Modern laboratory diagnosis of tuberculosis

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One-third of the global population is believed to be infected with bacteria of the *Mycobacterium tuberculosis* complex, the causative agent of tuberculosis. More than 8 million new cases of tuberculosis occur annually leading to 2 million deaths. Mortality is particularly high in those coinfected with HIV and where the bacteria are multiple-drug-resistant strains—ie, strains resistant to at least isoniazid and rifampicin. Early diagnosis of tuberculosis and drug resistance improves survival and by identifying infectious cases promotes contact tracing, implementation of institutional cross-infection procedures, and other public-health actions. This review addresses significant advances made in the diagnosis of infection, clinical disease, and drug resistance over the past decade. It proposes operational criteria for a modern diagnostic service in the UK (as a model of a low-incidence country) and explores some of the economic issues surrounding the use of these techniques.

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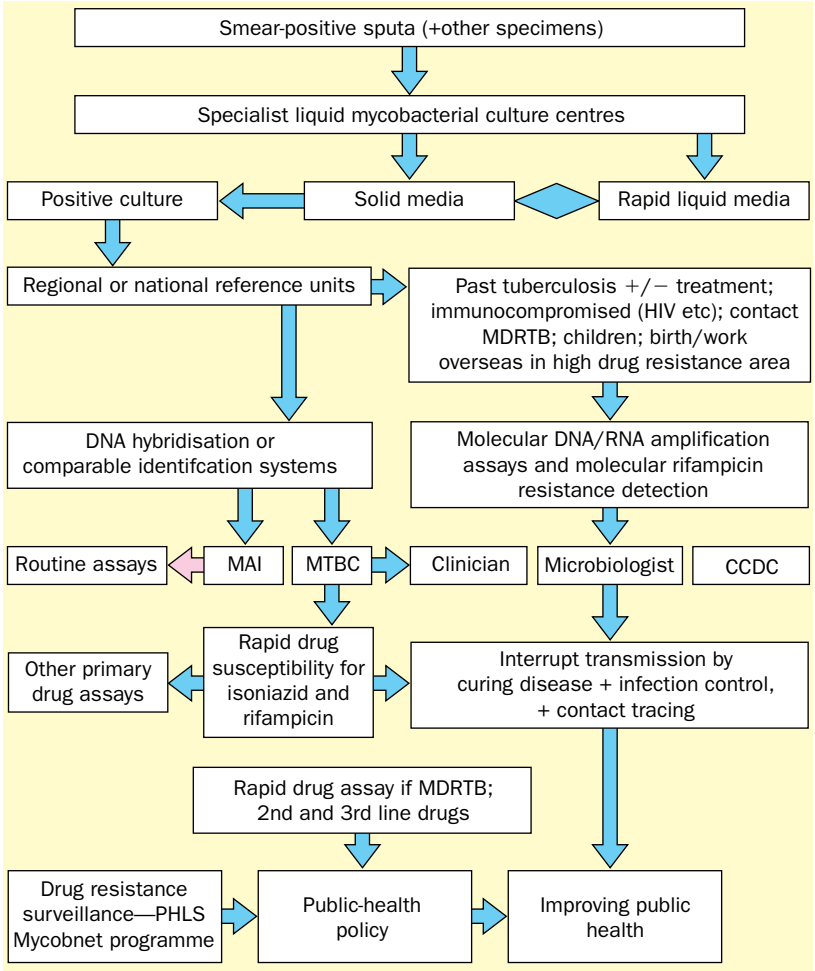

Model cost-effective national tuberculosis diagnostic and reference laboratory scheme. MAI=Mycobacterium avium-*intracellulare; MTBC*=Mycobacterium tuberculosis *complex; CCDC=consultant in communicable disease control; MDRTB=multidrug-resistant tuberculosis; PHLS=public health laboratory service.*

The 20th century saw many advances in the battle against tuberculosis but still this disease kills between 2 and 3 million people worldwide annually, and is resurgent in regions of the world where it was once thought to be conquered. It has been estimated that one-third of the world's population—almost 2 billion people—is infected with the causative bacterium, *Mycobacterium tuberculosis*. The emergence of drug resistance, especially multiple drug resistance, and increasing coinfection with HIV has fuelled the current pandemic.

