OCCURRENCE OF MULTI-DRUG RESISTANT TUBERCULOSIS AMONG PATIENTS WITH SUSPECTED TUBERCULOSIS IN KATSINA STATE NORTH WESTERN NIGERIA

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Abstract

Background: A couple of decades ago, experts in the study of Tuberculosis excogitated that multi drug resistant Tuberculosis (MDR-TB) is uncommon in sub-Saharan Africa due to the delayed introduction of rifamycin based regimens. However, previous studies showed that 21% of the global MDR-TB burden occurs in the region; with South Africa, Nigeria and Ethiopia ranking first second and third, respectively.

Aims and objectives: the objective of this study is to determine the prevalence of drug resistant tuberculosis in patients suspected of having tuberculosis. The aims are: to determine the prevalence of MDR-TB in the non HIV patients presenting with persistent cough, to determine the prevalence of MDR-TB in HIV infected patients and to appraise the extent of the association between MDR-TB and HIV in this region.

Methods: Eight hundred and twenty four (824) sputa were collected from suspected participants and analyzed for the presence *Mycobacterium tuberculosis* and rifampicin resistant strains using a nucleic acid amplification test based machine, Gene expert (Cepheid inc. USA).

Results: One hundred and seventy three (21.0%) of the 824 had MTB and 13(7.5%) of the MTB cases were MDR-TB.

Conclusion: There is a high prevalence of MDR-TB among patients with chronic cough in the region and it is found in both HIV positive and negative patients.

Key words: MDR TB, HIV, Katsina, North-Western Nigeria

INTRODUCTION:

Worldwide, it was estimated that 14.8% of all new Tuberculosis (TB) cases in adults are attributable to HIV infection (WHO, 2014). This proportion is much greater in Africa, where 79% of all TB/HIV co infections are found (STOP TB, 2015). In 2007, 456000 people globally died of HIV-associated TB, with Nigeria having an annual incidence of 311 per 100,000 cases and mortality rate of 81 per 100,000 people, ranking fourth in global TB burden in 2006 (Lawson *et al.*, 2010). This threat becomes more dangerous with the emergence of drug resistant strains of *Mycobacterium tuberculosis* causing multidrug resistant tuberculosis (MDR-TB). MDR-TB is the resistance to atleast rifampicin and Isoniazid with or without any other second line anti TB drug (Adegboyege *et al.*, 2014). Rifampicin resistance is most commonly found on the *rpo* gene of the tubercle bacilli and in more than 90% of cases, it invariably occurs with Isoniazid resistance.

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Therefore, detection of rifampicin resistance alone may serve as a diagnosis for MDR-TB particularly in resource limited settings (Charles *et al.*, 2007).

Globally, MDR-TB accounts for up to 5% of all TB cases, with a higher proportion of 20.5% among people previously treated for TB (WHO, 2014). Previous treatment for TB is the main risk factor for development of MDR-TB, particularly among patients with poor compliance. However, treatment-naïve patients are also at risk due to either spontaneous mutations or transmission of resistant strains (WHO, 2014).

Materials and Methods

Study area

The study was conducted in a General Hospital in Katsina state North West Nigeria. The hospital is a referral center for the diagnosis of suspected DR TB cases in the state. It as well serves the neighboring states of Kaduna and Zamfara. Katsina state has a total area of 24,192km^2, and a population of 6,483,429 by 2005 estimate (5th of the 36 states and FCT), it has a population density of 160/km^2 (NPC, 2006).

Study design

It is a cross sectional study

Study participants

The study consisted of eight hundred and twenty four (824) participants amongst which 440 were HIV negative patients who presented with persistent cough lasting more than two weeks and the remaining 384 were HIV positive participants who are suspected to have TB. Three hundred and eighty three 383(46.5%) were males and 441(53.5%) were females. all of them were adults, and volunteered to participate in the study, the samples were collected between May, 2014 and November, 2015.

