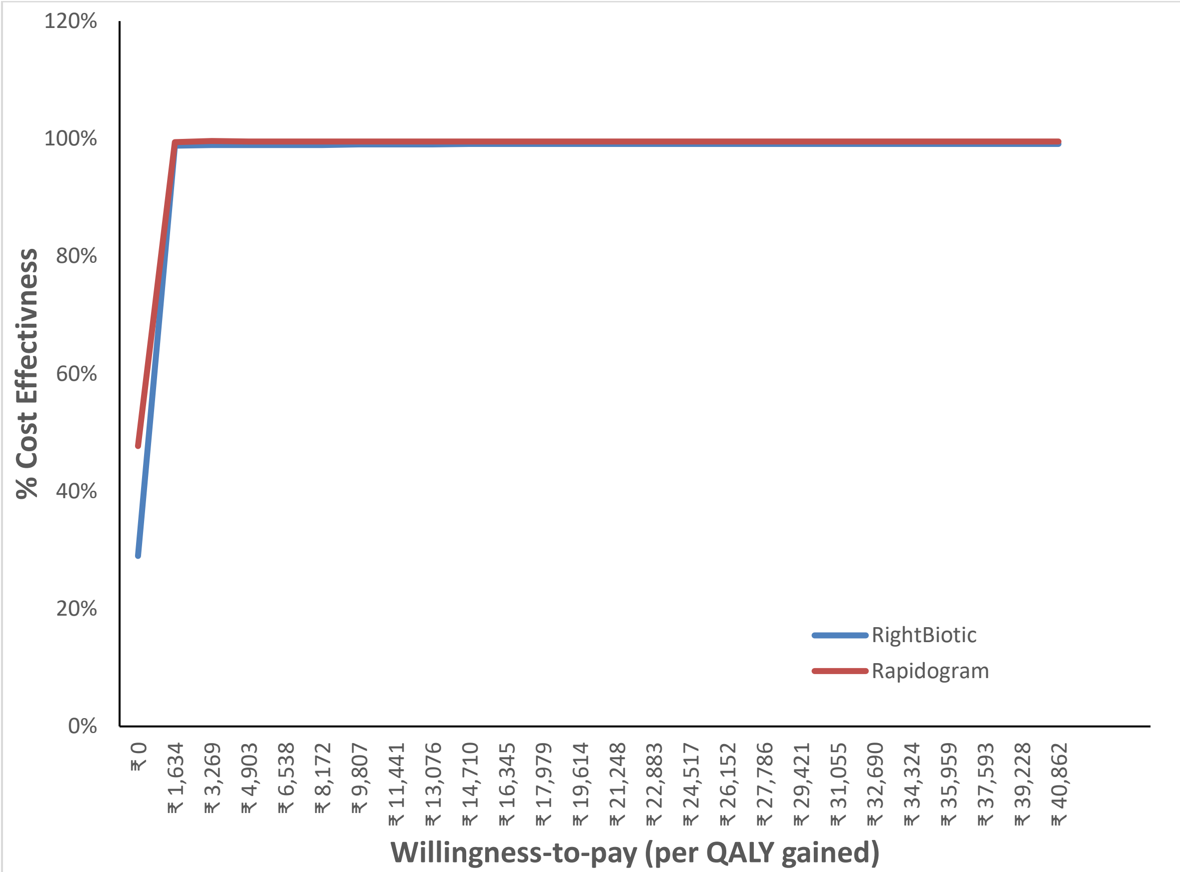



**Figure 5** Cost-Effectiveness Acceptability Curve

### 5.4 Scenario Analysis

Scenario analysis on the probability of the choice of right antibiotics in the empirical arm had high influence on the incremental cost and QALY of both RightBiotic and Rapidogram (Figure 6). The result of scenario analysis showed that the incremental cost of both RightBiotic and Rapidogram increases with the increasing probability of receiving right antibiotics in the empirical treatment i.e. comparator arm. Consequently, the total QALY in the empirical arm increased with the increasing probability of the choice of right antibiotics which resulted in decreased incremental QALY of RightBiotic and Rapidogram.