The incidence of *M tuberculosis* began to decline rapidly from the start of the 20th century in developed countries with improvements in sanitation and housing. These trends were accelerated by the introduction of BCG vaccination and the discovery of antimicrobials such as streptomycin, which were used in effective combinations established in a series of landmark trials by the British Medical Research Council, the USA Public Health Service, and their partners.[1] The development of these standardised short-course drug regimens of 6–8 months supported by accurate quality-assured laboratory services is at the core of modern tuberculosis-control programmes.

Here we review recent advances in the diagnosis of tuberculosis, clinical infection, and drug resistance, and propose a scheme for a modern diagnostic service in a low-incidence country (figure).

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Table 1. Major studies of commercial systems for the rapid detection in culture of *M tuberculosis*

Study	Number of specimens (% +ve)	Respiratory	Non-respiratory	Systems	Recovery rates (M tb)	Recovery rate NTM	Recovery rate all mycobacteria	TTD M tb	TTD NTM	TTD all
Chew	603	..	..	MGIT	92	..	93	22	..	22
et al 1998[5]	(12·8%)			Bactec 460 TB	97	..	95	14	..	14
				LJ	95	..	87	27	..	27
				7H11	76·0			27·3		
				Bactec 460 TB	90	50	75	15·2	..	12·5
				Solid media	79	67	69	Not given	..	..
Pfyffer	3095	2643	452	Bactec 9000	83·5	58·7	75	12·2(+)18·1(-)	15·1	15·9
et al 1997[3]	(14·6%)			Bactec 460	91·9	76·1	86·5	9·3(+) (15·6(-)	17·3	15·4
				Solid	85·5	33·6	67·6	28·4(+) 28·5(-)	31·3	27·2
Piersimoni	1766	..	..	MB/BacT alert 3D	91·3	51·6	78·8	11·5(+) 19·9 (-)	19·6	..
et al 2001[9]	(10·1%)			BACTEC	97·8	67·7	87·1	8·3 (+) 16·8 (-)	16·6	..
				LJ	78·3	47·1	64·2	11·7 (+) 21·3 (-)	27·8	..
Rohner	1078	633	445	MB/BacT	93·6	16·6	86·3	..	..	17·5
et al 1997[10]	(6·7%)			BACTEC 12B	..	33·3	91·8	..	..	14·3
				Egg-based media Bactec 460 TB	84·1	50	79·5	..	..	..
Somoskovi	377	339	38	MGIT 960	96·4	100	96·5	12·6 (+) 15·8 (-)	..	13·2
et al 2000[11]	(15%)			BACTEC 460 TB	92·7	100	93·0	13·8 (+) 17·7 (-)	..	16·8
				LJ	81·8	50	80·7	20·1 (+) 42·2 (-)	..	36·2
Tortoli	2673	1682	991	ESP culture system II	85·3	70	79	19·0	..	9·33
et al 1998[12]	(8·2%)			BACTEC 460 TB	97·7	77	89	18·6	..	17·77
(multicentre)				LJ	82·9	37·8	64·4	28·6		27·78
Tortoli	2567	1770	797	MGIT 960	88	61·2	80	14·3	..	13·34
et al 1999[13]	(9·2%)			BACTEC 460	92	71·6	85	14·9	..	14·8
(multicentre)				LJ	74	64	71	25·0	..	25·67
Williams-Bouyer	3151	1774	1377	MGIT 960	84·6	66·4	63·9	12·8	..	13·1
et al 2000[14]	(7·3%)			ESP culture system II	73·8	68	71·2	18·7	..	16·9
				Middlebrook 7H11	87·7	55·2	61·8	19·2	..	19·2
Van Griethuysen	2005	..	..	Bactec 9000	96·7	79·5	91·6	7·5	12·6	8·7
et al 1996[15]	(10·1%)			Septi-chek AFB	81·5	76·9	80·2	14·2	12·1	13·6
				LJ	83·5	57·0	79·9	10·7	18·9	12·2

