

Factorials Experiment for Directly Observed Treatment Short Course (Dots): Treatment of Tuberculosis Infection in Abia State, Nigeria

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ABSTRACT

In line with World Health organization (WHO's) directive, Nigeria established the Directly Observed Treatment Short-course (DOTS) centers in all states and local government of the federation to assist in the detection, monitoring and treatment of tuberculosis. The treatment outcomes measures the effectiveness of the drugs administered to the patients to control the spread. To evaluate patient's responses when administered with tuberculosis infection preventive treatment, drugs were administered to patients and monitored for three years and the result obtained were recorded and subsequently analyzed using the factorial design experiment. There was a high success rate of 48.6% of those under study, especially in category 3. The overall mean performances of the drugs were on the average equally well, with some degree of interaction.

Keywords: Tuberculosis, Interaction effect, Dots, Factorial experiment.

1. INTRODUCTION

Tuberculosis is a life threatening infection but is however, curable. The diagnosis and treatment drugs is made available at no cost to all the Directly Observed Treatment Short-course (DOTS) centres in Nigeria. The DOTS centres is the most cost effective way and best curative method to check and stop the spread of tuberculosis in local areas with high rate of prevalence. These DOTS services are provided in about 6000 health centres in Nigeria. To support the DOTS, a new molecular technology known as Gene Xpert, a machine that diagnoses TB and rifampicin-resistant TB within two hours had also been provided.

TB is caused by Mycobacterium tuberculosis. Those with TB disease in their lungs or throat release atoms in the air when they cough or sneeze. These atoms are called droplet nuclei and contain TB. Those affected with tuberculosis have symptoms like dry throat, enlargement of the neck etc. The disease is dormant in some patient and may not show any symptom but however, causes damage to the lungs and other organs of the body. The world health organization (WHO) declared tuberculosis (TB) a global emergency in 1993 and it remains the world's major causes of illness and death. One third of the world's population, two billion people, carries the TB bacteria. More than 9million of these become sick each year with active TB. That can be spread to others. More than 90% of new TB cases occur in developing countries. Nigeria rank 10th among the 22 high burden TB countries in the world. WHO estimated 320,000 prevalent cases of TB in 2010, there were 90,447 TB cases notified in 2010 with 41.6416 (58%) as new smear positives. 83% of cases notified in 2009 were successfully treated. However, the death rate has declined from 11% in 2006 to 5% in 2010. Lagos, Kano and Oyo have the highest Tb prevalence rate. The age groups commonly affected by TB are the productive age groups, with the 25-34 age groups accounting for 33.6% (15,303) of these positive cases registered in 2010.

The prevalence of HIV among TB patients increased from 2.2% in 1991 to 19.1% in 2001 and 25% in 2010. This shows that the TB cases in the country are HIV driven. The proportion of TB patients tested for HIV was 79% in 2010, with 25% TB-HIV co-infection rate.

Dim and Dim (2013) stated that the burden of tuberculosis in Nigeria is high. Unfortunately the data from the TB programme of the States ministries of health are usually unpublished, which possibly contribute to the prevailing ignorance and poor attitudes of Nigerians to the disease. [1] in the world health day in Abuja, revealed that about 250,000 lives are lost to the disease in Nigeria every year. The minister of Health gave poor diagnosis and non notification of the appropriate health authorities as the reasons militating against the battle of curbing the TB. He further stated that the 2015 Global TB report indicated that of the estimated 9.6 million tuberculosis cases globally, only six million had been detected and reported while 3.6 million had not been reported nor diagnosed. [1] also observed that 600,000 new cases of tuberculosis had occurred in Nigeria with 91,354 persons placed on treatment. He concluded that WHO has ranked Nigeria as the number three among the 22 countries with the highest prevalence of the disease.

[3] asserted that over 480,000 were affected with multi drug -resistant tuberculosis (MDR-TB) in 2013 globally. Nigerian researchers have identified awareness creation on the prevention, management and treatment of TB in communities' remains as panacea to reducing the burden of the disease in Nigeria. The Director General, NIMR [4] said that the death toll from the disease is still unacceptably high and efforts to combat it must be accelerated if the global targets set within the mdg's are to be met. Oni Idigbe (2015) is of the opinion that, if diagnosed and managed effectively, TB is curable. We have all the weapons to diagnose and manage the disease but by 2015, TB remains a big challenge. According to him it was documented that 37 million people were cured of TB in 2010 and 2013 because they were effectively diagnosed and efficiently cured using the right congregation of drugs.

This work evaluate patient's responses when administered with tuberculosis infection preventive treatment as to determine the effectiveness of the treatment drugs and groups of individuals that responds more or less to the treatment. It also discovers more avenues to prevent and treat affected TB patients so as to be free from the sickness within a specific period of time. It also Identify conditions that increase the risk of TB infection and ways in which tuberculosis is spread.

