PHARMACOECONOMIC EVALUATION OF DOXYCYCLINE AND TETRACYCLINE IN THE TREATMENT OF CHLAMYDIAL IMPLICATED NON-GONOCOCCAL URETHRITIS IN A TERTIARY HEALTHCARE INSTITUTION IN NIGERIA.

* Giwa A1, Osagbemi GK2, Olayinka BO3, Giwa HBF4. 1Department of Clinical Pharmacy and Pharmacy Administration, faculty of Pharmacy, University of Maiduguri, Nigeria. 2Department of Epidemiology and Community Health, College of Health Sciences, University of Ilorin, Nigeria; 3 Department Pharmaceutics and Pharmaceutical Microbiology, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Nigeria and 4 Department of Pharmacy, University of Ilorin Teaching Hospital, Nigeria
* Correspondence Email: abdulganiyugiwa@yahoo.com

ABSTRACT

With depressing nature of economy in many countries such as Nigeria where per capita income is low, there is need for utmost consideration for cost containment measures.  

Objective: The objective of this study is to conduct pharmacoeconomic evaluation of two anti-chlamydial indicated non-gonococcal urethritis therapeutic options and to make recommendations for inclusion of economic evaluation of drug therapies in health policy formulations and decision making.  

Methods: Cost effectiveness analysis was carried out retrospectively for prescribed/dispensed antibacterials to out-patients with chlamydial implicated non-gonococcal urethritis among other infectious diseases, by examining out-patient case notes between 2005 and 2007 in Ahmadu Bello University Teaching Hospital, Zaria Nigeria.  

Results: The result shows that doxycycline costs N1.33/unit of effectiveness while tetracycline costs N2.77/unit of effectiveness in the treatment of chlamydial implicated non-gonococcal urethritis. Doxycycline is therefore more cost effective than tetracycline capsules. Subjecting the costs and effectiveness to sensitivity analysis did not change this conclusion. There is statistically significant difference in the effectiveness (outcome) of doxycycline (78.8%) and tetracycline (58.7%) ( \( \chi^2 = 9.4; p<0.05 \) ) There is therefore association between effectiveness and therapeutic option chosen with doxycycline being a more cost-effective option. The result is significant because doxycycline is not currently included in the Essential Drug list of Nigeria. However, the result is in agreement with Zimbabwean Essential Drug list which recommended that tetracycline be replaced by doxycycline in all indications and should be used only when doxycycline is not available. Also doxycycline is a drug of choice for other disease like gonorrhea and syphilis in non-pregnant women. It was concluded that Doxycycline 100mg bd x 1/52 is more cost effective than Tetracycline 500mg qid x 1/52 in the treatment of chlamydial implicated non-gonococcal urethritis. Adoption of economic evaluation of drug therapies in Nigeria Health policy formulation and decisions is likely to enhance overall Health System cost effectiveness.  

KEYWORDS: Pharmacoeconomics, Cost effectiveness analysis, Doxycycline, Tetracycline, Non-gonocccal Urethritis.

INTRODUCTION:

The advancement in medical technology (both diagnostic and therapeutic options) have complicated the financial burden of Health Systems. Although they offer the potential to improve quality of care, these advances have significantly increased Health Systems operating costs. In spite of all aforementioned inherent and obvious predicaments, public expectation from healthcare providers and government is
increasingly becoming higher on a daily basis (3, 4).
Therefore, there is need for a useful scientific intervention that can facilitate rational decision-making, motivating healthcare practitioners to consider more compressive model for medical decision-making. All these trends have led to the evolution of Pharmacoeconomic, a relatively new discipline in Pharmacy (5, 6).
Cost-effectiveness analysis, a form of Pharmacoeconomics tool appears more effective if applied properly in therapeutic decision-making. The various outcomes of therapy namely; economic, clinical and humanistic (psychosocial) are considered (7). A comparative cost and outcome evaluation was carried out for Doxycycline and Tetracycline in the treatment of chlamydial implicated non-gonococcal urethritis in Ahmadu Bello University Teaching Hospital, Zaria, Nigeria.

MATERIAL AND METHODS
Time and motion studies in conjunction with standard cost-accounting techniques were used in this retrospective study.