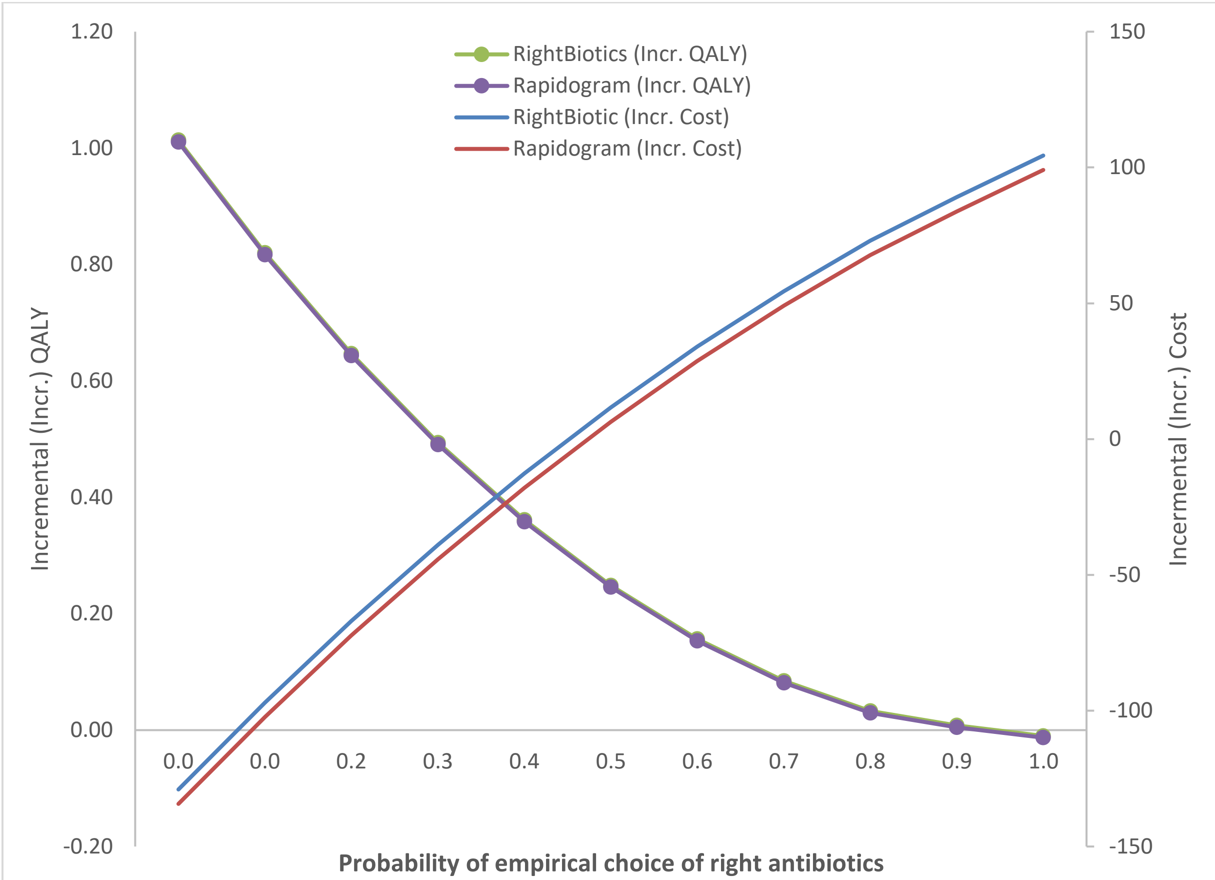



**Figure 6** Scenario analysis on choice of right antibiotic in the empirical treatment

### 5.5 Budget Impact analysis

Implementation of RightBiotic and Rapidogram at all the PHC's in India requires around 2.5% and 1.1% of the current national health budget in the first year, respectively (Table 2). During second year, RightBiotic and Rapidogram incur 0.94% – 0.95% cost of the national health budget. At state level (Tamil Nadu), the implementation of RightBiotic and Rapidogram requires 0.75% and 0.31% of the current state level health budget.

