

TB Laboratory Register for smear, Xpert MTB/RIF, culture and drug susceptibility testing (DST) (Page 1 of 3)

[illegible]

1 Indicate HIV infection as follows: Yes; No; ? = unknown

2 Indicate previous treatment as follows: Y = previously treated; N = not previously treated, ? = unknown

3 New patients or patients starting a re-treatment regimen; tick the appropriate box according to type of examination

4 Patient on TB treatment; indicate months of treatment at which follow-up examination is performed

5 Xpert MTB/RIF test result reported as follows : N = no TB detected; T = TB detected, not R-resistant; TR = TB detected, R-resistant

6 If Xpert MTB/RIF indeterminate result, indicate error code or 'invalid'

TB Laboratory Register for smear, Xpert MTB/RIF, culture and drug susceptibility testing (DST)[illegible]

7. Culture result reported as follows:

No growth reported
<10 colonies
10-100 colonies
>100 colonies
Innumerable or confluent growth

TB Control Programme

TB Laboratory Register for smear, Xpert MTB/RIF, culture and DST(Page 3 of 3)

H	R	E	S	Amk	Km

Treatment Unit	HIV infection ¹	Patient previously treated for TB ²	Type of examination			Results for examir	
			Diagnosis ³		Follow-up (month) ⁴	1 ⁵	2
			Smear	Xpert			

it; ? = Indeterminate result

) (Page 2 of 3]

Direct +Indirect costs			
All smear examinations	Culture	DST	XPRT

0
Report number of colonies
+
++
+++

Cm	FQ _____	Other _____	Other _____	Other _____	Other _____	Name of Person Reporting	Signature

ation	Environment		BMU and TB Register No.	Remarks ⁶
	Temp (°C)	Humidity		
3				

Notation Method for Recording Smears (for non-centrifuged)	
No AFB	0
1--9 AFB per 100 HPF	Scanty (and report
10--99 AFB per 100 HPF	+
1--10 AFB per HPF	++
> 10 AFB per HPF	+++

Form 04

ature			Date Results Reported	Comments

Summary

Background: Tuberculosis (TB) is caused by bacteria (*Mycobacterium tuberculosis*). Tuberculosis (TB) is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. Universal access to high-quality, patient-centered treatment for all TB patients is emphasized by WHO's Stop TB Strategy. This study aimed at evaluating the diagnostic impact, cost effectiveness and operational aspects related to the use of GeneXpert MTB in the rapid diagnosis of TB and RIF resistant TB in Iraq.

Methods: This cross-sectional study was conducted at the national reference laboratory (NRL) that is draining fresh sputum samples of new & retreated sputum positive pulmonary TB (SS+PTB) patients from randomly selected clusters from five governorates lie in the middle area of Iraq during Nov 1st 2013 to Oct 31st 2014. All patients were examined with DSM (initial test to enroll only SS+PTB patients, and then followed by Xpert assay, culture and conventional drug susceptibility testing (DST). SPSSv20 and EpiCalc 2000 statistical package were used to describe the sample and to obtain diagnostic validity of Xpert assay. Cost was calculated. In addition, In depth interviews of operating personnel were done to describe operational aspects and user satisfaction.

Results: Total sample was 408 SS+PTB. Average age was 39.6±17.6 year. Males were 221 (54%) & new patients were 360 (88%). All patients were Xpert positive for TB. Overall prevalence of rifampicin resistance (RR) and multidrug resistance (MDR) were 4.2% & 1.5% respectively. Xpert assay detected 71% of RR including all MDR patients. Regarding RR detection, Xpert was found to have sensitivity of 71%, specificity of 98%, positive predictive value of 60%, and Negative predictive value of 99%. Anyhow, indicators improve if this assay is directed to MDR-TB suspects. This assay was neither of cost benefit nor cost effective without discount price and necessity to confirm RR positive results with conventional methods. Users expressed easily operability of the assay but in presence of strict workplace conditions in Iraq (continuous stable power supply and 24 hour air conditioning during summer).

Conclusion: Due to presence of a considerable proportion of false positive results for RR by Xpert assay, this test is better to target MDR-TB suspects and due to difficult to achieve workplace environment it is better to expand its use for early detection of MDR-TB patients at central and intermediate but not at peripheral levels, at least during current situation of Iraq.

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Abbreviations

AFB	Acid Fast Bacilli
DRS	Drug Resistance Survey
DSM	Direct Smear Microscopy
DST	Drug Susceptibility Testing
FLD	First Line Drugs
INH	Isoniazid
MDR	Multidrug Resistance
MDR-TB	Multidrug Resistant Tuberculosis
NRL	National Reference Laboratory
NTP	National Tuberculosis control Program
NPV	Negative Predictive Value
PPS	Proportionate Probability Sampling
PPV	Positive Predictive Value
PTB	Pulmonary Tuberculosis
RIF	Rifampicin
RR	Rifampicin Resistance
SLD	Second Line Drugs
SN	Sensitivity
SP	Specificity
SPSSv20	statistical package for social sciences version 20
SS+	Sputum smear positive for AFB
TB	Tuberculosis
UNDP	United Nations Development Program

1. Introduction

1.1. Background:

Tuberculosis (TB) is caused by bacteria (*Mycobacterium tuberculosis*). Tuberculosis (TB) is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. In 2013, 9 million people fell ill with TB and 1.5 million died from the disease and an estimated 480 000 people developed multidrug resistant TB (MDR-TB)⁽¹⁾.

Universal access to high-quality, patient-centered treatment for all TB patients is emphasized by WHO's Stop TB Strategy⁽²⁾. The rapid detection of MTB in respiratory specimens and drug therapy based on reliable drug resistance testing results are a prerequisite for the successful implementation of this strategy. However, in many areas of the world, TB diagnosis still relies on insensitive, poorly standardized sputum microscopy methods⁽²⁾.

Ineffective TB detection and the emergence and transmission of drug-resistant MTB strains increasingly jeopardize global TB control activities. Effective diagnosis of pulmonary TB requires the availability - on a global scale - of standardized, easy-to-use, and robust diagnostic tools that would allow the direct detection of both the MTB complex and resistance to key antibiotics, such as rifampicin (RIF). The latter result can serve as marker for multidrug-resistant MTB (MDR-TB) and has been reported in > 95% of the MDR-TB isolates. The rapid availability of reliable test results is likely to directly translate into sound patient management decisions that, ultimately, will cure the individual patient and break the chain of TB transmission in the community⁽³⁾.

Cepheid's (Sunnyvale, CA, U.S.A.) Xpert MTB/RIF Assay meets the demands outlined above in a remarkable manner. It is a nucleic-acids amplification test for 1) the detection of MTB complex DNA in sputum or concentrated sputum sediments; and 2) the detection of RIF resistance-associated mutations of the *rpoB* gene. It is designed for use with Cepheid's GeneXpertDx System that integrates and automates sample processing, nucleic acid amplification, and detection of the target sequences using real-time PCR and reverse transcriptase PCR. The system consists of an instrument, personal computer, barcode scanner, and preloaded software for running

tests and viewing the results. It employs single-use disposable Xpert MTB/RIF cartridges that hold PCR reagents and host the PCR process. Because the cartridges are self-contained, cross-contamination between samples is eliminated ⁽⁴⁾.

This simple test can be implemented almost everywhere, and it provides results within a few hours. In low-income countries (LICs), however, its cost, environmental limitations (stable and regular electricity, adequate room temperature) and difficulties involved in supply and maintenance are major obstacles. While it may be suitable for major reference hospitals, operational research is needed to evaluate the test and its additional yield above high-quality smear microscopy and clinical algorithms before its use at the peripheral level. In the meantime, direct microscopy should remain the initial diagnostic test for TB suspects. In most LICs, the prevalence of RIF resistance among new TB patients is very low; an XpertMTB/RIF result indicating RIF resistance will thus always need confirmation by another test ⁽⁵⁾.

XpertMTP/RIF has a good test performance: sensitivity (SN) to detect TB is 88%, specificity (SP) is 99% and SN to detect RIF resistance is 95% ⁽⁶⁾.

Iraq had notified 8554 incident TB cases and 83 MDR-TB cases while WHO estimates for the same year were 15 thousands for incident TB cases and 310 MDR-TB cases out of notified⁽⁷⁾. This huge gap in case detection of drug sensitive and drug resistant TB questions for better diagnostic tools and if Xpert MTB/RIF machine, the new innovative diagnostic break through, can address this gap.

Xpert is newly introduced to Iraq as a rapid test method in Baghdad at the national reference laboratory (NRL) as a pilot project for future expansion with an intension for dispensing its services to the peripheral (district) units in the future. Since there is a need for early detection of MDR-TB for community prevention; Xpert device could be of high value for this purpose, thus further knowledge about this device is required for recommending its use in Iraq at central, intermediate and peripheral levels, expansion and type of candidates to be tested with it.

1.2.Objectives of the study:

General objective:

Evaluate the diagnostic impact, cost effectiveness and operational aspects related to the use of Xpert MTB in the rapid diagnosis of TB and RIF resistant TB in Iraq.

Specific objectives:

- 1-Compare the yields of using Xpert with the yields of conventional diagnostic methods (direct smear microscopy and culture and susceptibility) in the rapid diagnosis of drug susceptible and drug resistant TB cases.
- 2- Evaluate the diagnostic performance of Xpert MTB/RIF.
- 3- Evaluate the cost of one detected TB and MDR TB using Xpert MDR/RIF as compared to conventional diagnostic methods.
- 4- Highlighting operational aspects and obstacles related to Xpert Assay use.

2. Patients & Methods

2.1. Study area/setting:

This study conducted at the national reference laboratory (NRL) which performs culture and drug susceptibility testing for first line anti-tuberculosis drugs for the whole country. The Xpert MTB/RIF testing was located at the NRL during the study.

