Original Article

Efficacy of GeneXpert in Active Case Detection Among Contacts of Drug Resistant TB Patients

Sami Ahmad[1], Javed Iqbal[1], Saleha Zafar[3], Jaweria Aslam[2], Hamnah Zahid[2] and Wajih ur Rahman[2]

ABSTRACT

Objective: This study was undertaken to see the value of GeneXpert MTB Rif Assay in diagnosing the TB among suspicious household contacts and its incremental yield over smear microscopy and x-ray**.**

Study Design: Descriptive study

Place and Duration of Study: This study was conducted at the Department of Pulmonology, Bahawal Victoria Hospital, Bahawalpur from January 2017 to December 2022.

Materials and Methods: Systemic tool for active TB case detection was followed as devised by WHO that proposes an interview about symptoms of TB. Suspects were asked to submit a spot sputum specimen for ZN smear and GeneXpert MTB Rif Assay simultaneously at the time chest radiograph.

Results: A total of 545 index drug resistant TB patients were included for contact screening. A total of 2754 contacts with mean of 5.36±2.75 were verbally screened for tuberculosis using Baseline individual risk assessment questionnaire and a total 945 contacts were assessed for further investigation. Findings of x-ray suggesting any change in lungs of 7.1% contacts, smear positivity was found in 6.3% and GeneXpert MTB Rif Assay detected 9.8% of which 45.2% contacts were resistant to rifampicin.

Conclusion: Active case detection of contacts is important in high burden settings while modern GeneXpert is a great addition in diagnostic tools and equally valuable in detection of TB among contacts and showed higher yield of MTB case detection as 37.6% over smear microscopy and 39.8% over X-ray.

Key Words: GeneXpert, Tuberculosis, Diagnosis, Drug Resistance.

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INTRODUCTION

Tuberculosis (TB) is a contagion and communicable disease posing as one of the ten utmost causes of morbidity and mortality from a single infectious organism and ranked above Human immuno-deficient virus (HIV). Drug resistance TB is may be said as an advanced form of disease in which infectious strain of Mycobacterium Tuberculosis Complex (MTBC) becomes resistant to certain important primary drugs. Isoniazid and rifampicin are two important first line anti TB drugs and considered as back bone to form a primary regime of anti-tuberculosis treatment (ATT).[1]

[1.] Department of Pulmonology / Medicine[2], Bahawal Victoria Hospital, Bahawalpur.
[3.] Department of Pathology, Quaid-e-Azam Medical College, Bahawalpur.

Correspondence: Dr. Saleha Zafar, Assistant Professor of Pathology, Quaid-e-Azam Medical College, Bahawalpur.
Contact No: 03044480024
Email: salehasami61@gmail.com

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Various factors are involved in drug resistance and it may be divided into primary or acquired resistance. Acquired drug resistance in case of TB may occur among patients who took ATT for four weeks at least whereas primary drug resistance includes the patients who never took ATT and directly infected with drug resistant strain of MTBC.[4] Global rate of primary drug resistant TB has been reported to be 3.4% while acquired as 18% in most recent report of WHO, however in Pakistan rate of primary drug resistance is higher up to 4.2% while rate of acquired drug resistance remained to be 16%.[1] An exorbitant threat of extensively drug resistance (XDR) TB further complicate the situation in which MDR TB strain becomes resistant to floroquinolones and one of the injectable (i.e. capreomycin, kanamycin or amikacin) from second line of ATT. National TB Control Program (NTP) Pakistan met various challenges in past few years however there is a lot left to meet the sustainable development goals 2030. Prompt case detection and early treatment of TB is the key to control the disease and spread of infection. Culture on Lowenstein Jensen (LJ) medium is still a gold standard to diagnose the tuberculosis but utility is limited due to number of reasons including time constraints as the MTBC are slow growing organisms. Similarly smear microscopy, although easy, fast and specific but lacks sensitivity.[5]

GeneXpert MTB Rif Assay based on hemi-nested polymerase chain reaction has shown a great potential in not only early diagnosis of disease but also provides susceptibility testing of rifampicin to differentiate the drug resistant TB cases from susceptible ones.