Inclusion criteria

The following were included in the research: people living with HIV and happened to have TB symptoms, people previously treated for TB, People who defaulted after commencing an anti TB regimen and people with persistent cough lasting more than two weeks.

Exclusion criteria

Any other patient falling outside the above mentioned categories.

Ethical approval and informed consent

Ethical clearance was obtained from the hospital management before the commencement of the study.

Gene xpert test MTB/RIF test

The Gene Xpert MTB/RIFtest is a cartridge-based, fully automated polymerase chain reaction (PCR) based test for the detection of *Mycobaceterium tuberculosis* and Rifampicin (central first line anti TB drug) resistance. It purifies, concentrates, amplifies (via a speedy, real-time PCR) and identifies targeted nucleotide sequences in the Mycobacterial genome, and provides results from minimally treated sputum samples in less than 2 hours with little or no user intervention (Cepheid, 2012).

About 2mL of sputum samples, devoid of obvious food particles and solid particulates were collected from the participants in the recommended wide-mouthed screw-capped container. All samples were analyzed the day they were collected. The Samples were mixed with sample buffer (in a ratio of 1:2) and incubated for 15 minutes at room temperature. About 2ml of the preparation was transferred into the sample port of the Xpert MTB/RIF cartridge. The cartridge was inserted into the module chamber and the test was started within 30 minutes (Cepheid, 2014). After a holding time of 2 hours, the results were displayed on the monitor and documented.

Statistical analysis

Cross tabulations were made, charts were used where appropriate and Chi square test was used in determining significant relationships between variables considering 95% CI and P value <0.005 as a significant difference.

Results

Table 1: Distribution of MTB among the participants according to sex

Gender	No. Tested (%)	MTB Positive (%)
Male	383(46.5)	71(8.6)
Female	441(53.5)	102(12.4)
Total	824 (100)	173 (21.0)

TABLE 2: MTB distribution among the participants according to HIV status

HIV Status	MTB		Total (%)
	Positive (%)	Negative (%)	
Positive	76 (19.8)	308 (80.2)	**384 (100)**
Negative	97 (22.0)	343 (78.0)	**440 (100)**
Total	**173 (21.0)**	**651 (79.0)**	**824 (100.0)**

P<0.0001; χ^2=16.70; df=1; OR=0.4027 at 95% CI 0.2602 to 0.6232.

TABLE 3: Distribution of MDR-TB according to sex of the participants

Gender	MDR-TB*		Total (%)
	Positive (%)	Negative (%)	
Male	4 (2.3)	67 (38.7)	71 (41.0)
Female	9 (5.2)	93 (53.8)	102 (59.0)
Total	13 (7.5)	160 (92.5)	173 (100)

*MTB Positive. P=0.6243; χ^2=0.2398; df=1; OR=0.6169 at 95% CI 0.1823 to 2.088.

TABLE 4: Distribution of MDR-TB according to HIV status of the participants

HIV Status	MDR-TB*		Total (%)
	Positive (%)	Negative (%)	
Positive	6 (3.5)	70 (40.5)	**78 (17.9)**
Negative	7(4.0)	90 (52.0)	**97(56.0)**
Total	**13 (7.5)**	**160 (92.5)**	**173 (100.0)**

*MTB Positive. P=0.8980; χ^2=0.0164; df=1; OR=1.414 at 95% CI 0.3654 to 5.474.