**Table 2.3: Implementation cost of Right Biotic and Rapidogram (in crores)**

| Implementation cost | India (₹) | Impact on National Health Budget 22-23 (%) | Tamil Nadu (₹) | Impact on State Health Budget 22-23 (%) |
|---|---|---|---|---|
| **Right Biotic** | | | | |
| **1st year** | 2,140 | 2.58 | 134.2 | 0.75 |
| **2nd year** | 794 | 0.95 | 49.8 | 0.28 |
| **Rapidogram** | | | | |
| **1st year** | 887 | 1.06 | 55.6 | 0.31 |
| **2nd year** | 780 | 0.94 | 48.9 | 0.27 |

## 6. DISCUSSION

UTI is one of the most common reason for women to make healthcare visits. (22) Till date, clinical management of uncomplicated UTI is mainly based on empirical treatment. With the emerging public health threat of multi-drug resistance worldwide including in India, evidence based prescription of antimicrobial drugs at primary care levels becomes imperative. (23,24) The national report on antimicrobial resistant patterns in India have also documented varying levels of resistance to various common pathogens across India, necessitating drug prescription based on sensitivity analysis of pathogens from the visiting patients. (25) In recognition of the collateral damages due to empirical treatment followed at the primary healthcare levels, two drug sensitivity testing devices (Rapidogram and Rightbiotic) have been developed in India. These devices is expected to contribute towards evidence based antibiotic prescription at the primary healthcare level in India.

In the current study, we assessed the cost-effectiveness of these antibiotic susceptibility testing devices in the management of uncomplicated UTI. We found that both the devices were cost-effective, of which Rightbiotic was more cost-effective when compared to the Rapidogram. This finding carries an immense public health significance, as treatment initiation for uncomplicated UTI based on drug sensitivity would contribute towards preventing development of multi-drug resistant pathogens in the community, as well as produce considerable gains in the patients through preventing healthcare expenditure on UTI associated complications and consequent utility gain among the patients. In support of implementing such devices, the national treatment guidelines for anti-microbial use in infectious diseases recommends for urine culture before empirical treatment initiation at the primary care level. (26)

We found that both the devices were cost-effective by assuming that the probability of administering right antibiotic in the empirical treatment arm (comparator) as 49% percent. It is also well documented that the anti-microbial resistance rate in the community varies across states in the country. Therefore, implementing these devices in the communities having high levels of anti-microbial resistance might be a more cost-effective strategy, when compared to communities where anti-microbial resistance is less or the probability of administering correct antibiotic through the current empirical treatment is high. Therefore, rolling out these devices at the primary healthcare level in the country, would also necessitate information on the magnitude and tread of anti-microbial resistance across regions in the country. The study results also suggest that these devices would remain cost-effective in communities that have up to 90% success rate (probability of giving right antibiotic) in the management of uncomplicated UTI through the ongoing empirical treatment. In communities where the success rate is more than 90% in its empirical treatment, implementing these devices are found to be cost-ineffective.

This study is one of the firsts to have assessed the cost-effectiveness of indigenously developed rapid antibiotic susceptibility testing devices for management of uncomplicated symptomatic UTI among women in the country. One of the major determinants of cost-effectiveness of the two devices was the probability of choosing right antibiotic through the current empirical treatment. In cognizant of substantial variation across states in the probability of prescribing right antibiotic in the current empirical treatment in the country, we have carried out scenario analysis to investigate the influence of the same on the ICER estimates derived for the both the devices. As per the nature of the disease, the utility outcome for both treated and non-treated would attain same levels at the end of one month. In order to capture the variations in the utility during the illness period between the treated and non-treated groups, we have utilized utility values on intermittent days (0,3,4,7,14 and 28th day) during the patient's illness period.