2.2. Study design:

2.2.1 To study the diagnostic impact of GeneXpert assay on the detection of TB and RIF resistant (RR) TB, a cross-sectional design was used. The study covered five governorates lie in the middle of Iraq, namely: Baghdad, Salahelden, Anbar, Diala and Wasit, during a speicfied period (Nov 1st 2013 to Oct 31st 2014), samples from sputum smear positive PTB patients were taken immediately on diagnosis and sent without additives in screw cupt contained in a cool box within 72 hours of producing the samples to NRL in Baghdad for testing with both GeneXpert Assay and drug susceptibility testing (DST) using solid meda. Patient was fist put on first line anti-TB treatment till DTS result appear follwing the algorithm below (figure 1).

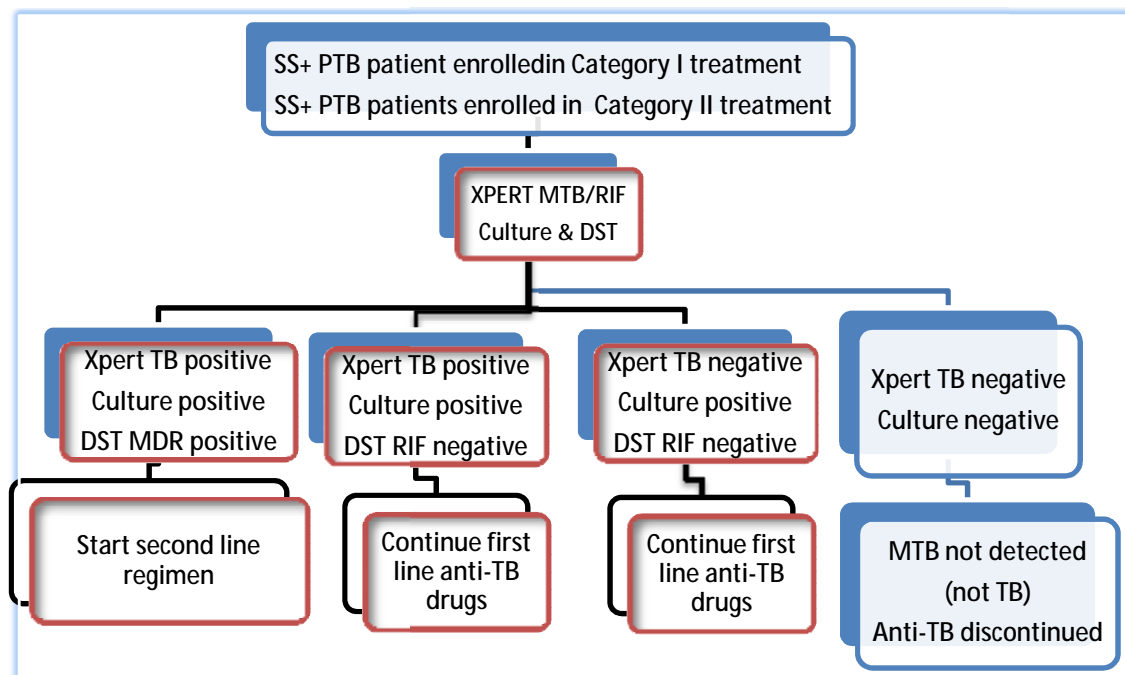


Figure 1: Study management guidelines for enrolled TB patients.

2.2.2. Cost per patients were calculated for using any and all mentioned test and theoretically compared to a hypothetical group where GeneXpert Assay not used in their investigation for calculated cost effectiveness of using GeneXpert Assay.

2.2.3. To assess the operational aspects of using this diagnostic machine in Iraq, at the end of data collection of GeneXpert Assay results, a qualitative study was conducted using in-depth interviews of the operating team collecting their personal experiences of dealing with this type of investigation.

2.3. Study subjects (patients): Pulmonary TB (PTB) patients who are acid fast bacilli (AFB) sputum smear positive (SS+) detected with direct smear microscopy (DSM) diagnosed during the period of sputum sample's collection (from Nov 1st 2013 to Oct 31st 2014), and were assigned to first line anti-TB treatment (category I and category II).

Exclusion criteria:

- 1- Patient who did not consent to participate in the study.
- 2- Patients with sputum smear negative PTB.
- 3- PTB Patient cannot produce sputum sample.
- 4- Patients with extra-pulmonary TB.
- 5- Any patient already known to have MDR-TB.

2.4. Sample size:

This study was designed to be conducted in parallel with the national drug resistance survey 2013-2014 utilizing the same patients sampled from the middle region of Iraq (according to DRS protocols; middle region of Iraq send sputum specimens of sampled patients to NRL for culture & DST, while other regions send only cultured samples to NRL for DST). The dedicated amount of GeneXpert assay cartridges for this study was for 500 examinations. Thus the end point of sampling patients was either approaching a total size of 500 or approaching the end of the specified duration for data collection.

2.5. Sampling technique:

2.5.1. For Category I patients: cluster sampling in a way the sample were proportionate to the population of interest-proportionate probability sampling(PPS) applied in the DRS to select new SS+ TB patients.

2.5.2. For Category II patients: Sampling were accidental (convenience) sampling that all SS+ patients with a history of previous treatment with anti-TB detected from the same clusters for new patients were included in the study.

2.5.3. The enrollment ratio for category one to category two were not subject to any rule, that those who are detected first (whether category one or two) were first to be enrolled in this study till achieving targeted sample size or ending sputum samples' collection period.

2.6. Data Collection methods, instruments used, measurements

2.6.1. instruments used for data collection

1. Questionnaire form collected both personal data and results of laboratory testing (Annex-1).
2. A laboratory register was modified to document the following data for each person: personal characteristics, direct sputum examination result, Xpert test results and culture and SN results. As well as contained columns for environmental conditions during operating Xpert machine (Annex-2).
3. User Satisfaction Questionnaire form for in depth interviews of Xpert Assay workers looking for their opinions and satisfaction in using Xpert machine (Annex-3).

2.6.2.Used techniques:

- 1- Direct smear microscopy (DSM) for examining sputum smears for acid fast bacilli (AFB).
- 2- Testing with MTB/FIR Xpert machine for TB bacilli and RIF resistant TB bacilli.

- 3- Culture for TB bacilli using solid media.
- 4- Drug susceptibility testing (DST) for TB bacilli growths (obtained from cultured samples) using solid media as well.

2.6.3. Quality control measures:

- 1- Two-day training for staff (review training) working on MTB/FIR Xpert machine.
- 2- One day training for staff working on data input.
- 3- NRL technicians who work on culture and susceptibility were already trained and are trainers for intermediate and peripheral level laboratories.
- 4- NRL manager daily supervised the use of MTB/FIR Xpert machine use.
- 5- Culture and drug susceptibility testing were subjected to DRS quality assurance protocols.

2.6.4. Period of data collection: It cost 17 months. This period covered the period of sputum samples' collection period (Nov 1st 2013 to Oct 31st 2014), the following four months (Nov 1st 2014 to Feb 30th 2015) that covered the process of culture, re-culture of some samples, and DST) and Mar 2015 for data input into a structured excel form (database).

2.7. Statistical analysis: Data entered on an excel file as a database and then exported to statistical package for social sciences version 20 (SPSSv20) for analysis. Descriptive statistics will be applied. Discrete variables presented as numbers and percentages and continuous variables presented as means with standard deviation. All tests used were 2-sided tests and 5% level of significance was used. EpiCalc2000 was used for estimating the diagnostic validity of the Xpert MTB/RIF will be evaluated in terms of SN, SP, positive predictive value (PPV) and negative predictive value (NPV). The cost of one case detected by the Xpert as compared to the conventional methods was studied.

2.7. Ethical Considerations:

2.7.1. Informed consent form:

1. All of participants were fully informed about the study including its importance and implications and those accept to participate signed on the informed consent form (Arabic version) (Annex-4).
2. All of the process was free for patients and treated free and properly according to NTP policy.

2.7.2 Institutional ethical clearance

An ethical clearance had been obtained before conducting the field work of the study. This clearance was issued by the ethical committee of Ministry of Health (Annex-5) after obtaining the scientific approval from the research committee of Public Health Directorate.

3. Results

3.1. Sample description:

This study enrolled 408 SS+ PTB patients. New PTB cases constituted 88.2% of the sample (360 patients) and the remaining 48 patients (11.8%) were category II patients (all of enrolled category II patients had a treatment history with anti-TB for more than 4 weeks) (Table 1). Age of patients varied from 12 to 85 years with an average of 39.6 ± 17.6 years.

Testing patients with GeneXpert Assay had labeled 388 (95.1%) patients as having TB bacilli sensitive to RIF and 20 (4.9%) patients as having TB bacilli resistant to RIF.

According to DST; Prevalence of resistance to anti-TB was as follow: 4.2% for RIF, 8.6% for INH, 3.4% for Ethambutol, 21.1% for Streptomycin, 1.5% for Multidrug resistance (MDR), 5.6% for polyresistance, and 20.8% for monoresistance. In 72.1% of sampled patients, TB bacilli did not express resistance to any of INH, RIF, Ethambutol and Streptomycin (Table 1).

Table 1: Distribution of all sampled patients according to study variables:

Variables	Categories	N=408	100.0%
Sex	Male	221	54.2%
	Female	187	45.8%
Patient Category	New	360	88.2%
	Previously treated	48	11.8%
Result of GeneXpert Assay	RIF sensitive	388	95.1%
	RIF resistant	20	4.9%
DST Results	INH Resistance	35	8.6%
	RIF Resistance	17	4.2%
	Ethambutol Resistance	14	3.4%
	Streptomycin Resistance	86	21.1%
Overall Drug Resistance Status	Susceptible	294	72.1%
	MDR	6	1.5%
	Polyresistance	23	5.6%
	Monoresistance	85	20.8%

3.2. GeneXpert Assay Results:

All sampled patients who were SS+PTB according to DSM were Xpert positive for TB bacilli, i.e. there was 100% agreement between Xpert Assay & DSM.