TTD=time to detection (days); Mtb=*M tuberculosis*; NTM=non-tuberculous mycobacteria; (+)=smear positive; (–)=smear negative

Microscopic examination

In 1882, Robert Koch demonstrated his microscopic staining technique for *M tuberculosis*. In spite of modern advances, microscopy remains a cornerstone of tuberculosis control because it identifies sputum-smear-positive (most infectious) cases and is rapid and cheap, although has a limited specificity. Fluorescent-staining methods offer higher specimen throughput and possibly greater sensitivity.

Modern rapid automated mycobacterial liquid culture systems

Traditionally, culture has been grown on solid and liquid media such as Löwenstein-Jensen (LJ), or Kirchner and the various Middlebrook formulations (7H9, 7H10, and 7H11). The time to detection of growth of a mycobacterial species can be shortened significantly with the use of an automated or semi-automated liquid culture system. Radiometric liquid culture using a broth with radiolabelled ^{14}C-palmitate as its sole carbon source has been available for many years.[2] The widespread adoption of semi-automated rapid liquid culture systems was frustrated by the demands on staff time and the difficulties associated with the disposal of radioisotopes.

New fully automated systems that rely on non-radiometric detection of growth have been developed such as the MB/BacT (Biomerieux), BACTEC 9000 (Becton Dickinson), and the Mycobacterial Growth Indicator Tube (MGIT; Becton Dickinson). Many studies have compared the different culture systems available.[3–8] These systems measure changes in gas pressure, carbon dioxide production, or oxygen consumption either fluorimetrically or colorimetrically. And need no further operator input (after loading) until the system signals positive. In general, studies have shown that mycobacteria from smear-positive sputa become detectable in roughly 14 days and most mycobacteria are isolated within 21 days.

Major recent studies are summarised in table 1. Hanna et al,[8] for example, did a multicentre evaluation of Bactec 460 tuberculosis, Bactec MGIT 960, and solid culture media for the isolation of mycobacteria. Their findings were that solid media (LJ slopes and Middlebrook 7H11 plates) gave recovery rates of 79% with mean time to detection of *M tuberculosis* of 24·1 days, whereas Bactec 460 tuberculosis had a mean time to detection of 15·2 days, and Bactec MGIT 960 14·4 days. The greatest isolation rates were obtained from a combination of solid media and Bactec 460, giving overall recovery rates of 97%. Solid media allows prolonged and inexpensive incubation of cultures. The importance of skilled and experienced staff cannot be overemphasised. Contamination rates have been high when inexperienced and untrained staff have used these systems.

Identification of cultures

The genus mycobacterium includes the *M tuberculosis* complex (*M tuberculosis*, *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium microti*, and *Mycobacterium*

Table 2. Major studies of commercial kits for the molecular detection of *M tuberculosis*