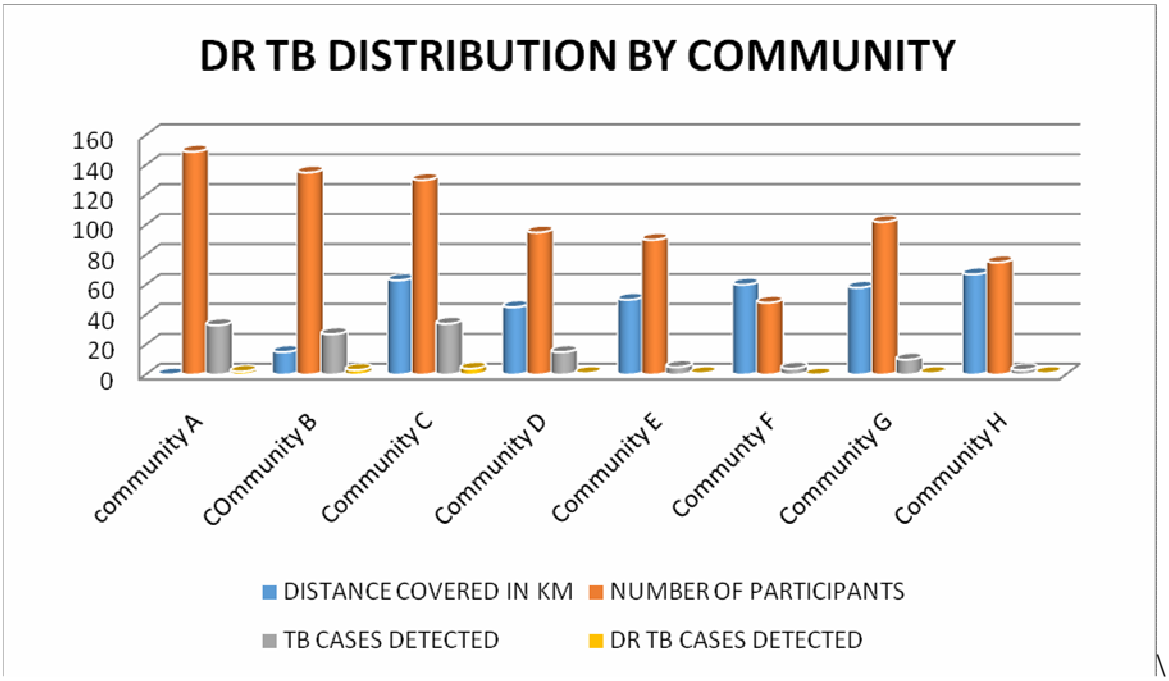

Figure 1: frequency distribution of TB, MDR-TB and distance covered to reach testing site

A total of 824 participants were enrolled in the study constituting 383(46.5%) males and 441(53.5%) females. Of the total 824 studied, 173(21.0%) were positive for MTB with 71(8.6%) males and 102(12.4%) females. From this study, the prevalence of MTB was found to be 21%. (Table 1).Of the 239 HIV positive participants, 28(3.4%) were co-infected with MTB, while the remaining 211(25.6%) were with HIV-mono-infection. On the other hand, 585(71.0%) were HIV negative among which 145(17.6%) were MTB positive and 440(53.4%) were MTB negative. A significant relationship exists between HIV positivity and development of MTB in these participants ($p<0.0001$) (Table 2). The overall prevalence of MDR-TB in the general population was 1.6% (13/824) and 7.5% (13/173) in MTB patients. Of the 13 MDR-TB cases, 4(2.3%) were males and 9(5.2%) were females. There was no any statistical relationship between the sex of the participants and the acquisition of MDR-TB ($p=0.6243$) (Table 3). Three(1.7%) of those with MDR-TB were HIV positive, while 10(5.8%) were HIV negative, with no statistical relationship between HIV status and development of MDR-TB ($p=0.8980$) (Table 4).The prevalence rate of MDR-TB in HIV infected individuals was1.3% (3/239) while that of MTB in HIV positive patients was 11.7% (28/239).

From figure 1 above, communities A, B, C and D have the highest number of participants; 149, 135,102 and 130 respectively. And also, participants from C,H,E and F covered the longest distance to reach the testing site located in Community A; 63km, 58km, 60km and 67km respectively.

Discussion

The prevalence of tuberculosis in the region was found to be 21%, this is a very alarming figure considering the fact these people have a symptomatic TB and none of them secretes less than 1000 copies of *Mycobacterium tuberculosis* per milliliter of expectorated sputum (sensitivity limit of gene expert machine) and as such, they are a potential threat to themselves and the people they live with. From this study, the disease burden was found to be slightly more in females (23.4%) than in males (18%).