Being communicable disease, TB has been remained risky for the close contacts due to easy transmission from air born aerosols. Close contacts of rifampicin resistance TB are also at higher risk of acquiring resistant TB from index patients. Since the poor implementation and non- adherence to infection control measures may become a potential threat as a case series study reported eight out of total thirteen households get infection one of the other.[6] Although there is a conflicting data regarding transmission amongst household contacts of TB and drug resistant TB where few report it as analogous risk to transmit amongst the groups while others oppose the phenomenon.[2,7]

Pakistan is facing an alarming situation due to overcrowding, poverty and socio-demographic characteristics and at higher risk of increasing in number of drug resistant TB cases. There has been remained a great necessity to not only rely on case detection and treatment but finding the cases as early as possible which showed success at various levels.[8] Various local studies have been undertaken to present transmission of infection amongst susceptible and resistant TB in Pakistan[2,8] or with limited objectives like case detection among prisoners,[9] X-ray based active case detection,[10] and incentive based case detection.[11] A study to observe the active case detection using multivariate approach was necessary and therefore, this study was undertaken to see the value of GeneXpert MTB Rif Assay in diagnosing the TB among suspicious household contacts and its incremental yield over smear microscopy and x-ray.

MATERIALS AND METHODS

This descriptive study was undertaken in department of pulmonology, programed management of drug resistant TB site, Bahawal Victoria Hospital, Bahawalpur from January 2017 to December 2022. A predesigned questionnaire was used to collect the information from household contacts. Household contacts were assumed the people living in the same premises and share the meals for at least 30 days afore diagnosis of drug resistant TB among index patients. Demographic data of index patients was obtained followed by a verbal case assessment on the basis of criterion laid

by the Centre for Disease control (CDC).[12] Individuals of either gender, aged ≥15 years and fulfilling the baseline TB risk assessment was target population in this study. Contacts of drug resistant TB patients already enrolled for ATT or having prior history of ATT were excluded from this study.

Present investigation was done after taking the consent from head of the households as well as from each individual participated in the study. Counseling was also done to convince the patients regarding safety of their data and credentials where necessary. After verbal screening suspects were referred for chest radiograph and service was provided free of cost in radiology department of Bahawal Victoria Hospital. Type and severity of abnormal radiographic findings were reported in a sequence. Type of radiographic findings included calcification, consolidation, infiltration and cavitation while severity was reported as mild, moderate and severe.

Suspects were asked to submit a spot sputum specimen simultaneously at the time chest radiograph. Samples were processed for Ziehl Neelsen (ZN) smears for acid fast bacilli (AFB) and GeneXpert MTB Rif Assay. A 100X oil field was used to screen the ZN smears and a minimum of 100 oil fields were mandatory to report a smear negative while any smear showed three AFB was considered positive. A first morning specimen was repeated in case of 1-2 AFB/100 oil fields for confirmation. After preparation of smears same samples were processed for GeneXpert MTB Rif Assay as accorded in otherstudies.[1]

Data was entered and analyzed by using social package for social sciences (SPSS). Qualitative variables like gender, history of prior treatment, marital status, socio-economic status and marital status were presented as frequency and percentages while quantitative variables like age, family size and education were presented as mean ± standard deviation.

RESULTS

A total of 545 index drug resistant TB patients were included for contact screening. These index patients consist of 304(55.8%) males and 241(44.2%) females with a female to male ratio of 1:1.26. Mean age of index patients remained to be 39.59±17.27 while highest frequency of index patients remained in age group of 15-24 years while a high number of patients had history of Cat- I or Cat-II TB treatment. Other demographic characteristics of these index patients including mean family size, treatment outcome of previous iteration, level of education and socio-economic status are presented in Table I.

A total of 2754 contacts of 545 index patients with mean of 5.36±2.75 were verbally screened for tuberculosis using Baseline individual risk assessment questionnaire and a total 945 contacts were assessed for close association with patient as 595 (63%), having co-morbidities 203(21%) or 147(16%) showing any of the important TB symptoms including cough from 3 weeks or more, pain in the chest, fatigue, weight loss or sweating at night as depicted in figure 1.