Patients
The analysis addressed adult outpatients in Out-Patient Department Ahmadu Bello University Teaching Hospital, Zaria, Nigeria with chlamydial implicated non-gonococcal urethritis among other infectious disease confirmed by necessary diagnostic tools (Table 3).

Consequently, interest in research to assess the outcomes of healthcare has been on the increase. Medical, ethical and societal concerns about costs, access and quality of care are also

Data Collection
One thousand and eighteen (1018) outpatient case notes for selected diseases were consecutively examined using diagnostic coding cards. These were essentially diseases that had antibacterial agents as the mainstay of therapy. One hundred and forty eight (148) of the patients suffered from chlamydial implicated non-gonococcal urethritis.

In all, 1527 dispensed prescriptions were sampled systematically and examined. Relevant information were extracted and recorded. These included prescribed/dispensed drugs between year 2005 and 2007. Others were dosage, duration of therapy, patient demographic data, diagnosis, concurrent illness, diagnosis tests (if any), physician’s remark on each visits and cost of drugs.

Computation of Data
The cost per Defined Daily Dosage (DDD) of each antibacterial was calculated. DDD units are recommended by World Health Organization (WHO) for analysis of drug use. DDD represents the usual daily dosage of antibacterial per day (8).

Cost-effectiveness Analysis
Analysis of costs in monetary units and effectiveness in natural units (eradication of bacteria and clinical cure) were carried out.
Conduction of cost-effectiveness analysis (9, 10)

Definition of Pharmacoeconomic problem: Should option I or II be recommended as therapy of choice for the treatment of chlamydial implicated non-gonococcal urethritis? (Table 3)

Definition of the goals and objective of problem situation: The objective was to determine which of the treatment options provide greater value for money for using effectiveness rating (Table 4), decision analysis (Table 5) cost of therapy (Table 6) and cost effectiveness analysis table (Table 7).

Perspective: Economic perspective of the Health institution was chosen since the drugs were prescribed there. However, patient perspective was considered where necessary.

Enumeration of the different ways to achieve the objective: (Table 4)

Consideration of available/preferred treatment options was made between doxycycline and tetracycline.

Determination of cost of therapy

Only direct medical costs were included in the analysis. These included overhead and operating costs such as acquisition costs of drugs, staff time (costs associated with preparation and dispensing of the product) where it differs from the two options considered. Others include equipment, disposables and transport costs to patients where applicable. The cost per defined daily dosage (C/DDD) of each drug was used (Table 6).

Time and motion studies were carried out for Pharmacists that differ between each option. There was no statistically significant difference between the frequencies of Physician visits among the two treatment options considered, being outpatients.

The time and motion studies involved observing the actual work of each personnel including dispensing of capsule. Each activity was timed using a stopwatch and the average time for 10 random observations for the completion of the task was determined.

The mean salary for the healthcare personnel was obtained from the Accounts section of the hospital.

Mean salary/sec = annual salary
                  Hours/week x Number of weeks/annum x 360

The individual costs were converted into cost per dosage regimen.

Discounting: No adjustment for inflation or discounting was made for the analysis. Costs were fairly stable and both options were used within each year under review. However, slight variation over the period under review.
in some cases led to the use of mean cost of each option.  

**Consequences (Outcomes of each treatment option).**  
The literature was reviewed for positive and negative outcomes of each treatment options (Table 4) (11-14)  

**Sensitivity Analysis**  
Sensitivity analysis was performed to test whether the decision changes when specific variables altered within reasonable range in favour of less cost effective option. This was carried out for the cost of treatment options and effectiveness (Table 8)  

**Data Analysis**  
Statistical analysis was carried out on the results obtained. The effectiveness rating (percentage, proportion) was compared by the use of Chi-square analysis.

