Using new TB diagnostic tools: What is (and is not) ready for prime time???

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Outline

- TB Burden in Kuwait
- Diagnosing TB
  - Active TB:
    - Conventional Methods
    - Non-conventional methods
- Kuwait Experience

Alarming Figures

TB Kills

- **1.7 million people**

  Every year
- Nearly 5,000 people

  Every day
- One person

  Every 20 seconds

TB background in Kuwait

معدلات ايجابي البصاق لكل 100,000 من السكان 7 سنوات سابقة

	2008	2009	2010	2011	2012	2013	2014
كويتي	4.3	3.7	4.7	2.3	3.5	4.2	3.2
مقيم	11.7	14.7	13.6	7.9	11.4	12.9	12.1
إجمالي	10.1	11.2	10.7	6.1	8.8	11.9	9.3

معدل مرض الدرن كل الأنواع لكل 100,000 من السكان 7 سنوات سابقة

	2008	2009	2010	2011	2012	2013	2014
كويتي	13.2	13.3	12.5	10	10.7	9.8	8.5
مقيم	30.9	33.5	33.5	22.5	24	21.9	25.1
إجمالي	25.4	27	26.8	18.5	19.7	18.1	20

WHO Table regarding, Incidence, notification and Case Detection Rates 1990-2012

In Kuwait

Year	population	Incidence including HIV		Incidence HIV positive		Notified New and Relapse		Case Detection
		Number (thousands)	Rate	Number (thousands)	Rate	Number	Rate	Percent
1990	2	0.32 (0.28-0.36)	15 (14-18)	N/A	N/A	277	13	87 (77-99)
1995	2	0.39 (0.34-0.44)	24 (21-28)	N/A	N/A	336	21	87 (77-99)
2000	2	0.59 (0.52-0.67)	31 (27-35)	<0.01 (0.01-0.01)	0.2 (0.1-0.49)	513	27	87 (77-99)
2005	2	0.59 (0.52-0.67)	26(23-29)	<0.01 (0.01-0.01)	0.2 (0.1-0.41)	517	23	87 (77-99)
2010	3	1.1 (0.96-1.2)	37 (32-42)	<0.01 (0.01-0.01)	0.1 (<0.1-0.31)	957	32	87 (77-99)
2011	3	0.77 (0.68-0.87)	25 (22-28)	N/A	N/A	672	22	87 (77-99)
2012	3	0.85 (0.74-0.96)	26 (23-30)	<0.01 (0.01-0.01)	<0.1(0-<0.1)	737	23	87 (77-99)

Statistics of Isolates of M. Tuberculosis From 2008-2013

Year	Total No. of Sensi	Pulmonary		Extra-pulmonary	
		Smear +ve	Smear -ve	Smear +ve	Smear -ve
2008	1207 K:151	406 K:42	376 K:55	110 K:9	315 K:45
2009	902 K:115	317 K:35	212 K:30	91 K:8	282 K:42
2010	950	341 K:45	228 K:30	107 K:10	274 K:38
2011	802 K:107	283 K:26	195 K:28	47 K:6	277 K:47
2012	764 K:86	329 K:35	193 K:16	44 K:7	198 K:28
2013	691 K:90	273 K:29	167 K:20	38 K:3	213 K:38

Trends in Rates of Drug Resistance in all M. Tuberculosis Strains From Pulmonary and Extrapulmonary Specimens