After risk assessment 945 contacts were screened simultaneously by x-ray chest, smear microscopy and GeneXpert MTB Rif Assay. Findings of x-ray suggesting any change in lungs of 67 (7.1%) of total

945 contacts screened. Similarly smear positivity was found in 60 (6.3%) and GeneXpert MTB Rif Assay detected 93 (9.8%) of the contacts. A total of 42 (45.2%) contacts from MTB detected cases with GeneXpert were found to be resistant to rifampicin also as presented in Table 2.

Coherence among three techniques was also observed and being highest positivity rate of GeneXpert was considered as gold standard and both the techniques were compared with it. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of ZN smear was calculated to be 62.4%, 99.8%, 96.7%, 96.1% and 96.8% while for X-ray 60.2%, 98.7%, 83.6%, 95.8% and 94.9% respectively as presented in table 3.

Table No.I: Demographic Characteristics of Index Patients (n=545)

Characteristics		Male (n=304) n(%)	Female (n=241) n(%)	Total (n=545) n(%)
Mean Age		39.60±17.26	39.58±17.28	39.59±17.27
Age Groups	15-24	47(15.5)	88(36.5)	135(24.8)
	25-34	56(18.4)	47(19.5)	103(18.9)
	35-44	45(14.8)	41(17.0)	86(15.7)
	45-54	77(25.3)	19(7.8)	96(17.6)
	55-64	46(15.2)	23(9.6)	69(12.7)
	≥65	33(10.8)	23(9.6)	56(10.3)
Previous History of ATT	Cat-I	212(69.7)	155(64.3)	367(67.3)
	Cat-II	53(17.5)	41(17.0)	94(17.3)
	None	39(12.8)	45(18.7)	84(15.4)
*Outcome of previous treatment	Cured	5(1.9)	3(1.5)	8(1.7)
	Completed	186(70.2)	142(72.5)	328(71.1)
	Failed	61(23.0)	42(21.4)	103(22.4)
	Relapse	7(2.6)	4(2.1)	11(2.4)
	defaulted	6(2.2)	5(2.5)	11(2.4)
Mean Family Size		7.4±3.2	7.3±2.8	7.4±3.0
Family Size Range		3-30	3-25	3-30
Education	Illiterate	117(38.5)	74(30.7)	191(35.0)
	Primary	54(17.8)	49(20.3)	103(19.0)
	Middle	42(13.8)	39(16.2)	81(14.8)
	High	33(10.8)	28(11.6)	61(11.2)
	Higher Above	58(19.1)	51(21.2)	109(20.0)
Socio- economic Status	Poor	207(68.1)	160(66.4)	367(67.3)
	Lower Middle	76(25.0)	56(23.3)	132(24.2)
	Upper Middle	21(6.9)	25(10.3)	46(8.5)

***Proportions calculated by total number of patients having history of Cat-I or Cat-II treatment.**

Table No.2: Performance of Various Techniques in Screening of Contacts

Diagnostic Technique		Findings	Frequency	Percentage
X-ray Chest		Infiltration	33	3.5
		Cavitation	15	1.6
		Consolidation	12	1.3
		Calcification	7	0.7
		No Change	878	92.9
ZN Smear		Negative	885	93.7
		Scanty (1-9 AFB)	17	1.8
		1+	43	4.5
GeneXpert	MTB	Not Detected	852	90.2
		Detected	93	9.8
	*Rifampicin	Resistant	42	45.2
		Sensitive	51	54.8