## RESULTS

### Table 1: COST EFFECTIVENESS ANALYSIS (CEA)

<table>
<thead>
<tr>
<th></th>
<th>Cost of therapy</th>
<th>Effectiveness (E)</th>
<th>CEA (€/€)</th>
</tr>
</thead>
</table>
| Doxycycline Option I  
100mg b.d x 1/52 | N104.3          | 78.8              | N1.33/unit of effectiveness |
| Tetracycline (Option II)  
500mg q.i.d x 1/52 | N62.5           | 58.7              | N2.77/unit effectiveness |

Using Doxycycline capsule (option I) in the treatment of chlamydial implicated non-gonococcal urethritis at a full course of 100mg bd x 1/52 cost N104.3 with effectiveness measure of 78.8 and cost effectiveness of N1.33/unit of effectiveness. While tetracycline capsules at a full course of 500mg qid x 1/52 (option II) when used for treatment of same condition cost N162.5 with effectiveness measure of 58.7 and cost effectiveness of N2.77/unit of effectiveness.

Doxycycline capsules 100mg qid 1/52 is therefore cheaper per unit of effectiveness than tetracycline capsules 500mg qid x 1/52 in the chlamydial implicated non-gonococcal urethritis and therefore more cost effective.

There is statistically significant difference in the effectiveness (outcome) of Doxycycline and tetracycline (58.7%) \((X^2 = 9.4; p< 0.05)\). There is therefore association between effectiveness and therapeutic option chosen.

### Table 2: SENSITIVITY ANALYSIS

<table>
<thead>
<tr>
<th>S/NO</th>
<th>ALTERATION IN VARIABLE</th>
<th>COST EFFECTIVENESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increasing the cost of doxycycline by 50%</td>
<td>N1.99/unit of effectiveness</td>
</tr>
<tr>
<td>2</td>
<td>Decreasing the cost of doxycycline by 40%</td>
<td>N1.66/unit of effectiveness</td>
</tr>
<tr>
<td>3</td>
<td>Increasing the effectiveness of tetracycline to 78.8 (Doxycycline value)</td>
<td>N2.006/unit of effectiveness</td>
</tr>
</tbody>
</table>

Sensitivity analysis (what if analysis) indicates the decision still remains valid, confirming doxycycline to be more cost effective, despite alterations
made in favour of less cost effective Tetracycline.

Table 3: Treatment Options For Cost-Effectiveness Analysis

<table>
<thead>
<tr>
<th>Diseases condition</th>
<th>Diagnostic tools</th>
<th>Treatment option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-gonoccal urethritis where chlamydial is implicated</td>
<td>Objective evidence of urethra discharge (Expressed by milking or ≥ 5PMIN/100 x field in the urethra secretion, with the exclusion of N. gonorrhoea by Gram’s stain and/or culture)</td>
<td>Doxycycline capsules 100mg bid x ½ Tetracycline capsules 500mg qid x ½</td>
</tr>
</tbody>
</table>

Table 4: EFFECTIVENESS RATING

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>CAP DOXYCYCLINE (OPTION I)</th>
<th>VALUE</th>
<th>CAP TETRACYCLINE (OPTION II)</th>
<th>VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spectrum of activity</td>
<td>Broad-spectrum antibiotic. Gram negative Gram-positive organisms and chlamydial are sensitive, as well as 70-90% of anaerobes. More active for resistant organisms 100% sensitivity of chlamydial infection assumed for both options in their respective dosages</td>
<td>100%</td>
<td>Broad-spectrum antibiotic. Gram negative Gram-positive organisms and chlamydial are sensitive, about 10% resistance for Gram-positive and 50% for some Gram-negative organisms reported, less active.</td>
<td>100%</td>
</tr>
<tr>
<td>Assumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a Pharmacokinetics</td>
<td>Oral absorption 93% Pre-system metabolism Nil Bioavailability 93% Plasma t½ (range) 18-22hrs Plasma protein binding 82-93% 0.d. or b.d</td>
<td>93% 75%</td>
<td>Oral absorption irregular &amp; incomplete Pre-system metabolism Nil Bioavailability 60% Plasma t½ (range) 8-5hrs Plasma protein binding 36-50% Qid</td>
<td>80% 25%</td>
</tr>
<tr>
<td>2b Frequency of administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Interaction</td>
<td>It can be taken with food or milk if gastric irritation is a problem although chelates multivalent cations the least for the tetracycline</td>
<td>50%</td>
<td>It cannot be taken with food or milk because of irregular and incomplete oral absorption. It is a chelating agent for multivalent cations</td>
<td>1%</td>
</tr>
<tr>
<td>4. Adverse Drug Reaction (ADR)</td>
<td>Nausea Vertigo Rash Phototoxicity Safe in renal insufficiency Each negative effect assumed to be 10% Tolerability = 100-40</td>
<td>60%</td>
<td>Nausea Vertigo Rash Phototoxicity Less safe in renal insufficiency Tolerability = 100-50</td>
<td>50%</td>
</tr>
</tbody>
</table>