Study	No specimens	Source	Tests	Overall (%)				Smear +ve specimens (%)				Smear –ve specimens (%)			
				Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV
Tortoli et al 1997[26]	511	362R 147X	LcX	95·5	99·3	97·3	98·8	97·8	100	100	92·3	85·7	99·2	85·7	99·2
Tortoli et al 1999[27] multicentre	697	584R	Amplicor	75·5	99·8	..	..	94	100	..	..	36	99·8	..	..
		113X	LcX	85·7	99·5	..	..	93	100	..	..	70·2	99·4	..	..
Eing et al 1998[28]	1681	943R	Cobas Amplicor	66·3	99·7	94·4	97·7	87·5	..	..	99·4	56·5	99·7	90·7	97·9
		738X	In-house IS6110 PCR	91·1	99·8	97·9	99·4	96·9	..	..	99·4	88·4	99·8	96·8	99·5
Scarparo et al 2000[29]	486	296R	AMTD II (R)	85·7	100	100	90·4	91·7	100	100	95·5	65·5	100	100	94·4
		190X	(X)	82·9	100	100	95·5	88·0	100	100	98·0	75·0	100	100	96·1
			Cobas Amplicor (R)	94·2	100	100	96·0	98·9	100	100	99·4	75·0	100	100	96·6
			(X)	85·0	100	100	96·1	95·8	100	100	99·3	68·7	100	100	96·7
Della-Latta et al 1998[30]	1385	1385R	AMTD	97·1	99·5	..	..	100	100	..	..	92·9	99·5	..	..
	1380	1380R	Amplicor	96·7	100	..	..	97·4	100	..	..	95·9	100	..	..
Piersimoni et al 1998[31]	457	273R	AMTD II (R)	92·8	99·4	98·5	97	100	100	100	100	85·3	99·4	96·7	97·3
		184X	(X)	78·6	99·3	95·6	96·2	100	100	100	100	64·7	99·3	91·7	96·2
			LCx (R)	75·7	98·8	96·4	90·5	91·6	100	100	98·3	58·8	98·8	90·9	92·7
			(X)	53·6	99·3	93·7	92·1	81·8	100	100	98·8	35·3	99·3	85·7	93·2
Gamboa et al 1998[32]	755	755R	Cobas Amplicor MTD	92·4	100	100	96·5	100	..	..	..	59·6	..	..	..
			Manual Amplicor MTD	90·8	100	100	95·8	100	..	..	..	51·0	..	..	..

Figures shown are after resolution of discrepant data· Sens=test sensitivity; Spec=test specificity; R=respiratory specimens; X=extra-respiratory specimens; PPV=positive predictive value; NPV=negative predictive value.

canetti), which can all cause tuberculosis in human beings, and other environmental and opportunistic pathogens such as *Mycobacterium avium*, *Mycobacterium intracellulare*, and *Mycobacterium kansasi*. Non-tuberculous-mycobacteria (NTM) usually cause disease in certain groups, particularly the immunocompromised. Mycobacterial cultures are typically identified by microscopic appearance, growth characteristics, and biochemical tests. More rapid identification of *M tuberculosis* complex can avoid unnecessary isolation of patients with NTM and implementation of costly and toxic treatment regimes.

Probe detection methods, such as Accuprobe (Gen-Probe Inc) targeting ribosomal RNA, can identify *M tuberculosis* complex, *M avium*, *M intracellulare*, *M avium* complex, *M gordonae*, and *M kansasii*. These methods are rapid and simple to do, giving results in 1–2 hours with accuracy estimated to be above 90%, but cover a limited range of species[16] An alternative approach to distinguish the *M tuberculosis* complex and NTM cultures using peptide nucleic acids has been used with success.[17,18]

Other commercially available rapid identification tests use PCR followed by reverse hybridisation to identify the most clinically significant mycobacteria (eg, LiPA Mycobacteria kit, Innogenetics, Ghent, Belgium).[19] The system proved reliable in routine evaluations with 100% sensitivity from cultures and greater than 99% specificity,[16,19] but the cost of these kits in routine use is prohibitive.

PCR restriction enzyme analysis of the *hsp65* gene is a more complex technique, but it is more economical, flexible, and can identify mycobacteria from culture in 1–2 days.[20,21]

Sequencing of the 16S rRNA gene also allows the rapid identification of mycobacteria, but is relatively labour intensive and is best suited to the reference laboratory, which can identify and monitor rare and less clinically significant mycobacteria as well as typical pathogens.[22]

The use of rapid identification tests in combination with rapid culture has greatly reduced overall turn-around times for mycobacteriology laboratories and is now the system of choice where funding is possible. In England and Wales all new cultures submitted to the Public Health Laboratory Service (soon to become the Health Protection Agency) Mycobacterium Reference Unit and Regional Centres (PHLS MRU and RCMs) have been analysed for *M tuberculosis* using these systems since 1999.