***Percentage of rifampicin susceptibility was calculated with GeneXpert MTB detected cases**

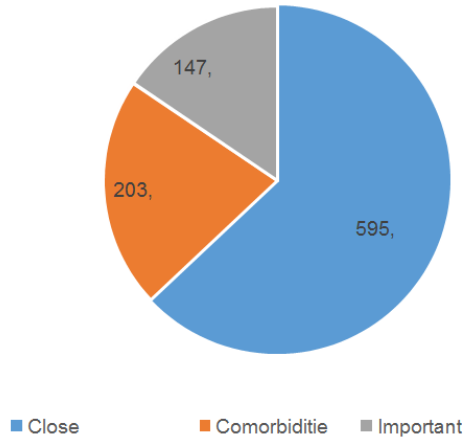

Figure No.1: Risk Groups

Table No.3: Comparison of ZN smear and X-ray outcomes with GeneXpert

Technique	Genexpert			
	MTB Detected (n=93)		MTB Not Detected (n=852)	
	n	%	n	%
Smear Positive	58	62.4	2	0.2
Smear Negative	35	37.6	850	99.8
X-ray Positive	56	60.2	11	1.3
X-ray Negative	37	39.8	841	98.7

DISCUSSION

Presently 9.8% of 945 contacts confirmed for TB screened by GeneXpert while ZN smear presented a lower positivity rate of 6.3% and not in agreement with studies showing a lower TB positivity rates of 2.5% and 5.29% respectively.[1,13] Another Indian study revealed 30.38% symptomatic TB contacts of MDR TB and confirmed 4.61% infected with MDR TB thus concluded that drug resistant TB patients have the potential to spread drug resistant or drug susceptible TB among their house hold contacts.[14] Although 42/93 (45.2%) among contacts were found to be Rifampicin resistant which is a big number and higher from the studies but considering whole number of screened cases it makes 42/945 (4.5%) of incidence of direct spread of drug resistant tuberculosis. Although this incidence looks high but considering whole number of contacts it may be further reduced and could be comparable to the incidences reported by WHO.[1]

Contact screening is much important due to easy mode of spread of pulmonary TB and in case of drug resistant TB patient; contacts may acquire direct exposure to resistant strains with decreased treatment options. On the other hand microbiological evidence is necessary for the diagnosis of TB and drug resistant TB but due to various reasons evaluation of drug resistance may take longer to get definite diagnosis. Under these circumstances GeneXpert MTB Rif Assay made its great importance being a molecular diagnostic technique, fully automatic with closed chambers for isolation and replication of DNA thus provides simultaneous detection of MTB and rifampicin susceptibility.[2,4]

Keeping above in view present study also showed highest detection rate of GeneXpert (9.8%) as compared to ZN smear and X-rays. A lot of work has been done to determine the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of GeneXpert thus reported to be 97.83%, 92.59%, 96.77%, 94.94% and 96.23% respectively.[15] Therefore, GeneXpert was taken as gold standard to calculate the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of ZN smear (62.4%, 99.8%, 96.7%, 96.1% and 96.8%) and X-rays (60.2%, 98.7%, 83.6%, 95.8% and 94.9%) respectively. Clear advantage of GeneXpert MTB Rif assay could be seen in present study that the technique provides diagnosis of MTB and rifampicin susceptibility in two hours with reported efficiency to detect 131 cfu/ml of the sample even better technique has been introduced as GeneXpert MTB Rif Ultra which takes around 90 minutes and have the ability to detect as low as only 16 cfu/ml of the sample.

Smear positivity of 6.3% in this study is neither in agreement to the study which presented a lower rate of 2.5% among contacts[2] nor in accordance to other studies that reported a higher rates of 15.6% and 12.5% in various studies respectively. An Iranian study however reported the comparable results with present study and described a smear positivity of 7.6% among contacts. X-ray

Importance of verbal screening could not be denied which helped to recruit 945(34.3%) out of 2754 contacts presently thus helped to find the target groups only as prescribed CDC and in other related literature.[1,12] Spouse and other important contact groups of index drug resistant patients are scarcely reported and interestingly wives (8.3%), fathers (7.0%), sisters (5.6%) and daughters in law (12.5%) acquired TB infection while none of the husbands got infected.[2] However this segregation of groups was not done in present study and this gap could be the future prospect to explore. Demographic characteristics of drug resistant TB patients presented in this study are somehow in agreement with previous studies regarding age groups, socio-economic status, education and previous histories of treatment.