Applying GeneXpert Assay to the 408 patients using DST as a gold standard test to validate GeneXpert Assay performance as a screening test for both RR and MDR, the following results were observed:

3.2.1. Performance of GeneXpert Assay as a screening test for RR:

In this study, by comparing GeneXpert Assay results to DST:

- GeneXpert Assay succeeded to detect 12 (71%) out of 17 RR cases.
- GeneXpert Assay had labeled 8 (2.0%) RIF susceptible patients RIF (out of 391 RIF susceptible cases) as RIF resistant (table 2: A).
- The validity indicators for GeneXpert Assay according to this study as a screening tool for RR were a SN of 71%, SP of 98% and an accuracy of 97%.
- PPV is not high (60%) which means a high probability of false positive results (table: 2-B).

Table 2: Performance of GeneXpert Assay as a screening test for RR for the whole sample (i.e. both categories I and II): A) Results compared to DST, B) Screening validity at a prevalence of around 4%.

A)

		RIF Resistance by DST		Total
		RIF Resistant	RIF Susceptible	
		N	N	N
GeneXpert Assay	RIF Resistant	12	8	20
	RIF Susceptible	5	383	388
Total		17	391	408

B)

Screening Performance Indicators	Value	[95% CI]
Prevalence of RR	0.04	[0.03; 0.07]
SN	0.71	[0.44; 0.89]
SP	0.98	[0.96; 0.99]
Accuracy	0.97	[0.94; 0.98]
PPV	0.60	[0.36; 0.80]
NPV	0.99	[0.97; 1.00]

3.2.2. Performance of GeneXpert Assay as a screening test for MDR-TB:

Assuming that all RR cases detected by GeneXpert Assay are also INH resistant, i.e. assuming that GeneXpert Assay detects MDR-TB, then the screening performance will be:

- GeneXpert Assay succeeded to detect all the six MDR cases among the 20 RR cases (table 3: A).
- The validity indicators for GeneXpert Assay to detect MDR-TB were a SN of 100%, SP of 97% and an accuracy of 97%.
- PPV is not high (30%) which means a high probability of false positive results (table: 3-B).

Table 3: Performance of GeneXpert Assay as a screening test for MDR for all sampled patients (i.e. both categories I and II): A) Results compared to DST, B) Screening validity at a prevalence of 1.5%.

A)

		DST		Total
		MDR	Not MDR	
		N	N	N
GeneXpertAssay	RIF Resistant	6	14	20
	RIF Susceptible	0	388	388
Total		6	402	408

B)

Screening Performance Indicators	Value	[95% CI]
Prevalence of MDR-TB	0.01	[0.01; 0.03]
SN	1.00	[0.52; 0.98]
SP	0.97	[0.94; 0.98]
Accuracy	0.97	[0.94; 0.98]
PPV	0.30	[0.13; 0.54]
NPV	1.00	[0.99; 1.00]

3.2.3. Comparing validity of GeneXpert Assay as a screening test for MDR according to patients' categories:

The validity indicators for GeneXpert Assay maintained a good validity levels at both patients categories but the PPV was much higher in category II patients (table: 4-B). This means the use of this test for category II patients yields more confidence with positive results compared to the yield false positive results.

Table 4: Performance of GeneXpert Assay as a screening test for MDR in NRL in Baghdad, 2013-2014: A) Results compared to DST, B) Screening validity at a prevalence of around 1%.

A)

		Patient Category					
		New			Previously treated		
		DST Result		Total	DST Result		Total
		MDR	Not		MDR	Not	
		N	N	N	N	N	N
GeneXpertAssay	RIF Resistant	3	11	14	3	3	6
	RIF Susceptible	0	346	346	0	42	42
Total		3	357	360	3	45	48

B)

	Patients Category	
	New	Previously treated
Screening Performance Indicators	Value[95% CI]	Value[95% CI]
Prevalence of MDR-TB	0.01 [0.00; 0.03]	0.06 [0.02; 0.18]
SN	1.00 [0.31; 0.98]	1.00 [0.31; 0.97]
SP	0.97 [0.94; 0.98]	0.93 [0.81; 0.98]
Accuracy	0.97 [0.94; 0.98]	0.94 [0.82; 0.98]
PPV	0.21 [0.06; 0.54]	0.50 [0.14; 0.86]
NPV	1.00 [0.99; 1.00]	1.00 [0.90; 1.00]

3.3. Cost analysis:

3.3.1. Costs of laboratory tests:

In Iraq, assuming no redoing/rechecking, from the diagnosis of TB (by DSM for AFB) and till confirming the picture of drug susceptibility (by DST using solid media) for each TB patient, i.e. using DSM at a cost of US\$ 5 followed by culture on solid media with a cost of US\$ 10 then followed with DST using solid media with a cost of US\$ 15, such a process costs US\$ 30 per patient (table 5).

If we add GeneXpert Assay testing to the previous series of testing (adding a cost of US\$ 25 per patient); then the total cost will be US\$ 55 per patient if the GeneXpert kit was brought to Iraq with a discounted price through United Nations Development Program (UNDP) (table 5).

Anyhow, we expect UNDP to leave Iraq by 2017 and then the cost of GeneXpert Assay testing per patient will be US\$ 70 instead of US\$ 25, and hence the overall cost of using direct smear microscopy (DSM) looking for AFB in sputum smears, GeneXpert Assay, culture and drug susceptibility testing using sold media together will be US\$ 100 (table 5).

Table 5: Costs of laboratory diagnosis for detecting TB and drug susceptibility:

Laboratory Test	Cost (US\$) per patient
Direct sputum smear microscopy for AFB (DSM)	5
Culture using solid media	10
DST	15
GeneXpert Assay, supported through UN agencies*	25
GeneXpert Assay, cost not supported**	70

*Cost discounted if cartridges sold through UNDP.

**Cost if cartridges sold from local markets without discounts (without UNDP interference).

3.3.2. Cost effectiveness of GeneXpert in detecting MDR-TB cases:

GeneXpert Assay has a high SN in detecting MDR-TB patients (100%) among both new and category II patients (table 4-B), and per patient, if we replace traditional tests used to detect TB and susceptibility to anti-TB drugs that cost US\$30 by GeneXpert Assay the decision of cost effectiveness depends upon whether the cost of GeneXpert Assay was supported (discounted) or not. If discounted then GeneXpert Assay is more

cost effective than traditional laboratory tests, but if the diagnostic cartridges will be bought from private local markets then using this test alone will exceed more than twice the cost of traditional tests' combination (US\$70 for GeneXpert versus US\$30 for traditional tests' combination "DSM + culture + DST"). If we use the test as add-on, then the diagnostic cost per patient will mount the burden upon National Tuberculosis control Program (NTP) more (total cost will be US\$ 100).

3.3.3. Cost benefit of GeneXpert in detecting MDR-TB cases:

In reference to Tables (3-B) and (4-B), we find that despite the high SN of GeneXpert Assay in detecting MDR-TB patients (on assuming RR patients are MDR patients), the PPV is not high (30% in total sample, 21% in new patients and 50% in category II patients), this reflects that positive GeneXpert result of RR still carry a high possibility of false positive results which in turn means exposing patients to second line drugs (SLD) (and their harms) and losing the opportunity to cure early with first line drugs (FLD) treatment.

In 2013, Iraq has registered 6112 new bacteriologically confirmed pulmonary TB (PTB) cases, 679 previously treated PTB cases and 83 MDR-TB cases⁽⁸⁾. If all of them were tested for drug susceptibility initially upon diagnosis then the cost will be as indicated in table 6.

Table 6: Expected cost burden of laboratory tests used to detect MDR-TB assuming a stable TB case notification in Iraq starting from 2013.

Diagnostic Tests for Detecting MDR	Cost (US\$)		
	New patients (n=6112)	Category II patients (n=679)	MDR-TB cases (n=83)
Traditional tests (DSM+Culture+DST)	183360	20910	2490
GeneXpert Assay (US\$25/test)	152800	20370	2075
GeneXpert Assay (US\$70/test)*	427840	47530	5810
Traditional tests + GeneXpert Assay (US\$25/test)	336160	37345	4565
Traditional tests + GeneXpert Assay (US\$70/test)*	611200	67900	8300

*no discount on cartridge price since cartridges expected to be bought from local private market.

In terms of diagnosing MDR-TB; though using GeneXpert Assay (discounted cartridge price) alone brings more cost benefit but if merged with traditional tests it brings no cost benefit at all.

Since the PPV is higher in category II patients, then the cost benefit will be higher in using GeneXpert Assay for category II patients in detecting a higher proportion of patients with lower total cost.

3.4. Operational Aspects:

3.4.1. Making readings:

Generally, operating staff reported no difficulties in collecting samples, sample preparation, cartridge registration or reading results apart that thick mucoid sputum samples need further processing (redoing digestion and decontamination).

3.4.2. Disposal & biosafety:

Cartridge disinfection, cartridge disposal, and biosafety were simple with easy to follow standard operating procedures (SOPs). Biosafety here is generally not complicated. Samples are processed under BSC class II and waste disposal is according to WHO recommendations.

3.4.3. Storage and supply of cartridges:

Cartridges are fairly bulky, needs a storage temperature varying from 2 to 28C°, with short shelf life. Such characteristics make it necessary to have a suitable warehouse of large capacity (the control of cartridge distribution is central in Iraq and a task of NRL) with continuous power supply for proper air conditioning taking into consideration the hot weather in summer (temperature may approach or exceed 50 C°) and shortage in power and frequent interruptions. The short shelf life means the NRL cannot request for large quantities that cover the country needs more than a year but the doubling in efforts paid for routine communication for both importing the cartridges and for distributing them.