Drug susceptibility testing

Drug susceptibility testing (DST) is only of value when it is quality controlled for accuracy. The UK (as well as European and World Health Organization) guidelines emphasise the importance of submitting mycobacterial cultures to the PHLS MRU and RCMs and Scottish Mycobacterium Reference Laboratory in Scotland.[23] In general, DST analysis should be done at specialist national and regional centres.

Rapid culture systems are also being applied to susceptibility testing and have shown potential reductions in turn-around times from 21 days for LJ-based testing to 9·5 days mean for MGIT-AST[24] and 4–12 days for Bactec 960TB.[25]

Molecular amplification for detection and drug susceptibility

Direct nucleic acid amplification methods have potential application in the rapid detection of mycobacteria in primary specimens, but problems of sensitivity remain. Major studies are summarised in table 2.[26–32]

There are two main commercially available nucleic acid amplification-based kits for the diagnosis of active tuberculosis that are currently approved by the US Food and Drug Administration—amplified *Mycobacterium tuberculosis* direct test (MTD test, Gen-Probe, approved 1995[33]) and Amplicor *M tuberculosis* test (Roche, approved 1996[34]).

Panel 1. Criteria for a modern mycobacterial service

1 Microscopy. Within the UK, all laboratories performing microscopy should screen samples, preferably using auramine-phenol within 1 working day.
2 Culture. Rapid automated non-radiometric continuous mycobacterial liquid culture systems should be used in addition to solid culture. Positive cultures should continue to be referred to regional or national reference units for identification and drug susceptibility testing (and to equivalent centres in other low incidence countries).
3 Identification. Positive cultures from these systems should be analysed using DNA hybridisation or comparable systems for the presence of *M tuberculosis*.
4 Drug susceptibility. Susceptibility to isoniazid and rifampicin as an absolute minimum should be established within 30 days; conventional analysis for remaining first-line drugs, should be done before the completion of the intensive phase of tuberculosis therapy (60 days), and within 30 days wherever possible.
5 The above will require a partnership between national disease control agencies and health services.
6 Molecular services such as those provided by the PHLS MRU, and other major centres for the diagnosis of tuberculosis in sputa, tuberculosis meningitis, and the detection of rifampicin resistance in primary and reference specimens should be provided only where there is an adequate infrastructure. All staff should be proficient in the methods used, appropriately qualified, use standardised methods with adequate and appropriate positive and negative controls. Smear-positive pulmonary specimens and precious specimens such as biopsies and cerebrospinal fluid should have priority.
7 A cost-effective approach to implementing the above would be a phased introduction of the new standards initially to cover all smear-positive samples, with the subsequent application of rapid culture, identification, and susceptibility testing for all mycobacterial specimens. As an absolute minimum, specimens from all infectious cases of tuberculosis, from putative cases of tuberculosis meningitis, and others taken through invasive means must be processed only by a laboratory meeting these standards.

Initially both tests were approved only for use on smear-positive clinical specimens but in 1999 a reformulated MTD test, MTD II, was approved for use in both smear-positive and smear-negative patients suspected of having pulmonary tuberculosis.[35] Both tests show comparable results, with the fully automated Cobas Amplicor system being more applicable to routine laboratories. MTD lacks an internal control and, although not affecting sensitivity of the initial test, such controls are useful indicators for repeat testing.