Notice o.d =100%, bid = 50%, qid = 25%
Table 5: Table Of Decision Analysis.

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>CAP. DOXYCYCLINE (OPTION I)</th>
<th>Cap. Tetracycline (Option II)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value (%)</td>
<td>Assigned Weight</td>
</tr>
<tr>
<td>1. Spectrum of activity</td>
<td>100</td>
<td>0.4</td>
</tr>
<tr>
<td>2a Pharmacokinetics</td>
<td>93</td>
<td>0.1</td>
</tr>
<tr>
<td>2b. Frequency of administration</td>
<td>75</td>
<td>0.1</td>
</tr>
<tr>
<td>3. Interaction</td>
<td>50</td>
<td>0.2</td>
</tr>
<tr>
<td>4. Tolerability (100-DR%)</td>
<td>60</td>
<td>0.2</td>
</tr>
<tr>
<td>SUM OF CRITERIA RATINGS</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

Table 6: Cost Of Therapy

Only direct medical costs, which included; drug acquisition cost and costs associated with dispensing were considered.

<table>
<thead>
<tr>
<th>OPTION I DOXYCYCLINE CAPSULES</th>
<th>OPTION II TETRACYCLINE CAPSULES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquisition Cost = C/DDD x DOT in days = 100mg bid x 1/52 - 14 x 7 = 98.00</td>
<td>Acquisition Cost = 500mg qid x 1/52 = 20 x 7 = N140.00</td>
</tr>
<tr>
<td>Cost of dispensing by Pharmacist = Mean salary/sec x time taken for dispensing ins seconds = 0.2680 x 24 = N6.43</td>
<td>Cost of dispensing by Pharmacist = 0.2680 x 84 = N22.51</td>
</tr>
<tr>
<td>Total cost = N104.43</td>
<td>Total Cost = N162.51</td>
</tr>
</tbody>
</table>

Physician office visit and patient traveling cost is assumed to be the same for both options.

Table 7: Cost Effectiveness Analysis (CEA)

<table>
<thead>
<tr>
<th>OPTION I DOXYCYCLINE CAPSULES</th>
<th>OPTION II TETRACYCLINE CAPSULES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost = 104.43, Effectiveness = 78.8</td>
<td>Cost = 162.51, Effectiveness = 58.7</td>
</tr>
<tr>
<td>CEA = 104.43/N1.33/unit of effectiveness</td>
<td>CEA = 162.51/N2.77/unit of effectiveness</td>
</tr>
</tbody>
</table>

Table 8: Sensitivity Analysis

i. Increasing cost of doxycycline by 50% (156.65)

CEA 156.65 = N1.99 unit of effectiveness

78.8

ii. Decreasing cost of tetracycline by 40% (97.51)

CEA 97.51 = N166 unit of effectiveness

58.7

iii. Increasing the effectiveness of tetracycline to 78.8 (Doxycycline value)

CEA 162.51 = N2.06 unit of effectiveness

78.8

Sensitivity analysis ("what if") indicates that the decision still remain valid, confirming doxycycline to be more cost effective.
DISCUSSION

The result of this study is significant because the Essential Drug List of Nigeria does not include doxycycline in spite of its cost-effectiveness over tetracycline as shown in this study. With NAFDAC’s recent commitment to registration of good quality drugs, economic evaluations in form of pharmacoeconomic trials reports should be required along with clinical trials report for the inclusion of a drug on the Essential Drugs List. With these, decisions for drug registration will be based on the principle that “if a drug is not better than a comparable product, it should not cost more. If it is superior to existing therapies but more expensive (a common situation), and funds are available, any extra expenditure should represent “value for money” (15).