3.4.4. Operating the machine:

3.4.4.1. Operating temperature: Air conditioning is always needed during summer to maintain room temperature between 15-30C°.

3.4.4.2. Electrical supply: In Iraq, to operate such a machine where power is interrupted in unscheduled pattern and the voltage is not well stabilized at 220 volt, here there are two conditions to connect such machine to power; Uninterrupted power supply device (UPS) (400 VA), and voltage stabilizer.

3.4.4.3. Training: training how to operate the machine/computer use and infection control is easy and not need a long time, but for managing the device in presence of trouble shooting is difficult since the trouble shooting is frequent and needs professionals/contact to maintaining company.

3.4.4.4. Average operating capacity a day: During the study conduct, the average work day allowed to do two runs of GeneXpert Assay operation, each run capacity was four patients yielding an average testing of eight patients a day for a device. Minimum operating capacity was single operation, i.e. testing for four patients and maximum operating capacity was testing for eight patients a day (two runs a day).

3.5. User satisfaction:

Laboratory technicians used the GeneXpert machine during this study reflected a convenience with using this laboratory test. Observations were registered in simple checklist in a daily register and operational maintenance notes were documented in a special register. SOPs were followed which were easy to follow and waste management was simple and laboratory staff were familiar with it as it is similar to that of direct smear microscopy.

3.6. Attitude towards peripheral use of GeneXpert Assay Machine:

Placing this device in peripheral settings requires the presence of continuous power supply and air conditioners. Vehicles provided with

refrigerators are necessary to transport cartridges from warehouse to peripheral settings. This device is simple to operate and not necessary to be operated by laboratory technicians but is necessary to be operated by staff can read/comprehend English language and able of using computers, who are not available at a considerable proportion of peripheral units. Without these conditions, this device cannot be used at peripheral settings.

4. Discussion

Accurate, rapid detection of TB and TB drug resistance is critical for improving patient care and decreasing TB transmission (Steingart et al. 2014)⁽⁸⁾. Xpert MTB/RIF assay showed acceptable sensitivity and excellent specificity for the diagnosis of PTB and detection of rifampicin resistance in areas with intermediate TB burden (Kwak et al. 2013)⁽⁹⁾. As an initial test replacing smear microscopy, Xpert® MTB/RIF pooled sensitivity was 89% pooled specificity 99% (Steingart et al. 2014)⁽⁸⁾. This semi-automated test can detect both the causative agent of TB and mutations that confer rifampicin resistance from clinical specimens within 2 h after starting the test (Shinnick et al. 2015)⁽¹⁰⁾, in the same time it provides an effective TB symptom screening and onsite results (Page-Shipp et al. 2014)⁽¹¹⁾. RIF result can serve as marker for multidrug-resistant MTB (MDR TB) and has been reported in > 95% of the MDR-TB isolates ⁽²⁾. Xpert® MTB/RIF provides accurate results and can allow rapid initiation of MDR-TB treatment, pending results from conventional culture and DST. The MTB/RIF test can effectively be used in low-resource settings to simplify patients' access to early and accurate diagnosis, thereby potentially decreasing morbidity associated with diagnostic delay, dropout and mistreatment ⁽³⁾. Anyhow, the tests are expensive (Steingart et al. 2014)⁽⁸⁾ evidences pointed out no increase on overall notification rates was observed, as in Brazil (Durovni et al. 2014)⁽¹²⁾, in addition, limited impact on patient outcomes suggests additional interventions are needed to enhance TB control (McNerney et al 2015)⁽¹³⁾. This is why the balance between benefits and expenses of such technology need to be carefully studied to be directed towards the best implementation strategy in Iraq. This study had studied all of diagnostic impact, cost analysis and operational aspects to highlight the best use (better outcomes) of this new diagnostic technology.

According to this study, Sensitivity of GeneXpert Assay regarding RR detection was 71%. Pooled SN were found as 95%, 94% by (Steingart et al. 2014)⁽⁸⁾ and (Weyer et al. 2013)⁽¹⁴⁾ respectively, while (Kwak et al. 2013)⁽⁹⁾ found it 57.1%. This variation could be explained by (Blakemore et al. 2010)⁽¹⁵⁾ who stated resistance detection was dependent on the particular mutation and required between 65% and 100% mutant

DNA to be present in the sample for 95% certainty of resistance detection. Another condition may affect sensitivity which is the prevalence of RR among tested individuals, (Steingart et al. 2014)⁽⁸⁾ has clearly illustrated that in the following hypothetical example: For rifampicin resistance detection, if the pooled accuracy estimates for Xpert® MTB/RIF [SN 95% & SP 98%] are applied to a hypothetical cohort of 1000 individuals where 15% of those with symptoms are rifampicin resistant, Xpert® MTB/RIF would correctly identify 143 individuals as rifampicin resistant and miss eight cases (Steingart et al. 2014)⁽⁸⁾, and correctly identify 833 individuals as rifampicin susceptible and misclassify 17 individuals as resistant (Steingart et al. 2014)⁽⁸⁾. Where 5% of those with symptoms are rifampicin resistant, Xpert® MTB/RIF would correctly identify 48 individuals as rifampicin resistant and miss three cases (Steingart et al. 2014)⁽⁸⁾, and correctly identify 931 individuals as rifampicin susceptible and misclassify 19 individuals as resistant.

This study found the specificity of GeneXpert Assay regarding RR detection was 98%, this study agrees with Pooled SP estimates found; 98% by (Steingart et al. 2014)⁽⁸⁾ and 97% by (Weyer et al. 2013)⁽¹⁴⁾. (Kwak et al. 2013)⁽⁹⁾ found it 100.0%.

While (Durovni et al. 2014)⁽¹²⁾ and (Kwak et al. 2013)⁽⁹⁾ found PPV 98% and 100.0% respectively and (Blakemore et al. 2010)⁽¹⁵⁾ suggested that false-positive results would be unlikely to occur, GeneXpert Assay PPV was found not high (60%) regarding RR detection in this study in a sample of RR prevalence of 4%. This study finding means there is a high probability of false positive results. This could be attributed to the low prevalence of RR which agrees with fact that predictive values are not intrinsic to the test; they depend also on the prevalence (Altman et al. 1994)⁽¹⁶⁾. All tests have poor PPV in settings with low levels of MDR-TB and good PPV in settings with high levels (Weyer et al. 2013)⁽¹⁴⁾. This as well explained by the same hypothetical example given by (Steingart et al. 2014)⁽⁸⁾ who stated: For rifampicin resistance detection, if the pooled accuracy estimates for Xpert® MTB/RIF [SN 95% & SP 98%] are applied to a hypothetical cohort of 1000 individuals where 15% of those with symptoms are rifampicin resistant, Xpert® MTB/RIF would

misclassify 17 individuals as resistant (Steingart et al. 2014)⁽⁸⁾. Where 5% of those with symptoms are rifampicin resistant, Xpert® MTB/RIF would misclassify 19 individuals as resistant. (Weyer et al. 2013)⁽¹⁴⁾ stated that the PPV for rifampicin resistance using Xpert MTB/RIF exceeds 90% in settings or patient groups where the underlying prevalence of rifampicin resistance is above 15% (Weyer et al. 2013)⁽¹⁴⁾. In settings or patient groups where rifampicin resistance is rare, the PPV of Xpert MTB/RIF (and any other test) is adversely affected, significantly diminishing when rifampicin resistance prevalence falls below 5% (Weyer et al. 2013)⁽¹⁴⁾.

Recent reports suggest that false-positive rifampicin resistance may be assigned by the Xpert MTB/RIF assay and the assay incorrectly assigned rifampicin resistance in 31% of cases (Williamson et al. 2012)⁽¹⁷⁾. Another justification to false positive results & low PPV: Resistance to rifampicin is nearly always due to point mutations in the *rpo* gene in the beta subunit of DNA-dependent RNA polymerase (Ormerod. 2005)⁽¹⁸⁾. A false-positive result was most likely, given the wild type *rpoB* gene sequence (Van Rie et al. 2012)⁽¹⁹⁾. The presence of a silent mutation in the *rpoB* gene, leads to the conclusion of a false-positive Xpert result (Mathys et al. 2014)⁽²⁰⁾.

This study found (in a sample with RR prevalence of 4%) the NPV for RR detection is 99%. This finding agree with (Kwak et al. 2013)⁽⁹⁾ who found it 94.9% and with (Weyer et al. 2013)⁽¹⁴⁾ who stated: The NPV is over 99% in settings with both low and high prevalence of rifampicin resistance, i.e. a negative result reliably *excludes* resistance and no further testing to confirm negative results is required.

Genetic probes which detect drug resistance to rifampicin with >95% accuracy are very suggestive of MDR-TB; <10% of rifampicin resistance is monoresistant, and so rifampicin resistance is a marker for MDR-TB in >90% of cases (Ormerod. 2005)⁽¹⁸⁾. In a population at high risk of RR, however, the PPV for RR by Xpert MTB/RIF is high, and identification of RR is an excellent proxy for multidrug-resistant TB (MDR-TB) ⁽⁵⁾. Such statements were agreed with by this study authors and as follow:

The validity of GeneXpert Assay for detecting MDR-TB in a sample of MDR-TB prevalence of 1%, the screening performance was: SN of 100%, SP of 97%, PPV of 30%, & NPV of 100%. Here this assay will detect all MDR-TB cases and exclude all non-MDR-TB cases but will get only 30% of assay positive cases are MDR-TB cases (70% of assay positive are not MDR-TB cases). Similar results were observed when applying this assay only to new patients. But applying this assay testing to retreatment patients (who are at risk for MDR-TB) yielded same SN and NPV and better PPV (50%). The PPV for rifampicin resistance using Xpert MTB/RIF (or any other test) can be substantially improved by careful risk assessment in individual patients and targeted testing of risk groups (Weyer et al. 2013)⁽¹⁴⁾. This agree with (Ou et al.2015)⁽²¹⁾ who found: For the detection of rifampin resistance in suspected MDR-TB cases, the sensitivity and specificity of MTB/RIF were 87.1% and 91.0%, respectively.