The present study did not account for the future benefits of the devices with respect to the prevention of anti-microbial resistance among the patients. Accounting this factor is likely to make these devices more cost-effective / cost-saving. Therefore, future studies shall incorporate these future benefits for ascertaining the cost-effectiveness of these devices. The utility score used in the study was taken from a study carried out among patients from the United States using Quality of wellbeing scale, which contradicts the current recommendation of HTAIn to use Eq5D5L based utilities in HTA studies in India. However, for the acute illnesses like UTI, it is recommended to use Quality of wellbeing scale that justifies the data used for this study. (20)

## 7. CONCLUSIONS

In the study, both the RightBiotic and Rapidogram were found to be cost-effective with the ICER per QALY gain of ₹ 36 and ₹ 16, respectively. The cost-effectiveness of both the devices were highly dependent on the probability of prescribing the right antibiotic in the current scenario. Therefore, we recommend for implementing RightBiotic and Rapidogram at communities having high levels of antimicrobial resistance.

**ANNEXTURE – I**
**RAPID UTI TESTING DEVICES**

**I RightBiotic**

RightBiotic (The Fastest Antibiotic Finder) is the flagship product of xBITS and the fastest system for carrying out culture and sensitivity testing. RightBiotic is affordable and yet provides you a report in just 4 hours as opposed to ~4days. The report consists of both the identification and AST (Antibiotic susceptibility test) results. The test has been developed by xBITS.


Figure 1: RightBiotic Diagnostic machine

**Principle**

RightBiotic, the solution provided by xBITS, is a rapid, portable, easy-to-use, less resource-intensive, and affordable, which provides bacterial identification and AST results within 4 h. This new technology integrates the basic tenets of clinical microbiology including bacterial growth in a medium optimized for pathogens and measurement of inhibition of bacterial growthin presence of specific antibiotic, with detection of bacteria based on nephlometry and chromogenic endpoint by enzymatic hydrolysis of different media cocktails by specific disease causing bacteria. The optical sensor-based measurement of endpoint output is analyzed using indigenous software, based on a lab-developed algorithm, which reports both the sensitivity of the pathogen to a customizable panel of antibiotics and bacterial load in the sample. This integrated technology platform can be used for diagnosing infection caused by bacteria and for suggesting effective antibiotics in all types of clinical settings to promote evidence-based prescription and minimize irrational use of antibiotics.

**Kit contents:**

1. Dehydrated Medium
2. Sterile water
3. Sterile filter
4. Sterile syringe
5. Loaded strips with 14 or 21 antibiotics (customizable)

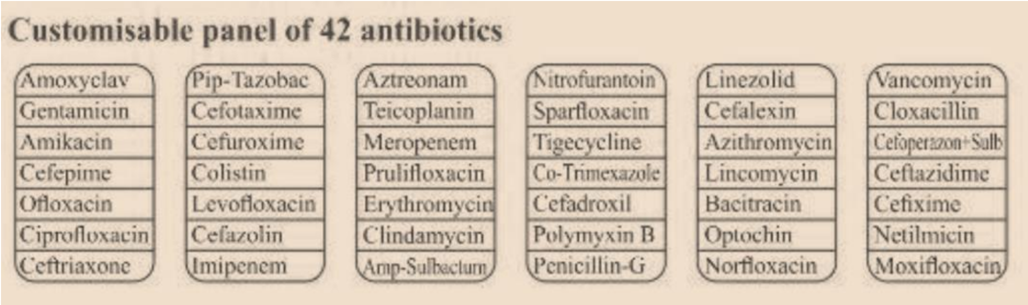
The machine is portable and table-top model and hence it can be deployed wherever the samples are being collected. This technology platform can be used in the doctor's clinic, small and midsize laboratories and in primary, secondary and district healthcare centre with no additional infrastructure requirement such as a lab, laminar flow hood, centrifuge or microscope. A minimally trained lab technician can perform the test very easily. The processing time per sample is just 20 minutes and hence in an 8hr day more than 20 samples can be processed per machine/per person. Time taken is 4hrs for urine samples with 105 bacteria/ml. Operating temperature of RightBiotic system is at room temperature (not above 42°C).