The result of this study is in agreement with Zimbabwean Essential Drugs List which recommended that tetracycline be replaced by doxycycline in all indications, and should only be used when Doxycycline is not available (2). Also Doxycycline is a drug of choice for other disease like gonorrhea and syphilis in non-pregnant women. This result is also similar to the outcome of a comparative study for doxycycline and co-trimoxazole in the non-gonococcal urethritis where conclusion was drawn that Doxycycline is superior to co-trimoxazole and may become the drug of choice for uncomplicated non-gonococcal urethritis (16). The findings of this study is in agreement with the report of the National Network for STD/HIV Prevention and Training Center that doxycycline at a course of 100mg bid x 1/52 for treatment of Chlamydial infection has an efficacy of 95-100%, lower cost and better tolerability than Erythomycin 2mg daily x 1/52 with 85-95% efficacy, higher cost and only fair tolerability (17).

The statistically significant difference in the effectiveness of Doxycycline (78.8%) and tetracycline (58.7%) ($X^2 = 9.4; p<0.05$) appear to be due to difference in their economic clinical and humanistic outcomes (7).

Doxycycline achieves bioavailability of 93% after oral absorption while tetracycline due to irregular and incomplete oral absorption has 60% bioavailability (11). This and once daily or twice daily dose of doxycycline as compared with four times daily dose of tetracycline, significantly favours the effectiveness rating of doxycycline over tetracycline. The fact that tetracycline cannot be taken with food or milk as compared with doxycycline which can be taken with food or milk if gastric irritation is a problem (14), also favours the effectiveness of doxycycline over tetracycline. Doxycycline is also the least affected by the multivalent reports of resistance to tetracycline. In terms of tolerability, doxycycline is reported to be safer in renal insufficiency than tetracycline(11, 12, 13). This also enhances effectiveness rating of doxycycline in cost-effectiveness analysis.
CONCLUSION AND
RECOMMENDATIONS
The results of this work has shown that
doxyccycline capsules at a course of
100mg bid x 1/52 is more cost effective
than tetracycline capsules at 500mg qid
x 1/52 for the treatment of chlamydial
implicated non-gonococcal urethritis at
p<0.05. This is enough justification for
ensuring that doxyccycline is included in
the revised Nigerian Essential Drug
List. Adoption of economic evaluation
of drug therapies in National health
policy formulation and decision is
therefore likely to guarantee the overall
Health System cost-effectiveness.
REFERENCES
antibacterial paradox: Essential
drugs, effectiveness and cost.
Bulletin of World Head
Organization: 73(3)
2. Essential Drug for Zimbabwe
including guidelines for
treatment of medical conditions
in Zimbabwe, Ministry of
Health, Harare, 1994
Century: Hospital Pharmacy in
changing healthcare delivery
system. Orlando.
Century: Hospital Pharmacy in
changing healthcare delivery
system. Orlando.
5. Townsend, R.H 1987 Post
Marketing drug research and
development. Drug Intelligence
and Clinical Pharmacy 21:134-6
6. World Health Organization,
1996 Health economics, drug
and health sector reform. WHO
Taskforce on Health-economics.
7. Kozmal, CM, Reeder, CE and
Scuiz RM Economic, Clinical
and Humanistic Outcomes: a
planning model for
pharmacoeconomic research.
Clinical Therapeutics. 1993;
Nov.-Dec. 15(6)1121-32;
discussion 1120.
8. Nerthemier, AI. The Defined
Daily Dosage system (DDD) for
drug utilization review Hospital
Pharmacy; 1986, 21:233-41
9. World Health Organization:
Cost analysis in primary
healthcare: A training manual
for program managers.
10. Cano, SB and Fujita, NK
Formulary evaluation of third
general Cephalosporins
decision analysis. American
Journal of Hospital Pharmacy;
1988, 45:566-9
11. Steigbgel, NH, reed LW,
Finland M. Absorption and
excretion of five tetracycline
analogous in normal young


14. Neuronen PJ Interaction with the absorption of tetracycline; *Drugs* 1976; 11:45