Though authors agree with (Weyer et al. 2013)⁽¹⁴⁾ that Patients at risk of drug resistance in whom rifampicin resistance is detected by Xpert® MTB/RIF should be placed on an appropriate MDR-TB regimen immediately and INH added until the DST result for INH is available. These patients should provide an additional sputum specimen for conventional culture and DST against other first and second line drugs according to WHO recommendations, and their treatment adjusted accordingly, this study authors as well highlight the importance of a conclusion given by (Van Rie et al. 2012)⁽¹⁹⁾ that: When decentralizing Xpert, test performance characteristics need to be understood by health care workers and methods of confirmation of RMP resistance need to be accessible.

Though Xpert® MTB/RIF remains expensive (Steingart et al. 2014)⁽⁸⁾ or a relatively costly test (Nicol et al.2013)⁽²²⁾, it provides accurate results and can allow rapid initiation of MDR-TB treatment, pending results from conventional culture and DST (Steingart et al. 2014)⁽⁸⁾. Its use was cost-effective in United States (Choi et al.2013)⁽²³⁾ and in an intermediate burden area like Hong Kong (You et al.2015)⁽²⁴⁾, However, after Xpert MTB/RIF Assay introduction, there was a limited impact on

patient outcomes (on global scale) (McNerney et al 2015)⁽¹³⁾ and in Brazil (Durovni et al. 2014)⁽¹²⁾ observed no increase on overall notification rates.

In Iraq, a country classified as an upper middle income country with a moderate TB burden (The Global Fund.2014)⁽²⁵⁾, the assay on replacing DSM and conventional culture method is cost-effective per patient only if the cartridges were supported (discounted price) by UNDP (cost change from US\$30 by DSM & conventional culture method to US\$25 using Xpert Assay alone). If no discount available, then the cost will exceed conventional methods by US\$45 (i.e. more than double the cost). If we use this assay as an add-on test to the already existing diagnostic protocol, then there will be an extra burden of US\$25 (US\$70 if discount is unavailable). In terms of detecting MDR-TB though using GeneXpert Assay (discounted cartridge price) alone brings more cost benefit on replacing the traditional methods (DSM, culture & DST) but if merged with traditional tests it brings no cost benefit nor cost-effectiveness at all. Existing data suggest cost-effectiveness in some, but not all, settings (Kirwan et al.2012)⁽²⁶⁾. Using it to test everyone with TB signs and symptoms is affordable in several middle-income countries, but financial viability in low-income countries requires large increases in TB funding and/or further price reductions (Pantoja et al.2012)⁽²⁷⁾. Such scenario is different in USA; Xpert testing of a single sputum sample from TB suspects is expected to result in lower total health care costs per patient (US2673) compared to diagnostic algorithms using only sputum microscopy and culture (US2728) and improved health outcomes. Compared to existing molecular assays, implementation of Xpert in the United States would be considered highly cost-effective (Choi et al.2013)⁽²³⁾.

GeneXpert result of RR according to this study carry a high possibility of false positive results which in turn means exposing patients to second line drugs (SLD) (and harms due to their adverse reactions) and losing the opportunity to cure early with first line drugs (FLD) treatment.

Since the predictive value is higher in category II patients, then the cost benefit for the health system will be higher in using GeneXpert Assay for category II patients (instead of all TB suspects) in early detecting MDR-TB.

Decentralization of this test means the extra cost burdened by the cost of transportation under storage temperature conditions and electricity cost (as well extra cost of local generators maintenance) and the maintenance of 24 hour working air-conditioners at many peripheral TB units' wear-houses to maintain storage temperature of kits at Iraqi hot summer. (Schnippel et al.2012)⁽²⁸⁾ Concluded placing Xpert technology at points of treatment is substantially more expensive than placing the instruments in smear microscopy laboratories.

The Xpert® MTB/RIF system consists of an instrument, personal computer, barcode scanner, and preloaded software for running tests and viewing the results ⁽²⁾. The sample processing, nucleic acid extraction, amplification and detection of known mutations related to rifampicin resistance are performed in a single cartridge in this integrated system and the results are obtained in two hours ⁽⁴⁾. Moreover, the MTB/RIF test provided sensitive detection of tuberculosis in less than two hours ⁽⁴⁾. The test is simple to conduct and requires basic sputum handling facilities only. These characteristics render it a promising close-to-patient test for TB in various settings (Bowles et al.2011)⁽²⁹⁾. While considerations before implementation included safe, effective sputum collection; uninterrupted electricity supply; stringent instrument verification and provision of onsite results (Page-Shipp et al. 2014)⁽¹¹⁾, a distinct advantage of Xpert® MTB/RIF is its suitability for use at district and sub-district level and the technology should therefore not be restricted to central/reference laboratory level only (Weyer et al. 2013)⁽¹⁴⁾.

In this study, generally, operating staff reported no difficulties in collecting samples, sample preparation, cartridge registration, reading results (apart that thick mucoid sputum samples need further processing due to redoing digestion and decontamination), or in cartridge disposal. Xpert® MTB/RIF assay is an automated test that can detect both TB and rifampicin resistance with minimal hands-on technical time (Steingart et al. 2014)⁽⁸⁾, and hence sample processing and detection are largely automated, Xpert MTB/RIF is potentially suitable for implementation in resource-limited settings (Nicol et al.2013)⁽²²⁾. MTB/RIF is a useful assay for rapid diagnosis of tuberculosis, considering that the results can be given in the same day of sample collection and the assay is superior in sensitivity than microscopic

examination (ÖZKÜTÜK et al.2014)⁽³⁰⁾. Both the preparation of specimens and the running of the Xpert MTB/RIF test require the same biosafety conditions as are used for conventional direct sputum-smear microscopy (WHO.2013)⁽³¹⁾.

Cartridges are fairly bulky, needs a storage temperature varying from 2-28 °C, and this is true for specimen reagent (WHO.2014)⁽³²⁾, with short shelf life which is 12 months (WHO.2013)⁽³¹⁾. Such characteristics make it necessary to have a suitable warehouse of large capacity with continuous power supply for proper air conditioning taking into consideration the hot weather in summer (temperature may approach or exceed 50 °C) and shortage in power and frequent interruptions. The short shelf life means the NRL cannot request for large quantities that cover the country needs more than a year but the doubling in efforts paid for routine communication for both importing the cartridges and for distributing them.

Air conditioning is always needed during summer to maintain room temperature between 15-30 °C. The manufacturer's recommended ambient operating temperature for the GeneXpert instrument is limited to a maximum of 30 °C (WHO.2013)⁽³¹⁾. In settings where the ambient temperature regularly exceeds 30 °C, the room where the assay is being done may need to be air conditioned (WHO.2013)⁽³¹⁾.

The GeneXpert instrument requires a stable electric power supply: even a short-term interruption in power may cause results to be lost, cartridges to be wasted, and the need to obtain another specimen. An unstable supply of electricity may also damage the electronics of the instrument and the computer, which may not be covered by the manufacturer's warranty. Therefore, a power line stabilizer and an uninterrupted power supply unit (UPS) are recommended for the GeneXpert instrument (WHO.2014)⁽³²⁾. In Iraq, to operate such a machine where power is interrupted in unscheduled pattern and the voltage is not well stabilized at 220 volt, here there are two practical conditions to connect such machine to power; Uninterrupted power supply device (UPS) (400 VA), and voltage stabilizer.

Space and power requirements have a significant effect on installation costs. Countries need to carefully consider the placement of Xpert machines based on the quality and size of the available infrastructure (Abdurrahman et al.2014)⁽³³⁾.

(Weyer et al. 2013)⁽¹⁴⁾ reported that the sophisticated nature of the device requires care of handling, i.e. a stable and uninterrupted electrical supply to avoid interruption of the procedure and subsequent loss of results, an ambient temperature under 30 C, security against theft, adequate storage space for the cartridges, and the need for sufficient staff to perform testing (Weyer et al. 2013)⁽¹⁴⁾.

Training how to operate the machine/computer use and infection control is easy and not need a long time. Minimal training is required for personnel ⁽⁶⁾. But for managing the device in presence of trouble shooting it is difficult to take over by operating facility since the trouble shooting is frequent and needs professionals/contact to maintaining company. Since April 2012, new GeneXpert instruments have an initial 2-year warranty that is conditional upon modules being regularly calibrated (WHO.2013)⁽³¹⁾.

The maximum capacity of a single, 4-module GeneXpert instrument is 16–20 specimens per day (WHO.2013)⁽³¹⁾. During the study conduct, the average work day allowed to do two runs of GeneXpert Assay operation, each run capacity was four patients yielding an average testing of eight patients a day for a device. Minimum operating capacity was single operation, i.e. testing for four patients and maximum operating capacity was testing for eight patients a day (two runs a day).

Laboratory technicians used the GeneXpert machine during this study reflected a convenience with using this laboratory test. Observations were registered in simple checklist in a daily register and operational maintenance notes were documented in a special register. SOPs were followed which were easy to follow and waste management was simple and laboratory staff were familiar with it as it is similar to that of direct smear microscopy.