	Year of Isolation									
	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Total no. of Isolates	574	547	754	763	1207	902	950	802	764	691
% Isolates resistant to										
Any drug	10.5	14.1	9.9	11.9	13	11.9	15.2	9.1	9.2	10.4
INH	8.2	11.7	6.7	8.4	10.2	8.9	11.2	6.1	7.2	7.4
RMP	1.4	1.1	1.5	2	2.7	1.1	1.4	1.2	2	0.9
EMB	1.6	1.8	0.9	1.8	2.1	1	1.9	1.5	0.5	0.7
SM	4.3	4.5	4.4	5.2	5	4.5	6.4	4.2	3	4.2
MDR	1.2	1.1	1.1	1.7	2.6	1.1	1.2	1.4	1.8	0.7
Pulmonary isolates no.	328	291	423	444	782	529	569	478	522	440
% Isolates resistant to										
Any drug	11.6	15.8	11.1	11.7	13.7	12.3	15	9.6	8.8	9
INH	9.1	14.4	8	8.8	10.2	9.1	10.5	6.5	6.7	6.8
RMP	1.5	2.1	2.1	2.7	1.6	1.3	2.1	1	1.5	0.7
EMB	1.5	2.4	1.4	2	2	1	1.6	1	0.6	0
SM	4	4.8	2.6	2.5	2.6	2.5	6.8	3.5	2.9	3.9
MDR	1.2	2.1	2.4	2.3	2.6	1.3	1.9	0.8	1.5	0.7
Extrapulmonary isolates no.	246	256	331	319	425	373	381	324	242	251
% Isolates resistant to										
Any drug	8.9	12.1	8.5	12.2	11.8	11.3	15.4	8.3	10	12.7
INH	6.9	8.6	5.4	8.8	10.6	8.2	12	5.5	7.8	8.4
RMP	1.2	0	0.6	0.9	3	0.7	0.5	1.5	2.9	1.2
EMB	1.6	1.2	0.3	1.6	3.8	0.9	2.4	2.1	0.4	1.6
SM	4.9	4.3	4	4.4	5.7	4.2	5.7	5.2	4.1	4.8
MDR	1.2	0	0.3	0.9	3	0.8	0.3	2.2	2.5	0.8

Diagnosis of Active TB

New TB Diagnostic tools: What is ready for prime time??

Traditional
Diagnostic Methods

No-traditional
Diagnostic Methods

Detection of Mycobacteria

Non-traditional Methods

Rapid detection

Why?