This is not in line with the findings of (Cassels *et al*., 1982; Paolisso *et al*., 1995; Imam-Oyeyi 2008; Frank *et a*l., 2012 and Bruchfeld, 2002) who reported that tuberculosis is more in males than in females. This variation might have been due to the fact that females seek medical attention early more than males particularly among those living with HIV infection for fear of stigmatization and confidentiality, another reason may be the fact that males (adults in particular) claim some level of busyness and as such, they may not have enough time to report themselves to the hospital promptly.

The rate of HIV/TB coinfection is 19.8%, this is somewhat higher than the values reported by (Onipede *et al.,* 1999, Iliyasu-Babashuni, Daniel et al., 2004 and Daniel *et al*., 2007) that reported a HIV/TB coinfection of 12%, 10%, 10.5% and 14.9% respectively. However, it is grossly lower than the report of (Pennap *et al*., 2009) 41.2%. The reason for this low HIV/TB coinfection compared with the other group (HIV negative participants) may be that most of these non HIV participants have some clinical and radiographic evidence of TB and some have previously been treated for TB (high risk group) as such there is a high probability of them having TB. Contrarily the HIV positive participants may not give similar findings due to their weakened immunity and also, the HIV positive participants are likely being over suspected of having TB probably due to the well established notion of a positive association between HIV and TB.

The prevalence of MDR-TB in the general population is 1.6%; this is in concord with WHO annual reports of 2013 and 2014 with 2.9% and 1.7% respectively (WHO, 2014). It appeared that there is declining trend in the prevalence of MDR-TB which might be as a result of improved availability of treatment centers which are appreciably equipped with man power, infrastructure and drugs; coupled with increased health education in the general public. From the study, the prevalence of MDR-TB among all TB cases was found to be 7.5%. This is smaller than the report of (Lawson *et al*., 2010) that showed Rifampin and Isoniazid resistance to occur at 19 and 21% respectively. The figure (7.5%) is obviously higher than the findings of 5 that estimated MDR-TB to account for only 2% of all TB cases in Nigeria (7969/395,281). This may reflects variations in testing methodology, study participants recruitment and the degree of correction of other confounding variables. However, the findings tallies with the WHO global report of 2014 (WHO, 2014) that stated that 10% of all TB cases are MDR-TB cases. It is also slightly more common in females than in males possibly for similar reasons presented above. However, MDR-TB occurs at near equal proportion in HIV positive and HIV negative and participants (3.5 & 4.0%). This so possibly because, a good proportion of the HIV negative participants were previously treated for TB, as such resistance more likely to occur in them than in any one else. Also the fact the HIV patients are sent to the laboratory for the test without much clinico-radiological proofs of TB and most of them are in WHO stage I&II HIV disease; as such even if they have a TB infection it has not yet been manifested and the rate of secretion of tubercle bacilli is below the detection limit of the GENE EXPERT machine (<1000 copies/ml of sputum).

People in Communities like C,F,G and H need to have the gene expert machine in their respective general hospitals and or comprehensive health centers, this is more so considering the distance they have to cover to reach the testing site. Making the machines available in these hospitals is a very important step in ensuring early case detection and prompt enrollment into the treatment.

Conclusion and Recommendations

Multidrug resistant tuberculosis is a fact and not a fallacy in this region, it is found in both HIV positive and negative people.

Early diagnosis/case detection more accurate and sensitive machine like the gene expert is strongly recommended. Capacity building trainings and or seminars should be regularly organized for health personnel on MDR-TB diagnosis and management.

Author's contribution

Hayatu Saidu, designed the research, led the laboratory work and the initial draft of the paper. Ahmad AE and Nura Garba analysed the result, Adamu D, Mukhtar A and Nasir A critically review and contribute to the draft of the final manuscript. Hayatu S and Ahmad AE are the guarantors of the paper.