From the experience of investigators with this assay use in practice, many considerations should be put in consideration and planning before thinking of using this instrument in peripheral settings in a country like Iraq. Placing this device in peripheral settings requires the presence of continuous power supply and air

conditioners. Vehicles provided with refrigerators are necessary to transport cartridges from warehouse to peripheral settings. This device is simple to operate and not necessary to be operated by laboratory technicians but is necessary to be operated by staff can read/comprehend English language and able of using computers, who are not available at a considerable proportion of peripheral units. Without these conditions, this device cannot be used at peripheral settings. There are, however, a number of practical constraints to the use of Xpert at the point-of-care (Nicol et al.2013)⁽²²⁾. (Durovni et al.2014)⁽³⁴⁾ stated: For nationwide scale-up, a local service provider is needed to maintain the Xpert system. Ensuring cartridge availability is also essential. The capacity to perform smear microscopy should be retained. In addition, (Lippincott et al. 2015)⁽³⁵⁾ highlighted that optimal use of Xpert in diverse settings will require knowledge of challenges when interpreting the results.

Another consideration to be taken before expanding use of Xpert towards peripheral use is the returns of this expenditure in terms of cost benefit and health outcomes. (Dlamini-Mvelase et al.2014)⁽³⁶⁾ found that despite the rapidity of the Xpert results, only about 70% of patients had been initiated treatment at one month. In south African (intermediate setting) Xpert results took twice as long as AFB results to reach clinicians. Replacing AFB with centralized Xpert may delay TB diagnoses in some settings (Cohen et al.2014)⁽³⁷⁾. The introduction of MTB/RIF could increase the accuracy of detection of MTB and rifampin resistance in peripheral-level TB laboratories in China (Ou et al.2015)⁽²¹⁾.

5. Conclusions & Recommendations

5.1. Conclusions:

5.1.1. Compared to DSM and conventional DST, GeneXpert Assay is a fruitful device in the early detection of both TB and RR-TB, and MDR-TB but has a considerable yield of false positive output for RR results.

5.1.2. PPV for TB detection as a post-test criterion for GeneXpert Assay is excellent (GeneXpert Assay gave no negative result for any SS+PTB patient). But SN and PPV of this assay for RR were not high (71% & 60% respectively).

5.1.3. In Iraq, without the discount in Xpert Cartridge prices (from US\$70 to US\$25 per patient); there is no cost effectiveness or cost benefits in terms of diagnostic costs on replacing GeneXpert Assay DSM & conventional DST tests. In addition, false positive results burden more the momentary cost by the sustained need for confirmation with conventional diagnostic methods, but decreasing only diagnostic delay of RR & MDR-TB.

5.1.4. This assay is easily operable but requires personnel capable of using computers, and a facility with: Adequate space for storing cartridges & specimen reagents under continuous stable power supply and 24 hour air conditioning in summer. Such workplace environment favors the expansion to intermediate level (Governorate level Chest Clinics) but not the peripheral use (not suitable for district level use in current situation of Iraq), at least during current situation of Iraq.

5.2. Recommendations:

5.2.1. Authors encourage the expansion of this Assay use at the peripheral level (Chest Clinics) where the workplace environment fulfils operational requirements and the staff is aware of interpreting results according to patients' clinical history.

5.2.2. A genetic study need to be conducted to study patients labeled as false positive RR by GeneXpert Assay and disclose the reason behind this elevated percentage rate.

5.2.3. In presence of global intensions to expand the use of this assay at peripheral level, a further study looking for the impact of this device upon the followings:

1. If the early detection of RR is associated with early treatment for MDR-TB (if early DR-TB detection is associated with decrease in treatment delay).
2. Health outcomes of those detected with GeneXpert assay & enrolled in SLD.
3. Notification rates for both susceptible- & DR-TB compared with pre-Xpert era.

6. References

1. Tuberculosis Factsheet Fact sheet N°104. Geneva. World Health Organization.
(<http://www.who.int/mediacentre/factsheets/fs104/en/> accessed 22nd April 2015)
2. Bodmer T, Ströhle A. Diagnosing pulmonary tuberculosis with the Xpert MTB/RIF test. *J Vis Exp*. 2012 Apr 9;(62):e3547.
3. Boehme CC, Nicol MP, Nabeta P, Michael JS, Gotuzzo E, Tahirli R, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet*. 2011 Apr 30; 377(9776): 1495–1505.
4. Ciftçi IH, Aslan MH, Aşık G. Evaluation of Xpert MTB/RIF results for the detection of *Mycobacterium tuberculosis* in clinical samples. *Mikrobiyol Bul*. 2011 Jan;45(1):43-7.
5. Trébucq A, Enarson DA, Chiang CY, Van Deun A, Harries AD, Boillot F, et al. Xpert® MTB/RIF for national tuberculosis programmes in low-income countries: when, where and how? *Int J Tuberc Lung Dis*. 2011 Dec;15(12):1567-72.
6. WHO. Xpert MTB/RIF implementation manual Technical and operational ‘how-to’: practical considerations. WHO. 2014: 12-13.
7. WHO. Global Tuberculosis Report. Key indicators for the WHO Eastern Mediterranean Region. Geneva. Tables CD.2 & CD.5.
(http://www.who.int/tb/publications/global_report/en/ accessed 22Apr 2015)
8. Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev*. 2014 Jan 21;1:CD009593. doi: 10.1002/14651858.CD009593.pub3.
9. Kwak N, Choi SM, Lee J, Park YS, Lee CH, Lee SM, et al. Diagnostic accuracy and turnaround time of the Xpert MTB/RIF assay in routine clinical practice. *PLoS*

One. 2013 Oct 29;8(10):e77456.doi: 10.1371/journal.pone.0077456. eCollection 2013.

10. Shinnick TM, Starks AM, Alexander HL, Castro KG. Evaluation of the Cepheid Xpert MTB/RIF assay. *Expert Rev Mol Diagn.* 2015 Jan;15(1):9-22. doi: 10.1586/14737159.2015.976556. Epub 2014 Nov 6.

11. Page-Shipp L, Stevens W, Clark D, Scott L, Olsen F, Kisbey-Green H, Mametja D, et al. Successes, challenges and lessons from a novel deployment of XpertW MTB/RIF at a major South African public event. *INT J TUBERC LUNG DIS.* 2014;18(4):438–440.

12. Durovni B, Saraceni V, van den Hof S, Trajman A, Cordeiro-Santos M, Cavalcante S, et al. Impact of replacing smear microscopy with Xpert MTB/RIF for diagnosing tuberculosis in Brazil: a stepped-wedge cluster-randomized trial. *PLoS Med.* 2014 Dec 9;11(12):e1001766. doi: 10.1371/journal.pmed.1001766. eCollection 2014.

13. McNerney R, Zumla A. Impact of the Xpert MTB/RIF diagnostic test for tuberculosis in countries with a high burden of disease. *Curr Opin Pulm Med.* 2015 Mar 11. [Epub ahead of print]

14. Weyer K, Mirzayev F, Migliori GB, Van Gemert W, D'Ambrosio L, Zignol M, et al. Rapid molecular TB diagnosis: evidence, policy making and global implementation of Xpert MTB/RIF. *Eur Respir J.* 2013 Jul;42(1):252-71. doi: 10.1183/09031936.00157212. Epub 2012 Nov 22.

15. Blakemore R, Story E, Helb D, Kop J, Banada P, Owens MR, et al. Evaluation of the analytical performance of the Xpert MTB/RIF assay. *J Clin Microbiol.* 2010 Jul;48(7):2495-501. doi: 10.1128/JCM.00128-10. Epub 2010 May 26.

16. Altman DG, Bland JM. Statistics Notes: Diagnostic tests 2: Predictive values. *BMJ.* 1994;309 (6947); 102. doi:10.1136/bmj.309.6947.102.

17. Williamson DA, Basu I, Bower J, Freeman JT, Henderson G, Roberts SA. An evaluation of the Xpert MTB/RIF assay and detection of false-positive rifampicin

resistance in *Mycobacterium tuberculosis*. *Diagn Microbiol Infect Dis*. 2012 Oct;74(2):207-9. doi: 10.1016/j.diagmicrobio.2012.06.013. Epub 2012 Jul 20.

18. Ormerod LP. Multidrug-resistant tuberculosis (MDR-TB): epidemiology, prevention and treatment. *Br Med Bull*. 2005 Jun 14;73-74:17-24. Print 2005.

19. Van Rie A, Mellet K, John MA, Scott L, Page-Shipp L, Dansey H, et al. False-positive rifampicin resistance on Xpert® MTB/RIF: case report and clinical implications. *Int J Tuberc Lung Dis*. 2012 Feb;16(2):206-8. doi: 10.5588/ijtld.11.0395.

20. Mathys V, van de Vyvere M, de Droogh E, Soetaert K, Groenen G. False-positive rifampicin resistance on XpertW MTB/RIF caused by a silent mutation in the *rpoB* gene. *INT J TUBERC LUNG DIS*. 2014;18(10):1255–1257.

21. Ou X, Xia H, Li Q, Pang Y, Wang S, Zhao B, et al. A feasibility study of the Xpert MTB/RIF test at the peripheral level laboratory in China. *Int J Infect Dis*. 2015 Feb;31:41-46.

22. Nicol MP, Whitelaw A, Wendy S. Using Xpert MTB/RIF. *Curr Respir Med Rev*. 2013 Jun;9:187-192

23. Choi HW, Miele K, Dowdy D, Shah M. Cost-effectiveness of Xpert® MTB/RIF for diagnosing pulmonary tuberculosis in the United States. *Int J Tuberc Lung Dis*. 2013 Oct;17(10):1328-35.

24. You JH, Lui G, Kam KM, Lee NL. Cost-effectiveness analysis of the Xpert MTB/RIF assay for rapid diagnosis of suspected tuberculosis in an intermediate burden area. *J Infect*. 2015 Apr;70(4):409-14. doi: 10.1016/j.jinf.2014.12.015. Epub 2015 Jan 6.