Ligase chain reaction (LCx, Abbott Laboratories)[36] is a more recent addition to the market and has been assessed with apparently high sensitivity (97–99%) and specificity (90–100%).[25,37]

Panel 2. Rapid diagnostic techniques would:

1 Allow the most infectious tuberculosis patients to be identified earlier, reducing transmission
2 Allow drug-resistant and particularly MDRTB patients to be identified earlier
3 Prevent the emergence of MDRTB by identifying single drug resistance earlier; drug-resistant cases are more difficult to treat and require more prolonged (and more costly) therapy
4 Allow the early appropriate isolation of MDRTB patients in negative pressure rooms, reducing the number of future cases.
5 Reduce the transmission of MDRTB, particularly in hospitals and residential care facilities and allow the early institution of correct therapy to MDRTB patients improving survival and reducing infectivity.

A fourth commercially available kit for the detection of *M tuberculosis* in clinical samples is the Rif LiPA tuberculosis, which has the additional benefit of identifying rifampicin resistance. This kit shows concordance rates with culture of 92–100% for the identification of rifampicin resistance from culture,[38,39] and showed 94·7% correlation with culture for identification from primary sputa and broncheolavage specimens and 100% correlation with subsequent susceptibility testing.[39]

Many laboratories have developed in-house PCR tests for detection from clinical samples. The majority of these are based on the *IS6110* insertion sequence, due to its presence in multiple copies in most isolates. Other target genes include *MBP64*, *rpob*, and *hsp65*.[40–42] Smaller scale in-house diagnostic assays using mRNA have also been developed.[43,44] The development of microarray technology permits speciation and identification of mutations in genes associated with drug resistance;[45,46] but the mechanism of resistance is understood only in the case of selected first-line or second-line drugs. The expense and limitations of these tests at present limit their routine application to cases of patients in which multidrug-resistant tuberculosis (MDRTB) or rifampicin monoresistance is suspected.

All assays must be rigorously assessed before incorporation into routine diagnostic use and a quality control scheme has to be implemented to ensure the continued accuracy and performance of the test. This scheme should include tests for non-specific inhibition, with positive and negative control samples present each time the test is done. This requirement was shown in a blind comparative study across seven laboratories by Noordhoek et al,[47] which showed false-positive rates of 3–20%, and 77% in extreme cases. In a later analysis involving 30 laboratories in 18 countries only five laboratories correctly identified the presence or absence of mycobacterial DNA in blinded panels of 20 sputum samples containing 0, 100, or 1000 mycobacterial cells.[48] Seven laboratories correctly detected mycobacterial DNA in all positive samples and 13 laboratories correctly reported the negative samples; reliability was not associated with any particular method. Results should always be interpreted in parallel with clinical findings and a negative result should not exclude the diagnosis of tuberculosis.

Phenotypic detection

PCR-based detection assays are not yet suitable for laboratories in very resource-poor settings. Alternative phenotypic assays based on mycobacteriophages have been developed and also applied to the determination of drug resistance.[49–54] The incorporation of the *lux* gene, which codes for luciferase, into the phage allows detection of mycobacteriophage through emission of light and thus

indirectly allows detection of viable *M tuberculosis*.[49] Although this technology is expensive, cheaper solutions using polaroid film chambers have been produced. An alternative for detection of replicating phage involves the manual plating of phage onto a lawn of the rapidly growing host *Mycobacterium smegmatis*. Plates can then be read visually by enumeration of clear areas or plaques on the lawn.[50–52] This technology can also be applied to susceptibility testing of *M tuberculosis*.[52–55]

Extrapulmonary tuberculosis

Extrapulmonary tuberculosis can present particular problems of diagnosis, especially neural tuberculosis where bacterial numbers in the cerebrospinal fluid (CSF) are very low and consequently smear has a sensitivity of only 10–20%. Alternative methods have been developed to combat this low sensitivity, the most widely applied being PCR, with several commercially available kits being assessed for use on CSF and other extrapulmonary specimens. As mentioned earlier, many laboratories have developed in-house PCR methods; sensitivities and specificities are high but the same precautions regarding contamination prevention and use of rigorous control procedures apply as to PCR on pulmonary samples. High performance liquid chromatography methods for the detection of tuberculostearic acid in CSF and other samples,[56–59] show high sensitivity and specificity but are costly and require skilled laboratory personnel and so are unlikely to be widely applied outside a reference setting.