Conflict of interest

The authors declare no conflict of interest.

Donation

None received.

References

AdegboyegaT. T., Thomas B. T.,Agu Georgia C., Abiodun A.T., (2014) Can Nigeria Sustain the Fight against Drug Resistant Mycobacterium tuberculosis? *J of Microbiology Research 4(2): 72-77 DOI: 10.5923/.20140402.05*

Bruchfeld J. (2002) Molecular epidemiology and drug resistance of Mycobacterium tuberculosis isolates from Ethiopian pulmonary tuberculosis patients with and without HIV infection. *Journal of Clinical Microbiology vol. 40:1636–1643.*

Cassels A., Heineman E., Le C.S. (1982) Tuberculosis case-finding in Eastern Nepal. *Tubercle 63:173-185.*

Cepheid 2014 User manual

Charles, D., Wells, J., Peter C., Lisa, J., Nelson, K. F., Timothy H., Holtz, A.F., Kenneth G. C., and Karin W.(2007) HIV Infection and Multidrug-Resistant Tuberculosis—The Perfect Storm *The journal of infectious diseases*: 10.1086/518665 vol 2, p122=129 · Source: PubMed

Daniel, O.J., Ogunfowora, O.B. and Oladapo, O.T (2007) HIV seroprevalence among Children diagnosed with TB in Nigeria. Trop. Doc.; 37(4): 268-269

Daniel, O.J., Salako, A.A., Oluwole, F.A., Alausa, O.K. and Oladapo, O.T. (2004). HIV seroprevalence among newly diagnosed adult PTB patients in Sagamu. *Nig. J. Med.* 13(4): 393-397.

Frank-Peterside N., Onwuka A.P. and Okonko I.O. (2012). Epidemiology of Pulmonary Tuberculosis in the University of Port-Harcourt Teaching Hospital: Gender Related Disparities. *New York Science Journal*. Vol. 5 (7) p 12-16

Iliyasu, Z. and Babashuni, M.(2009) Prevalence and Predictors of TB coinfection Among HIV seropositive patients attending Aminu Kano Teaching Hospital, Northern Nigeria. *J. Epid*.; 19(2): 81-87.

Imam, T. S. and Oyeyi, T.I (*2008*). A retrospective study of pulmonary tuberculosis prevalence amongst patients attending infectious disease hospital Kano, Nigeria. *Bayero Journal of Pure and Applied Sciences*. 15*Bajopas Vol. 1 Number1* p 10 – 15

Indira SoundiramXpert MTB/RIF Training Cepheid Company 2012 USA

Lawson L. A. G., Habib, M. I.,Okobi, D., Idiong I.,Olajide, N., Emenyonu N., Onuoha L. E., and Cuevas, S. O. (*2010*) Pilot study on multidrug resistant tuberculosis in Nigeria *Annals of African Medicine Vol. 9, No. 3;:184-7* DOI: 10.4103/1596-3519.68355

National population commission 2006 census Retrieved on 28/3/2016 from:www.population.gov.ng state/state-population

Nigeria stop TB partnership strategic plan 2013-2015

Onipede, A.O., Idigbe, O., Ako-Nai, A.K., Omojola, O., Oyelese, A.O., Aboderin, A.O., Komolafe, A.O. and Wemambu, S.N.C. (1999) Seroprevalence of HIV antibodies in TB patients in Ile-Ife. *E. Afr. Med. J.*76 (3): 127-132.

Paolisso M., Leslie J.,(1995) Meeting the changing health needs of women in developing countries. *Soc.Sci Med.* 40(1):55-65.

Pennap G, S Makpa, S Ogbu (2009) The Prevalence of HIV/AIDS Among Tuberculosis Patients In a Tuberculosis/Leprosy Referral Center in Alushi, Nasarawa State, Nigeria..*The Internet Journal of Epidemiology*. Vol 8 Number 1 p23-27

WHO Drug resistant Tuberculosis surveillance and response (Supplement global tuberculosis report 2014)