To accomplish this objective, the choice of factorial design of experiment was chosen for the analysis. Factorial experiment is a design whose experiment consists of two or more factors each with discrete possible values or levels and whose experimental units take on all possible combinations of these levels across all factors. Experimental design involves not only the selection of suitable predictors and outcomes, but planning the delivery of the experiment under the statistical optimal conditions given the constraints of available resources. We intend to study not only the effects of the two independent variables (drugs and age group), but also how the combinations of the two influence the dependent variable (treatment of Tuberculosis).

2. METHODOLOGY

This data was collected from the medical records unit and tuberculosis ward/section of the infection and disease hospital (IDH), Aba, Abia State Nigeria. 40 patients were selected between 2012 and 2014. Other information obtained includes the patient's age, sex, marital status, education, type of tuberculosis, duration, family history and type of treatment. With assistance of the lab technologist, patient with their lab result that contains four levels of (TB) tuberculosis (0, +1, +2 and +3) were selected and stratified according to their age group. Drugs of different categories were administered to Patients with different age groups and the effect of those drugs were monitored and patients that were cured, transferred, dead and those that completed their treatment were identified and recorded during the period. Design of factorial experiment was applied to analyze the data.

2.1 Factorial design of experiment

Factorial experiment is any investigation in which the treatments are made up of factors at combinations of different levels and the effect of these factors are investigated simultaneously. The investigator is interested in the main effects and the interaction effects among several factors. The main effect is the average of the components single factor experiments that make up the factorial experiment. Interaction is the comparison among the simple effects of the component experiments. We use factorial experiment to study the main effect and the interaction effect. If the outcomes are different, interaction is present. The analysis of variance ANOVA is the statistical tool for the analysis.

The model for the factorial experiment is

$$Y_{ijk} = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij} + \varepsilon_{ij}$$

$$i = 1, 2 \dots a$$

$$j = 1, 2 \dots b$$

$$k = 1, 2 \dots r$$

Where k levels are obtained for each treatment combination

μ is the overall mean

α_i is the effect of the i th treatment of factor a

β_j is the effect of j th level of factor b

$(\alpha\beta)_{ij}$ is the interaction on α_i and β_j

ϵ_{ijk} is the random error associated with the i th treatment on the j th block with the k th replicate.

The H_o for the two factor experiment are: $\alpha_i = 0, \beta_j = 0, \text{ and } (\alpha\beta)_{ij} = 0$.

Sum of squares

The total sum of squares treatments for a two factor factorial experiment is partitioned into components for each factor and each interaction.

$$SS_T = SS_A + SS_B + SS_{AB} + SS_E$$

Where

$$CF = \frac{T_{...}^2}{abr}$$

$$SS_A = \sum_{i=1}^a \frac{T_{i..}^2}{br} - CF$$

$$SS_B = \sum_{j=1}^b \frac{T_{.j.}^2}{ar} - CF$$

$$SS_{AB} = \sum_{i=1}^a \sum_{j=1}^b \frac{T_{ij}^2}{r} - CF - SS_A - SS_B$$

$$SS_{Total} = \sum_{i=1}^a \sum_{j=1}^b \sum_{k=1}^r Y_{ijk}^2 - CF$$

Table 1: ANOVA table for a two factorial experiment

Source	Degrees of freedom	Sum of Squares	Mean Squares	F- Ratio
A	a-1	SS_A	$MS_A = \frac{SS_A}{a-1}$	$F_A = \frac{MS_A}{MS_E}$
B	b-1	SS_B	$MS_B = \frac{SS_B}{b-1}$	$F_B = \frac{MS_B}{MS_E}$
AB	(a-1)(b-1)	SS_{AB}	$MS_{AB} = \frac{SS_{AB}}{(a-1)(b-1)}$	$F_{AB} = \frac{MS_{AB}}{MS_E}$
Error	Ab(r-1)	SS_E	$MS_E = \frac{SS_E}{ab(r-1)}$	

The decision rule is to reject the null hypothesis when

$$F_{cal} > F_{\alpha}$$

Two factorial design with different drugs (A, B, C & D) and various classes of age groups (0-20, 21-40, 41-60 & 61+), on the treatment of tuberculosis infection. A symmetrical design was carried out with $r = 4$ replicates for each of the (drug & age) factor combinations. N =64 measurements were taken in a completely randomized order. The results are as shown in table 3.

Table 2: Statistical Application of two factorial design experiments.

Drugs	Age group				Total
	0 – 20	21 – 40	41 – 60	61+	
A	1, 7, 1, 2 (11)	12, 22,10,18 (62)	61, 15, 3, 8 (32)	2, 2, 1, 3 (8)	113
B	3, 1, 1, 3 (8)	16,20,21,21 (78)	12, 12, 6, 9 (39)	2, 1, 2, 1 (6)	131
C	2, 6, 2, 4 (14)	22, 30, 9, 3 (64)	5, 14, 9, 4 (32)	3, 2, 1, 2 (8)	118
D	13,13,6,5 (37)	3,12,5,6 (26)	6,6,3,3 (18)	4,11,1,14 (30)	111
Total	70	230	121	52	473

Table 3: Condensed table

Drugs	Age groups				Total
	0-20	21-40	41-60	61+	
A	11	62	32	8	113
B	8	78	39	6	131
C	14	64	32	8	118
D	37	26	18	30	111
Total	70	230	121	52	473

Table 4: Condensed means table

Drugs	Age groups				Means	Total
	0-20	21-40	41-60	61+		
A	2.75	15.5	8	2	7.06	28.06
B	2	19.5	9.75	1.5	8.19	32.75
C	3.5	16	8	2	7.38	29.5
D	9.25	6.5	4.5	7.5	6.94	27.75
Means	4.38	14.38	7.56	3.25	29.57	-
Total	17.5	57.5	30.25	13	-	-

3. COMMENTS

The effect of changing drugs from A to B depends on the response of the class of age group.