**Sensitivity and Specificity**

- N= 2324 cases (Clinical Urinary Tract Infection cases at several hospitals/labs)
- Sensitivity= 95.4% (95% CI- 92.44 to 97.48)
- Specificity= 85.6% (95% CI: 82.10 to 86.11)
- Positive Predictive Value 90.68% (95% CI: 79.82 to 83.57)
- Negative Predictive Value 97.91% (95% CI: 92.14 to 94.77)

**Bacterial profile**

*E. Coli, Klebsiella, Staphylococcus, Enterococcus, Pseudomonas, Proteus, Enterobacter Acinetobacter,* and *Citrobacter species*



**Customisable panel of 42 antibiotics**

| | | | | | |
|---|---|---|---|---|---|
| Amoxyclav | Pip-Tazobac | Aztreonam | Nitrofurantoin | Linezolid | Vancomycin |
| Gentamicin | Cefotaxime | Teicoplanin | Sparfloxacin | Cefalexin | Cloxacillin |
| Amikacin | Cefuroxime | Meropenem | Tigecycline | Azithromycin | Cefoperazon+Sulb |
| Cefepime | Colistin | Prulifloxacin | Co-Trimexazole | Lincomycin | Ceftazidime |
| Ofloxacin | Levofloxacin | Erythromycin | Cefadroxil | Bacitracin | Cefixime |
| Ciprofloxacin | Cefazolin | Clindamycin | Polymyxin B | Optochin | Netilmicin |
| Ceftriaxone | Imipenem | Amp-Sulbactum | Penicillin-G | Norfloxacin | Moxifloxacin |

Figure 2: Bacterial panel that can be tested with RightBiotic

**Test Procedure**

After dispensing the media in pre-functionalized strips, these strips have to be incubated for 2 and 3 hours at 37° C. These strips are then read in the **RightBiotic** machine. The machine givesa printout in the form of a report with bacteria name and sensitivity profile for antibiotics.

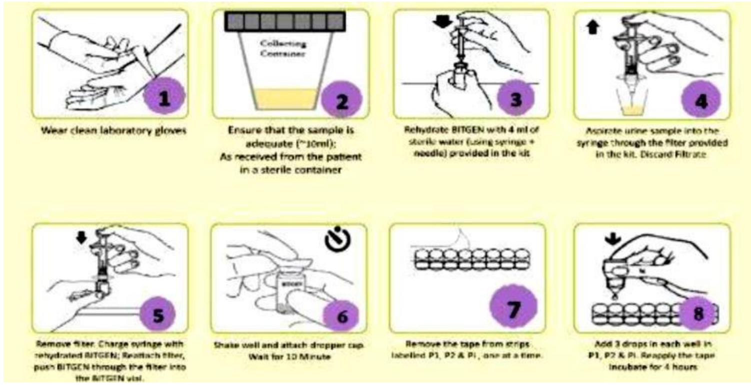



Figure 3: Test procedure

This enables the doctor to prescribe the "Right Antibiotic" from the very beginning of the treatment from Day 1. **RightBiotic** machine is portable and conducting the test does not requireany other additional infrastructure.

### II Rapidogram

This "**Rapid diagnostic kit with antibiotic sensitivity for UTI"** is based on the surmise that the clinician needs to know both whether the patient has UTI, and the antibiogram (antibiotic sensitivity pattern of the causative pathogen) as early as possible. This POC device will hence help the clinicians to decide whether to initiate an antibiotic therapy or not and also the most suitable antibiotic to be used.

### Test Principle

The urine sample from the patient is used in the kit. The kit is self-sufficient and contains everything needed for testing except an incubator at 37 0C. The vial marked control will give whether the patient has significant bacteriuria and this can be read visually by observing change in colour from green to yellow. The antibiotic sensitivity / resistance is detected by the changein colour of the test vials having labels of the various antibiotics on incubation from green to yellow. The change in colour depends upon growth of the pathogen. If the bacterium is resistantto the antibiotic used, color of the contents of the vial will turn from **green** to **yellow**. If the bacterium is sensitive to the antibiotic tested the **original green colour will be retained**. The kit doesn't need sophisticated equipment and can be done in a primary health centres or the Doctor's clinic by anyone who can read and follow instructions. The doctor can have information on whether patient has UTI and also which antibiotic can be used within 3 to 6 hours. The kit has a panel of twelve antibiotics currently.