Latent tuberculosis and skin testing

The ability of tuberculosis to infect a patient and remain latent for many years before reactivation is a key obstacle to the control and elimination of tuberculosis. Failure to identify and treat latently infected individuals allows the chain of transmission to continue. Testing for latent tuberculosis has typically been done by health-care workers in the form of tuberculin skin testing (TST). The widespread use of BCG vaccination in countries such as the UK, crossreacting environmental antigens, and the presence of anergy in rare cases confounds this test and a more accurate replacement is required.

The recent development of the ELISPOT assay which measures interferon γ production from whole blood or peripheral blood mononuclear cells (PBMC) stimulated with either purifies protein derivative (PPD) or more specific antigens has shown promise as a test for latency.[60–62] The Quantiferon tuberculosis test (Cellestis Ltd, WA, USA), which uses PPD to stimulate whole blood, recently gained FDA approval.[63] Studies using ESAT-6 or CFP-10, two antigens that are absent from the BCG vaccine, have also shown a great deal of promise in outbreak investigations. This test is still being assessed and is not yet commercially available.[60]

The MPB64 skin-patch test provides an approach to distinguish active tuberculosis from PPD-positive healthy controls. During initial evaluation in Japan[64] this test showed a sensitivity of 98%, with specificity of 99%. A later assessment in Manila, Philippines, saw a slightly lower sensitivity of 88% with specificity still high at 100%.[65]

Aim and strategy for a modern integrated service

Countries such as the UK, USA, and those in western Europe have a similar geographical tuberculosis distribution—a low overall tuberculosis incidence with "hot spots" of high incidence (eg, London, New York City, Paris).

The Centers for Disease Control and Prevention (CDC) in the USA formulated recommendations for the diagnosis and control of tuberculosis in 1993,[66,67] which have been revised for the UK. The CDC recommendations included laboratory standards for the detection by smear and culture, and for identification and antibiotic susceptibility for bacteria of the *M tuberculosis* complex. Microscopic smear examination using auramine-based staining should occur within 24 h of receipt of the specimen. Isolation and identification of *M tuberculosis* complex should occur within 14–21 days. The whole process, including first-line susceptibility results, should be completed within 30 days of specimen receipt.

We have proposed revised criteria in which the 30-day target is retained for primary culture, identification, and determination of resistance to isoniazid and rifampicin as a minimum, with drug susceptibility for remaining first-line drugs available before the completion of the intensive phase of tuberculosis therapy at 60 days,[68] and within 30 days wherever possible. Panel 1 summarises the principal recommendations for a modern mycobacterial service for a low incidence country like the UK. Panel 2 summarises the benefits of a rapid mycobacterial diagnostic service. The UK Department of Health is developing an action plan for the management of tuberculosis that emphasises the importance of early accurate diagnosis.

So why modify the original USA standard? At that time, our understanding of resistance at the molecular stage was just developing and only a handful of centres were able to identify mutations associated with resistance. The modified standard agrees that identification and drug-susceptibility testing for isoniazid and rifampicin resistance should be done within 30 days, as an absolute minimum, with remaining first-line drug susceptibility determined within 60 days. Technological and quality issues have meant that the performance of ethambutol and pyrazinamide resistance testing has lagged behind that of isoniazid and rifampicin resistance.