- For age group (0-20), the drug effect = $2 - 2.75 = -0.75$
- For age group (21-40), the drug effect = $19.5 - 15 = 4$
- For age group (41-60), the drug effect = $9.75 - 8 = 1.75$
- For age group (61+), the drug effect = $8.19 - 7.06 = 1.13$

The effect of changing drugs from B to C depends on the class of age group.

- For age group (0-20), the drug effect = $3.5 - 2 = 1.5$
- For age group (20-40), the drug effect = $16 - 19.5 = -3.5$
- For age group (41-60), the drug effect = $8 - 9.75 = -1.75$
- For age group (61+), the drug effect = $2 - 1.5 = 0.5$

The effect of changing drugs from C to D depends on the class of age group.

- For age group (0-20), the drug effect = $9.25 - 3.5 = 5.75$

- For age group (21-40), the drug effect = 6.5 – 16 = -9.5
- For age group (41-60), the drug effect = 4.5 – 8 = -5.5
- For age group (61+), the drug effect = 7.5 – 2 = 5.5

3.1 Comment 1

In the estimated effect of drugs A and B

- i. -0.75 is significantly different from 4. Interaction exists.

In the estimated effect of drugs B and C

- ii. 1.5 is significantly different from -3.5. There is interaction.

In the estimated effect of drugs C and D

- iii. 5.75 is significantly different from -9.5. Interaction exists.

$$CF = \frac{T_{...}^2}{abr} = \frac{(473)^2}{4 \times 4 \times 4} = \frac{223729}{64} = 3495.765$$

$$SS_{TOTAL} = \sum_{i=1}^a \sum_{j=1}^b \sum_{k=1}^r ij^2k^2 - CF$$

$$= 11^2 + 62^2 + 32^2 + + 30^2 - CF$$

$$= 6339 - 3495.77 = 2843.23$$

$$SS_A = \sum_{i=1}^a \frac{T_{i..}^2}{br} - CF$$

$$= \frac{113^2 + 131^2 + + 111^2}{16} - CF$$

$$= 15.17$$

$$SS_B = \sum_j \frac{T_{.j.}^2}{ar} - CF$$

$$= \frac{70^2 + 230^2 + + 52^2}{16}$$

$$= 1200.79$$

$$SS_{AB} = \sum_{i=1}^a \sum_{j=1}^b \frac{T_{ij.}^2}{r} - CF - SS_A - SS_B$$

$$= 11^2 + 62^2 + + 30^2 - CF - SS_A - SS_B$$

$$= 640.02$$

$$SS_E = SS_T - SS_A - SS_B - SS_{AB}$$

$$= 2843.23 - 15.17 - 1200.79 - 640.02$$

$$= 987.25$$

Table 5. The anova table

Sources of Variation	Degree of Freedom	Sum of Squares	Means Squares	F-ratio	$F_{0.05}$	Decision
SSA	3	5.17	5.06	0.74	2.76	Accept H_0
SSB	3	1200.79	400.26	19.46	2.76	Reject H_0
SS(AB)	9	640.02	71.11	3.46	2.76	Reject H_0
SSE	48	987.25	20.57			
SST	63	2843.23				

3.2 Comment 2

Since $F_{ratio} = 0.74 < F_{0.05} = 2.76$, we accept H_0 and conclude that A has no significant effect. Also, since $F_{ratio} = 19.46$ and $3.46 > F_{0.05} = 2.76$ we reject H_0 and conclude that AB has significant effect.

4. DISCUSSION/ SUMMARY

In applying different drugs ranging from drugs A –D to individual age specific groups the following observations were noted. In comment 1, the estimated effect of drugs A and B showed that -0.75 is significantly different from 4 indicating that there is interaction. In the estimated effect of drugs B and C, 1.5 is significantly different from -3.5. There is also interaction. Besides, in the estimated effect of drugs C and D, 5.75 is significantly different from -9.5. There is existence of interaction. The combination of the 4 drugs showed interaction.

In comment 2, drug A showed no significant effect while drug B showed significant effect. Drug B is more effective than drug A. The combination of drugs A and B showed significant effect and the existence of interaction.

5. CONCLUSION

The combination of the drugs is most effective in the treatment of tuberculosis. For the age specific groups, 21-40 responds more to drugs A and B, 0-20 responds more to drugs B and C while 0-20 and 61+ responds more to drugs C and D. the age group 0-20 is more receptive to the drugs than other age groups. We however suggest that it is necessary to research on drugs that could effectively treat tuberculosis infection especially those of age group 41-60.

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