Figure 4: Rapidogram kit

The UTI test kit is designed for individual test. Each test kit consists of 12 antibiotic vials, reaction vial, normalizing solution, control vial and accessories. The antibiotics are selected such that they belong to various generations of antibiotics which are commonly used for treatment of urinary tract infection. Fresh urine is the sample. The result will be available from3-6 hours. The approximate would be around Rs 500 /- per kit which could be specially priced for rural setting and as manufacturing volumes increases prices will automatically come down.The Sensitivity/ accuracy when compared to gold standard was 96%. UTI causing Gram negative Bacteria (*E.coli, Klebsiella, Proteus* etc in Enterobacteriacea ). Antibiotic panel testedare:

1. Ampicillin, 2. Amoxycillin + Clavulanic acid, 3. Cephalexin, 4. Cefuroxime, 5. Cefotaxime, 6.Ciprofloxacin 7. Trimethoprim/Sulphamethoxazole8.Gentamicin, 9.Amikacin, 10.Nalidixic acid, 11.Nitrofurantoin, 12. Norfloxacin.

Growth of bacteria is analysed and sensitivity to the panel of antibiotics is also based on bacterial growth which causes change in colour from green to yellow for growth and can be read with naked eye. Accelerated (ageing studies) stability studies indicate a shelf life of 1 year.

## ANNEXTURE – II

## AII. COST ESTIMATIONS

**Table A1** Unit Cost of Uncomplicated Urinary Tract Infection treatment at PHC

| S.no | Parameters | INR |
|---|---|---|
| 1. | Per OPD visit in PHC | 971 |
| 3. | Per OPD visit in District Hospital | 2, 642 |
| 4. | Antibiotic cost | |
| | a. Tab. Nitrofurantoin* | 96 |
| | b. Tab. Co-trimoxazole^ | 22 |
| | c. IV. Amikacin 500 mg^ | 58 |
| | Average Antibiotic cost | 59 |

*5 days; ^3 days

**Table A2** Unit Cost of Acute Pyelonephritis Treatment in Out Patient Department

| S.no | Parameters | INR |
|---|---|---|
| 1. | Urinalysis | 300* |
| 2. | Urine Culture | 390* |
| 3. | Ultrasonogram | 790* |
| 4. | Oral Antibiotic[#] | |
| | a. Tab. Co-trimoxazole | 108 |
| | b. Tab. Cephalexin (Keflex) | 459 |
| | c. Tab. Nitrofurantoin | 134 |
| | d. Levofloxacin | 91 |
| | Average oral antibiotic cost | 198* |
| 5. | IV antibiotic^ | |
| | a. Inj. Amikacin (500mg) | 58 |
| | b. Inj. Piperacillin 1gm+Tazobactum | 4,712 |
| | Average IV antibiotic cost | 2,385* |

| | | |
|---|---|---|
| 6. | OPD Visit in District Hospital | 5,284* |
| | Total Cost | 9,347 |

**cost included in total cost, ^IV antibiotics are assumed to be given for 3 days*

**Table A3** Per Unit Cost incurred for Acute Pyelonephritis Treatment (IPD)

| S.no | Parameters | INR |
|---|---|---|
| 1. | Urinalysis | 300* |
| 2. | Urine Culture | 390* |
| 3. | Ultra Sound Graph | 790* |
| 4. | IV antibiotic | |
| | a. Inj. Piperacillin +Tazobactum 1.125gm | 7,560 |
| | b. Inj. Ertapenam | 24,500 |
| | Average IV antibiotic cost | 16,030* |
| 5. | OPD Visit in District Hospital | 44,400* |
| | Total Cost | 61,420 |

**cost included in total cost*

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