25. The Global Fund. Eligibility List 2014. Geneva.
(http://r.search.yahoo.com/_ylt=A9mSs28dR6tVfKUA8MBLBQx.;_ylu=X3oDMTByaW11dnNvBGNvbG8DaXIyBHBvcwMxBHZ0aWQDBHNlYwNzcg--/RV=2/RE=1437317021/RO=10/RU=http%3a%2f%2fwww.theglobalfund.org%2fdocuments%2fcore%2feligibility%2fCore_EligibleCountries2014_List_en%2f/RK=0/R S=0UcRtYthTDhbujeGe55xvXbg5Dw- accessed 19 July 2014)

26. Kirwan DE, Cárdenas MK, Gilman RH. Rapid implementation of new TB diagnostic tests: is it too soon for a global roll-out of Xpert MTB/RIF? *Am J Trop Med Hyg.* 2012 Aug;87(2):197-201. doi: 10.4269/ajtmh.2012.12-0107.
27. Pantoja A, Fitzpatrick C, Vassall A, Weyer K, Floyd K. Xpert MTB/RIF for diagnosis of tuberculosis and drug-resistant tuberculosis: a cost and affordability analysis. *Eur Respir J.* 2013 Sep;42(3):708-20. doi: 10.1183/09031936.00147912. Epub 2012 Dec 20.
28. Schnippel K, Meyer-Rath G, Long L, Macleod W, Sanne I, Stevens WS, et al. Scaling up Xpert MTB/RIF technology: the costs of laboratory- vs. clinic-based roll-out in South Africa. *Trop Med Int Health.* 2012 Jun 12. doi: 10.1111/j.1365-3156.2012.03028.x.
29. Bowles EC, Frey   B, van Ingen J, Mulder B, Boeree MJ, van Soolingen D. Xpert MTB/RIF  , a novel automated polymerase chain reaction-based tool for the diagnosis of tuberculosis. *Int J Tuberc Lung Dis.* 2011 Jul;15(7):988-9. doi: 10.5588/ijtld.10.0574.
30.   ZK  T  K N, S  R  C  O  LU S. Evaluation of the Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary tuberculosis in an intermediate-prevalence setting. *Mikrobiyol Bul.* 2014 Apr;48(2):223-32.
31. WHO. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update. WHO. 2013:41-42.
32. WHO. Xpert MTB/RIF implementation manual Technical and operational ‘how-to’: practical considerations. WHO. 2014: 26-28.
33. Abdurrahman ST, Emenyonu N, Obasanya OJ, Lawson L, Dacombe R, Muhammad M, et al. The hidden costs of installing Xpert machines in a tuberculosis high-burden country: experiences from Nigeria. *Pan Afr Med J.* 2014 Aug 5;18:277. doi: 10.11604/pamj.2014.18.277.3906. eCollection 2014.

34. Durovni B, Saraceni V, Cordeiro-Santos M, Cavalcante S, Soares E, Lourenço C, et al. Operational lessons drawn from pilot implementation of Xpert MTB/Rif in Brazil. *Bull World Health Organ.* 2014 Aug 1;92(8):613-7. doi: 10.2471/BLT.13.131409. Epub 2014 May 1.
35. Lippincott CK , Miller MB , Van Rie A , Weber DJ , Sena AC , Stout JE . The complexities of Xpert(®) MTB/RIF interpretation. *Int J Tuberc Lung Dis.* 2015 Mar;19(3):273-5. doi: 10.5588/ijtld.14.0432.
36. Dlamini-Mvelase NR, Werner L, Phili R, Cele LP, Mlisana KP. Effects of introducing Xpert MTB/RIF test on multi-drug resistant tuberculosis diagnosis in KwaZulu-Natal South Africa. *BMC Infect Dis.* 2014 Aug 16;14:442. doi: 10.1186/1471-2334-14-442.
37. Cohen GM, Drain PK, Noubary F, Cloete C, Bassett IV. Diagnostic delays and clinical decision making with centralized Xpert MTB/RIF testing in Durban, South Africa. *J Acquir Immune Defic Syndr.* 2014 Nov 1;67(3):e88-93. doi: 10.1097/QAI.0000000000000309.

Annex 1: Clinical Information Form

First Name الاسم الأول	Second Name الاسم الثاني	Third Name اسم الجد ١	Forth Name اسم الجد ٢	ENRS-TB register ID رقم المريض في سجل التدرن				
Enrollment Number رقم المريض حسب التسلسل في المسح			Sex الجنس	Age العمر	Dist القطاع		Gov المحافظة	
					Name	Code	Name	Code
<div style="display: flex; justify-content: space-between;"> الإجابة/رمز الإجابة Xpert MTB/RIF test </div>								
1.	Treatment Category: 1. (New/Category I) 2. (Retreatment/Category II)							
2.	Date sputum specimen was collected (dd/mm/yyyy)? تاريخ أخذ نموذج القشع							
3.	Sputum specimen in preservative? 1. (Yes) 2. (No) هل تم وضع النموذج في مادة حافظة							
<div style="display: flex; justify-content: space-between;"> اسم تقني المختبر في وحدة منسق التدرن: التوقيع: التاريخ: </div>								
<div style="display: flex; justify-content: space-between;"> الإجابة/رمز الإجابة رمز المحافظة التي عمل فيها الفحص </div>								
4.	Code of the governorate if TB clinic							
5.	Specimen ID code 1.(A) 2.(B) 3.(C) الرمز المميز للنموذج							
6.	Date specimen received in the Laboratory تاريخ استلام المختبر لنموذج القشع							
7.	Laboratory register ID رقم المريض في سجل المختبر							
8.	Specimen processing: 1.Petroff. 2. NALC. 3. Direct							
9.	Date of reporting Xpert MTB/RIF results							
10.	Result of Xpert: 1.(Neg) 2.(RIF Sensitive) 3.(RIF Resistant)							
<div style="display: flex; justify-content: space-between;"> اسم الفاحص: التوقيع و التاريخ: اسم مدير العيادة: التوقيع و التاريخ: </div>								
<div style="display: flex; justify-content: space-between;"> الإجابة/رمز الإجابة Culture Result نتيجة الزرع الجرثومي </div>								
11.	Culture done at 1.(TB clinic) 2.(NRL) مكان الفحص (المختبر المرجعي/ مختبر عيادة صدرية)							
12.	Code of the governorate if culture is at TB clinic							
13.	Date specimen received in the Laboratory تاريخ استلام المختبر للنموذج							
14.	Date of culture results reporting تاريخ ظهور نتيجة فحص الزرع الجرثومي							
15.	<div style="display: flex; justify-content: space-between;"> Result of Culture نتيجة فحص الزرع الجرثومي </div> <div style="display: flex; justify-content: space-between;"> 1.(Contaminated) 2.(Neg.) 3.(Non-TB mycobacteria) </div> <div style="display: flex; justify-content: space-between;"> 4.(1-9 colonies) 5.((1+)-10-100 col) 6.((2+) >100-200 col) 7.((3+) >200 col) </div>							
<div style="display: flex; justify-content: space-between;"> اسم الفاحص: التوقيع و التاريخ: اسم مدير العيادة: التوقيع و التاريخ: </div>								
<div style="display: flex; justify-content: space-between;"> الإجابة/رمز الإجابة Result of Drug Susceptibility Test (DST) at NRL </div>								
16.	Date specimen received in NRL تاريخ استلام النموذج							
17.	Date of DST testing تاريخ فحص الحساسية الدوائية							
18.	Date of DST Results Reporting تاريخ ظهور نتيجة فحص الحساسية الدوائية							
19.	INH: 1.(Susceptible) 2.(Resistant) 3.(Contaminated) 4.(Not Done)							
20.	Rifampicin: 1.(Susceptible) 2.(Resistant) 3.(Contaminated) 4.(Not Done)							
21.	Ethambutol: 1.(Susceptible) 2.(Resistant) 3.(Contaminated) 4.(Not Done)							
22.	Streptomycin: 1.(Susceptible) 2.(Resistant) 3.(Contaminated) 4.(Not Done)							
23.	Resistance Type: 1.(Susceptible) 2.(MDR) 3.(Polyresistance) 4.(Monoresistance)							
<div style="display: flex; justify-content: space-between;"> اسم مدير المختبر المرجعي: اسم الفاحص: </div> <div style="display: flex; justify-content: space-between;"> التوقيع و التاريخ: التوقيع و التاريخ: </div>								

يرجى كتابة التاريخ كالتالي: 21/09/2013, e.g. dd/mm/yyyy, Please write date as

Annex -3- User Satisfaction

Operational Aspects: Observations and user satisfaction

Comment on:

- Sample collection
- Sample preparation
- Cartridge registration
- Reading of results
- Cartridge disinfection
- Cartridge disposal
- Waste management – as for sputum containers
- Storage & supply – (cartridges fairly bulky, 2 - 28°C, 12month shelf life)
- Operating temperature – (currently approved 15-30°C; >40°C error message)
- Electrical supply – UPS (400 VA) or battery packs
- Training – minimal (computer use, prevention of contamination)
- Biosafety – as for smear microscopy
- Annual calibration – module replacement/swop out
- Security – against theft (computer)

Minimum operating capacity a day:

Maximum operating capacity a day:

Average operating capacity a day:

Annex -3- User Satisfaction

User satisfaction:- In depth interview (attitude and satisfaction)

Observational check list

Wast management

Peripheral use

SOP followed or not?