Effective therapy

Limit further development of resistance

Prevent spread of MDR-TB

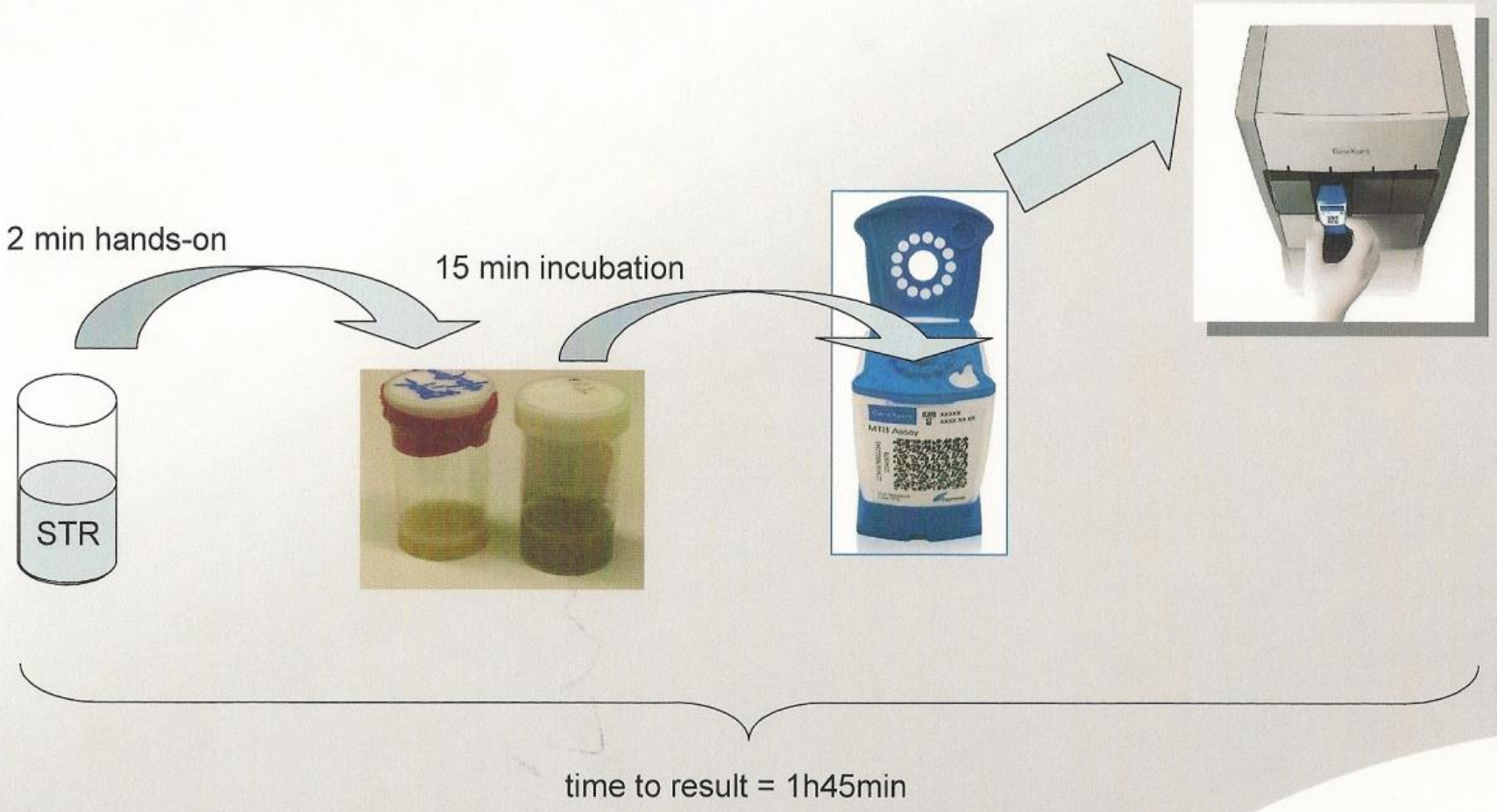
Techniques available

- **BD ProBETec standard displacement amplification method method. Only for pulmonary specimens**
- HAIN Lifescience, Germany
- Geneprobe, USA
- Amplicor, Roche,Switzerland
- **Xpert MTB: Cephide GeneXpert System**

Principle of Xpert MTB

- Detects *M.tuberculosis* and rifampicin resistance utilizing the *rpoB* gene
- Time to result:
  - **1h45min**

Xpert MTB Protocol



Introduction of Molecular methods for diagnosing TB in Kuwait

For the diagnosis of:
a. Pulmonary
&
b. Extrapulmonary TB

ProbTec PCR ET
(Becton & Dikinsen)
January, 2010

Gene Xpert MTB/RIF
(Cephide)
November, 2011

Experience with GeneXpert in Kuwait

in comparison with other molecular methodologies

A. Pulmonary TB

Period from November 2011 till May 2013

One and half year

A total of 1668 pulmonary specimens:
Sputum, BAL, ETTs, Gastric aspirates

DSM

TB culture using MGIT960 (Becton & Dikinsen)

ProbTec PCR ET (Becton & Dikinsen)

Gene Xpert MTB/RIF

	AFB Grown		AFB Not grown		Total
	AFB smear positive	**AFB Smear negative**	**AFB smear positive**	**AFB Smear negative**	
Both molecular lines are positive	82 **TP**	74 **(Early detection)**		**7** (4 of them TB suspect clinically & 3 unknown) **Improved sensitivity**	**163**
Both molecular lines are negative	11 (all NTM) 0 FN	16 (2 of them NTM) **14 FN**		1462 **TN**	**1489**
ProbTec PCR ET positive and Gene Xpert MTB/RIF negative		2 **(Early detection)**		**1** TB suspect clinically **Improved sensitivity**	**3**
ProbTec PCR ET negative and Gene Xpert MTB/RIF positive	1 **TP**	8 **(Early detection)**		**4**(2 of them TB suspect clinically & 2 of them unknown) **Improved sensitivity**	**13**
Total	**94**	**100**		**1474**	**1668**

A. Extra-Pulmonary TB

Period from November 2011 till August 2013

20 months

A total of 1660 extra-pulmonary specimens

890
Cavitary fluids

482
FNA + pus

85
CSF

67
Urine

102
Tissue

36
Others

A total of 1660 extra-pulmonary specimens

DSM

TB culture using MGIT960 (Becton & Dikinsen)

ProbTec PCR ET (Becton & Dikinsen)

Gene Xpert MTB/RIF

1660

34 were AFB-SM positive

157 were culture positive

197 yielded a positive culture and/or a clinical diagnosis of TB.