With an emphasis on the early identification of isoniazid and rifampicin, the two most important therapeutic agents, susceptibility testing for these two drugs can be separated from the rest, which are technically more difficult to do. The immediate goal should be the identification of *M tuberculosis* complex and rifampicin resistance, at least in sputum-smear-positive samples, within 1 week. This would allow early identification of patients with MDRTB, and also the identification of those patients who have risk factors for drug resistance but who do in fact have drug-sensitive disease. Increasingly, clinicians have decided that using molecular services to identify rifampicin resistance as a surrogate for MDRTB within 1 week is of value.[68]

Rapid drug-susceptibility testing within 30 days would be done for the key drugs, isoniazid and rifampicin, for those reasons given above. Drug susceptibility results for remaining

Search strategy and selection criteria
Data for this review were identified by searches of Medline for papers on "and diagnosis" and "tuberculosis and drug susceptibility testing" and references from relevant articles. Since the review was concerned with modern methods of diagnosis only papers published in the past 10 years were considered (from 1992). Papers were considered where they included specific data on the diagnosis of tuberculosis in specimens or cultures, with or without other data on mycobacteria. Only English language papers were reviewed.

first-line drugs should, as a minimum, be available before the completion of the intensive phase of tuberculosis therapy (60 days) and wherever possible within 30 days

Financial considerations

In any service the cost of the analysis needs to be offset against the individual clinical and population public-health benefits. The cost of universal application of molecular-amplification-based technology cannot currently be supported. Application should be targeted at high-risk groups such as the immunocompromised, those with risk factors for drug-resistant tuberculosis, and those groups in which failure to diagnose tuberculosis will lead to catastrophic consequences (for instance, tuberculosis meningitis). The cost-benefit calculation could of course be subject to change, for example if the incidence of MDRTB—currently around 1% of all UK cases—was to undergo a significant increase.

For automated rapid liquid culture systems, the containment and infrastructure costs of automated media systems need to be considered carefully. The early and efficient identification of patients with MDRTB (and the equally important proof of drug sensitivity) can ensure that MDRTB therapy and patient isolation is appropriately targeted. Considerable savings can result. For example, at one London centre rapid tuberculosis identification and determination of rifampicin susceptibility in patients inappropriately isolated would have produced potential savings of between £50 000 and £150 000 in 1 year.[68,69]

A 1997[70] report into the use of rapid diagnostic tests for tuberculosis in the USA concluded that a change to rapid methods would enable laboratories to diagnose patients 38% faster, doctors to initiate therapy 4·6 days sooner, and mortality would be reduced by 31%. The reduction in medical costs achieved would be 18% (US$272) per patient assessed. Further advances in rapid culture have since been introduced and savings are also likely to have increased.

The number and/or scope of contact-tracing investigations would also be reduced in scenarios where an infectious case has risk factors for MDRTB but is shown subsequently to be drug sensitive on rapid testing.

A cost-effective modification of the above standards is outlined in the figure, which focuses on the identification of infectious and drug-resistant cases reflecting the fact that more than 90% of tuberculosis cultures in the UK are drug sensitive. In this scheme all hospital laboratories would, as a minimum, send smear-positive pulmonary specimens from a patient (together with precious samples such as cerebrospinal fluid) for culture in appropriate centres. This process would ensure that the most infectious patients and those with drug-resistant isolates were identified at the earliest possible time wherever they appeared nationally. Such a process should be funded publicly throughout the UK.

Conclusion

There is a need to urgently address deficiencies in the diagnostic service for tuberculosis. There have been many advances in methodology for tuberculosis diagnosis and earlier diagnosis is of value clinically, and through the early institution of appropriate drug therapy is of public-health benefit. Nevertheless, many diagnostic tests have given promising results initially only to prove less effective in routine use. This is frequently due to bias resulting from non-independent interpretation of test results.

While, at present many of these techniques are only economically viable in the developed nations, it is to be hoped that recent advances will lead to the development of novel diagnostic strategies applicable to use in developing nations, where the burden of tuberculosis is greatest and effective intervention most urgently required.

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Conflicts of interest

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