CONCLUSION

In conclusion, active case detection of contacts of drug resistant TB patients is pertinently important in high burden settings for better control and timely management of disease to meet the sustainable

development goals of 2015-30. Similarly modern GeneXpert is a great addition in diagnostic tools and equally valuable in detection of TB among contacts and showed higher yield of MTB case detection as 37.6% over smear microscopy and 39.8% x-rays.

Author's Contribution:

Concept & Design of Study:	Sami Ahmad
Drafting:	Javed Iqbal, Saleha Zafar
Data Analysis:	Jaweria Aslam, Hamnah Zahid, Wajih ur Rahman
Revisiting Critically:	Sami Ahmad, Javed Iqbal
Final Approval of version:	Sami Ahmad

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Rehman S, Kashif Munir M, Iqbal R, Ahmed Salam A, Saeed S, Masud F, Aasim M. Active case detection among household contacts of multi drug resistant tuberculosis patients in a tertiary care setting. Pak J Med Res 2014;53(3):55-9.
2. Munir MK, Rehman S, Iqbal R, Saeed MS, Aasim M. Comparison of gene Xpert MTB/RIF assays with conventional standard proportion method for determination of drug susceptibility in multidrug resistant TB suspects. Annals of KEMU 2018;24(1).1-7.
3. Munir MK, Rehman S, Iqbal R. Meeting the challenge, making a difference: Multidrug resistance tuberculosis in Pakistan. Pak J Med Res 2018;57(1):1-2.
4. Muhammad KM, Sana R, Rizwan I. A Need for Tuberculosis Infection Control Measures: A Case Series Study in Pakistan. Asian J Med Biomed 2017;1(1):19-22.
5. Zignol M, Hosseini MS, Wright A, Weezenbeek CL, Nunn P, Watt CJ, et al. Global incidence of multidrug-resistant tuberculosis. J Infect Dis 2006;194(4):479-85.
6. Iqbal R, Munir K, Bashir S, Arif A, Rao MH, Mirbahar A, et al. Screening for tuberculosis among household contacts of index patients. Pak J Med Res 2013;52(4):96-101.
7. Jamal W, Azeemi K, Waqar M, Ikram K, Zaidi SA, Habib S. Active case finding for tuberculosis among prisoners in Karachi, Pakistan. European Respirat J 2019;54: PA2954.
8. Habib S, Azeemi K, Zaidi SA, Jamal W, Kazmi T, Waqar M. Utilizing chest X-ray based active case finding approach for early tuberculosis case detection in Pakistan. European Respirat J 2019; 54:PA2951.
9. Hussain H, Mori AT, Khan AJ, Khowaja S, Creswel J, Tylleskar T, et al. The cost-effectiveness of incentive-based active case finding for tuberculosis (TB) control in the private sector Karachi, Pakistan. BMC Health Services Res 2019;19(1):690.
10. Munir MA, Zafar S, Rauf N, Ahmad S, Sarwar MI, Khaliq S. Value of chest x-ray in diagnosis of smear negative pulmonary tuberculosis at thalassemia center, Sheikh Zayed Hospital, Rahim Yar Khan. JSZMC 2019;10(3): 1748-1751.
11. Singla N, Singla R, Jain G, Habib L, Behera D. Tuberculosis among household contacts of multidrug-resistant tuberculosis patients in Delhi, India. Int J Tuberc Lung Dis 2011;15(10): 1326- 30.
12. Paul D, Kollikkara S. Spread of tuberculosis among household contacts of multi drug resistant tuberculosis (MDRTB) patients. Eur Resp J 2014; 44(Suppl 58):1435.
13. Iqbal R, Munir K, Bashir S, Arif A, Rao MH, Mirbahar A, et al. Screening for tuberculosis among household contacts of index patients. Pak J Med Res 2013;52(4):96101.
14. Underwood BR, White VL, Baker T, Law M, Moore-Gillon JC. Contact tracing and population screening for tuberculosis–who should be assessed? J Public Health 2003;25(1):59-61.
15. Khalilzadeh S, Masjedi H, Hosseini M, Safavi A, Masjedi MR. Transmission of Mycobacterium tuberculosis to households of tuberculosis patients: a comprehensive contact tracing study. Arch Iran Med 2006;9(3):208-12.