	AFB Grown		AFB No Growth		Total
	AFB smear +ve	AFB smear -ve	AFB smear +ve	AFB smear -ve	
Both molecular lines are positive	26 **TP**	102 **(Early detection)**	7	27 **Improved sensitivity**	**162**
Both molecular lines are negative	1 (NTM) 0 FN	13 one of them (NTM) **12 FN**	0	1463 **TN**	**1477**
ProbTec PCR ET positive and Gene Xpert MTB/RIF negative	0	0	0	0	**0**
ProbTec PCR ET negative and Gene Xpert MTB/RIF positive	0	15 **(Early detection)**	0	6 **Improved sensitivity**	**21**
Total	**27**	**130**	**7**	**1496**	**1660**

Conventional Culture

17%
Sensitivity

80%
specificity

Gene Xpert

93%
Sensitivity

100%
specificity

ProbTec-E

82%
Sensitivity

100%
specificity

The sensitivity of Xpert was higher for:

Biopsies, FNA and pus, urine and CSF than in cavitary fluids.

Xpert more sensitive than PTec-ET
detected EPTB in 15 more AFB-SM-negative, culture-positive and
6 more AFB-SM-negative, culture-negative specimens

Xpert detected EPTB in 40 FNA with clear histological evidence of infection of which only 7 samples were AFB-SM-positive but none of these 40 samples yielded a positive culture.

	AFB Grown		AFB No Growth		Total
	AFB smear +ve	AFB smear -ve	AFB smear +ve	AFB smear -ve	
Both molecular lines are positive	26 **TP**	102 **(Early detection)**	7 FNA	27 **Improved sensitivity** FNA	**162**
Both molecular lines are negative	1 (NTM) 0 FN	13 one of them (NTM) **12 FN**	0	1463 **TN**	**1477**
ProbTec PCR ET positive and Gene Xpert MTB/RIF negative	0	0	0	0	**0**
ProbTec PCR ET negative and Gene Xpert MTB/RIF positive	0	15 **(Early detection)**	0	6 **Improved sensitivity** **FNA**	**21**
Total	**27**	**130**	**7**	**1496**	**1660**

New TB Diagnostic tools: What is not ready for prime time??

Discordance between Xpert MTB[illegible] 960 cul[illegible] of rifan[illegible]*rium tuberculosis* isolates in a low TB incidence country

Accepted for presentation in JCM

Eiman Mokaddas, Suhail Ahmad, Hanaa S. Eldeen, Noura Al-Mutairi

452 Xpert MTB/RIF (Xpert) and MGIT 960 system (MGIT) positive samples, both pulmonary (287) and extrapulmonary (165)

440 and 10 *Mycobacterium tuberculosis* were detected as rifampin-susceptible and rifampin-resistant, respectively by both methods.

Discrepant Results

Two rifampin-susceptible isolates by MGIT were rifampin-resistant by Xpert. *rpoB* sequencing identified a silent (CTG521TTG) mutation in one and a missense (GAC516TAC) mutation in another isolate

This is excellent performance considering that the pooled sensitivity and specificity of Xpert assay for RMP resistance detection in pulmonary samples has been reported as 95% and 98%, respectively . The data also support the high (99%) negative predictive value of Xpert for RMP resistance detection as suggested by WHO data for settings of low prevalence for RMP resistance.

The Current WHO Recommendation

To use Xpert assay as the initial diagnostic test and start treatment as MDR-TB if RMP resistance result is expected

OR

If unexpected, to repeat Xpert testing on another sputum sample, particularly for settings where the prevalence of RMP-resistant TB is <15%.