How to place it in peripheral level

Can other than technicians operate it

How to do transportation in peripheral level

Annex-4- Informed Consent Form

الموافقة المستنيرة للمرضى

١. عنوان الدراسة: دراسة لتقييم جهاز أكسبرت في التشخيص السريع لمرض التدن و مقاومة عصيات التدن الدوائية لعقار الريفادين في العراق (الأثر، التأثير من ناحية الكلفة و سمات التشغيل)
٢. الغرض من الدراسة:
- الدراسة هي مشروع تجريبي لمعرفة فعالية جهاز فحص للتشخيص السريع لكل من التدن و المقاومة الدوائية للتدن من أجل دراسة امكانية التوسع في تطبيق الجهاز بشكل أوسع.
٣. الإجراء
فحص القشع بواسطة الجهاز (أكسبرت).
٤. المخاطر/المتاعب
لا توجد مخاطر ناتجة عن مشاركتك في هذه الدراسة حتى وإن قررت عدم المشاركة.
٥. الفوائد
توجد منفعة شخصية للمشاركة من حيث امكانية الكشف المبكر للمرض من حيث اختصار وقت التشخيص من عدة أشهر الى أيام. ومن المتوقع وجود منافع مجتمعية عن الدراسة حيث ستعمل السلطات الصحية على الاستفادة من معلومات الدراسة لتحسين الخدمات الصحية المقدمة لمرضى السل والمجتمع.
٦. حقوق المشاركين
تعد مشاركتك طوعية ومن حقك الاستفسار عن اية معلومة غير مفهومة.
٧. السرية
لن يتم التصريح عن المعلومات التي تخصك لأي شخص وستدون المعلومات التي تخصك مدونة في السجلات المعتمدة من قبل برنامج مكافحة التدن التابع لوزارة الصحة العراقية و حسب السياقات المتبعة. ولن يتم ذكر اسمك بالنتائج الخاصة بالدراسة.

نموذج الموافقة

موافقة المشارك

أعلن أنه قد تم تزويدي بالمعلومات أعلاه وتم شرحها لي وكان لدي كامل الفرصة في طرح الأسئلة وحصلت على إجابات كافية حول كافة الأسئلة التي طرحتها. وأعلن عن مشاركتي الطوعية في هذه الدراسة وأنا على معرفة بحقي الكامل في الانسحاب من الدراسة دون أي شروط.

اسم المشارك:-----

توقيع المشارك:-----

في حال عدم قدرة المشارك على قراءة النموذج وحاجته لشخص لشرح/ترجمة النموذج.


اسم الشخص الذي قام بشرح/ترجمة النموذج:-----

عنوان الشخص الذي قام بشرح/ترجمة النموذج:-----

توقيع الشخص الذي قام بشرح/ترجمة النموذج:-----

توقيع القائم بالمقابلة:-----

نظام الموافقة على مشروع بحث

 <p>وزارة الصحة العراقية Iraqi Ministry of Health تأسست 1925</p>	<p>جمهورية العراق وزارة الصحة مركز تدريب وتطوير الملاكات شعبة البحوث والوسائل التعليمية</p>
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١ - استمارة الموافقة المبدئية لمشروع بحث

يمكن الحصول على النموذج من موقع وزارة الصحة الالكتروني www.moh.gov.iq

١. رقم المشروع (يملأ من قبل شعبة البحوث)

٢. أسم مشروع البحث (باللغة العربية / الانكليزية)

Xpert MTB/RIF assay for the rapid diagnosis of TB and RIF resistant TB in Iraq [impact, cost effectiveness and operational aspects]

٣. أسم الباحث الرئيس: Dr Ahmed Asmer Mankhi

الدرجة العلمية طبيب اختصاص / ماجستير أمراض

عنوان الباحث الرئيسي بغداد السيدية الهاتف ٠٧٩٠١٤٩٩٨٧٩
البريد الالكتروني ahmed.ntp@gmail.com

٤. أسم المشرف العلمي إن وجد :

٥. الباحثون المشاركون

Dr Layth Ghazi Al-Salihi

٦. أ- موقع مشروع البحث للباحث : الوزارة: الصحة

٧. الدائرة/ الكلية مركز الأمراض الصدرية و التنفسية التخصص التابع لدائرة الصحة العامة

ب - كتاب تأييد من دائرة الباحث العدد / / في

الدراسة هي مبادرة شخصية لغرض الفائدة العلمية

ج - المواد (العينات) المطلوبة من مؤسساتنا الصحية (احصائيات، عينات مختبريةالخ)

١ - قائمة أسماء المرضى المتسربين عن العلاج حيث سيتم مقابلتهم و ملئ معلومات تخصهم و الظروف التي أدت الى تركهم العلاج

د - الموافقة المبدئية للمؤسسة التي يجرى فيها البحث

البحث شخصي و لا يتبع مؤسسة معينة

٨. مجال مشروع البحث:

أ- علوم طبية إحيائية (Biomedical sciences) * فرع البحث الدقيق ()

ب- علوم سكانية (Population sciences) فرع البحث الدقيق ()

ج- علوم السياسات الصحية (Health policy sciences) السياسات الصحية، الأنظمة الصحية، التحليل الاقتصادي

فرع البحث الدقيق ()

د - أخرى تذكر (مسح لجمع معلومات حول سبب التسرب مع علاج التدن ()

٩. الجهة الممولة للمشروع WHO تفاصيل الدعم نوع الدعم مادي فقط

١٠. مدة المشروع سنة تقويمية من ٢٠١٣/١/١ إلى ٢٠١٤/١/١

١١. الجدول الزمني لإنجاز المشروع

Tasks	2012						2013						Jul
	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	
Proposal development													
Ethical clearance													
Release of funds													
Recruiting staff including non-NTP coordinators													
Defining the TOR													
Study preparation													
Training and pilot phase including international TA													
Field work													
Data entry, management and analysis ,													
Final report													

١٢. نوع المشروع: بحث أولي ()

(بحث ثانوي) *

(وأخرى تذكر)

هدف/ أهداف البحث

أهداف عامة:

تقييم الجهاز المختبري MTB/RIF Xpert من حيث الجدوى الاقتصادية و السمات التشغيلية في الفحص المبكر للعدوى و التدنر المقاوم

أهداف خاصة:

مقارنة نتائج استخدام الجهاز مع الطرق التقليدية في التشخيص.
تقييم الكلفة لكل حالة مشخصة بالتدنر و التدنر المقاوم مقارنة بطرق التشخيص التقليدية

تسليط الضوء على السمات و المعوقات التشغيلية للجهاز.

١٣. عناوين أهم البحوث العراقية والأجنبية التي تناولت مجال وأهداف البحث منذ خمس سنوات ولحد الآن:

14. WHO. Tuberculosis, a manual for medical students. Ait-Khaled N, Enarson D. WHO. 2005. P: 76. (access October 2012)
15. WHO. Iraqi National Tuberculosis Program Guideline. 2008. P:5.
16. [Bodmer T](#), [Ströhle A](#). Diagnosing pulmonary tuberculosis with the Xpert MTB/RIF test. [J Vis Exp](#). 2012 Apr 9;(62):e3547. (access October 2012)
17. [Boehme CC](#), [Nicol MP](#). Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. [Lancet](#). 2011 Apr 30;377(9776):1495-505. (access October 2012)
18. Ciftçi IH, Aslan MH, Aşık G. Evaluation of Xpert MTB/RIF results for the detection of Mycobacterium tuberculosis in clinical samples. Mikrobiyol Bul. 2011 Jan;45(1):43-7. (access October 2012)
19. Trébucq, A.; Enarson, D.A.; Chiang, C.Y.; Xpert® MTB/RIF for national tuberculosis programmes in low-income countries: when, where and how? INT J TUBERC LUNG DIS 15(12):1567–1571 (access October 2012)
20. Specialized Chest and Respiratory Disease Center-Personal communication

١- الأسباب المنطقية لإجراء البحث :

○ تعتبر هذه الدراسة الاولى من نوعها في العراق حيث سيتم ادخال الجهاز حديثا الى المختبرات التابعة لبرنامج التدرب من أجل التشخيص المبكر للتدرب و التدرب المقاوم للعقار و بالتالي فان تقييمه كجهاز فحص و كجدوى اقتصادية في غاية الأهمية قبل التوسع في استخدامه على مستوى العراق.

٢١. طرق البحث:

أ- دراسة طولية لجمع المعلومات حول مرضى التدرب و متابعتهم

ب- الدراسة مقطعية ستجرى مع دراسة الحساسية الدوائية لعصيات التدرب مطلع و خلال العام ٢٠١٣ حيث سيتم وضع الجهاز في المختبر المرجعي للتدرب و شمل عينة عشوائية من عينات المرضى ايجابيي القشع المشمولين بدراسة الحساسية الدوائية و كالتالي: نصف مرضى الفئة الثانية من العلاج، ١٠٠ مريض فئة أولى اضافة الى المشتبه اصابتهم بالتدرب من ملامسي مرضى التدرب المقاوم و من مرضى نقص المناعة المكتسب الفايروسي حيث مقدر المجموع الكلي للمرضى المشمولين بالدراسة ٥٠٠ مريض. سيتم تحويل سجل المختبر بشكل مناسب و ادخال المعلومات على فايلات أكسس أو أكسل خلال فترة جمع المعلومات ثم سيتم استخدام برنامج (SPSS v 20) لتحليل المعلومات.

ت- حجم العينة ٥٠٠ مريض

ث- الطرق الإحصائية لتحليل البيانات SPSS version 18

٢٢. موافقة اللجنة الأخلاقية المبدئية: نلهد أن مشروع البحث نال الموافقة المبدئية من اللجنة

عضو
الاسم
المهنة

عضو
الاسم د. أحلام خريز الج
المهنة طبيبة أسنان

عضو
الاسم د. فتيمة تاجم إبراهيم
المهنة طبيبة مساعده

رئيس اللجنة
الاسم د. رجب جويلى
المهنة صا وصادير عام

عضو
الاسم ضيف الله
المهنة حشرك في المزارع
١١/١١

دائرة الصحة العامة
١١/١١