Acknowledgement

Dr. Hana Saad ElDeen
Mrs Najah Ayed
All technical staff

Kuwait National TB Reference Laboratory

Conclusion

TB
Here Today
Gone Tomorrow

A basic Principle of Medical Practice

Diagnosis

before

Treatment

GeneXpert MTB/RIF

A Game Changer for TB Diagnosis

GeneXpert MTB/RIF

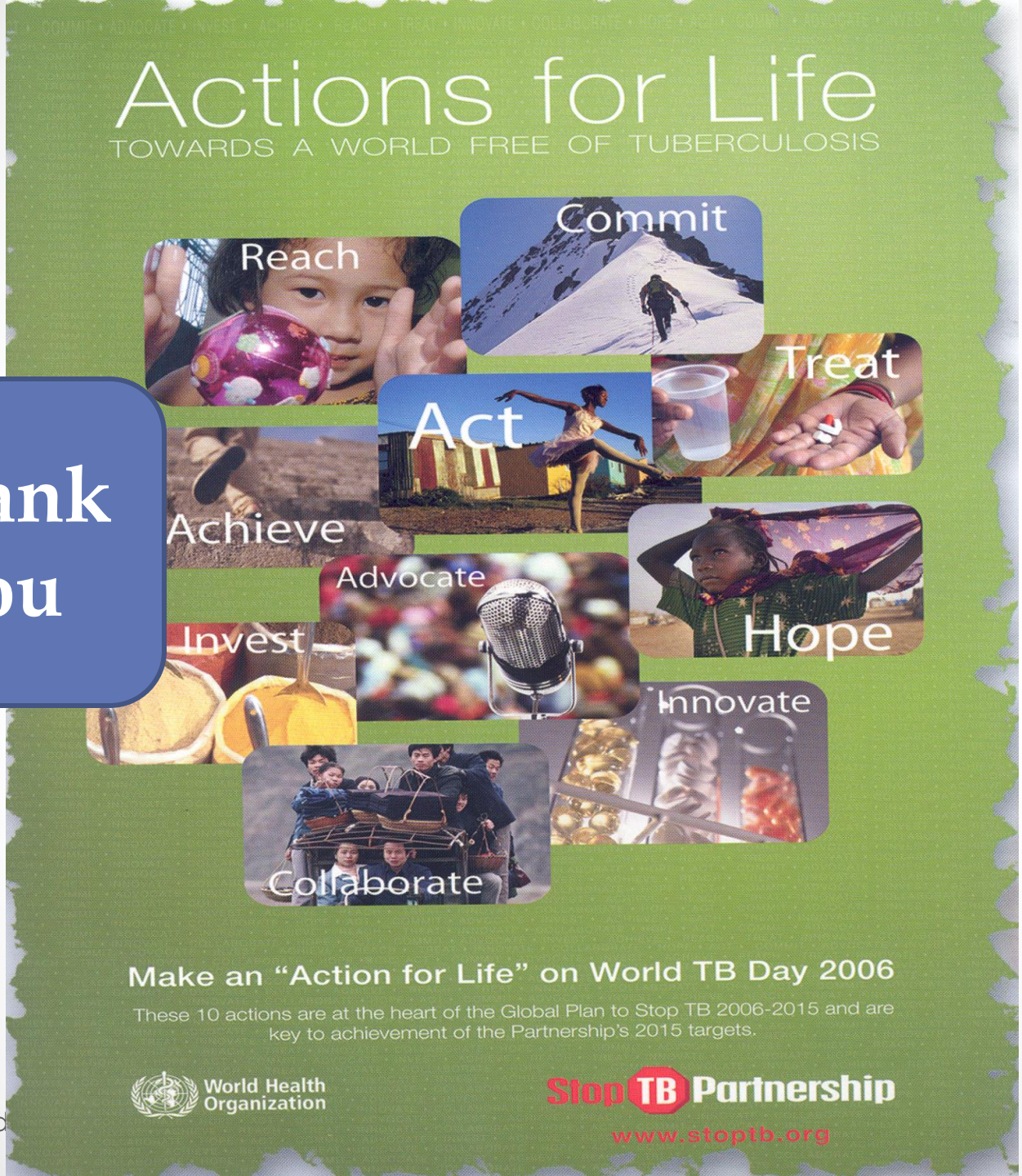
A Game Changer for TB control


Stop TB Partnership

The war against TB: A fight to the finish

Finish of the *M.tuberculosis*

Thank You


Actions for Life
TOWARDS A WORLD FREE OF TUBERCULOSIS
Commit
Reach
Treat
Act
Achieve
Advocate
Hope
Invest
Innovate
Collaborate
Make an "Action for Life" on World TB Day 2006
These 10 actions are at the heart of the Global Plan to Stop TB 2006-2015 and are key to achievement of the Partnership's 2015 targets.
World Health Organization
Stop TB Partnership
www.stoptb.org