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Diagnostics for tuberculosis
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FOREWORD

A public health perspective...

Every year there are 8.8 million new active TB cases and nearly 2 million TB deaths worldwide – 5,000 every day – mostly in the poorest communities of the developing world. One third of the world’s population has latent TB which may later develop into an active form of the disease. TB has also become the leading cause of death among people with HIV. Multidrug-resistance is also a growing problem. A key challenge for the public health community is to be able to effectively diagnose patients so that valuable resources and medicines are not wasted on misdiagnosis and repeat treatments.

Despite huge advances in technology, most countries around the world are still using the same microscopy examination of sputum that was used over 100 years ago. With only 40-60% test sensitivity under field conditions, this falls as low as 20% when patients are co-infected with HIV. Preventive therapy effectively reduces progression to active disease, but today there is no way to predict who is at greatest risk and who could gain the most from treatment.

The lack of accurate diagnosis leads to an unacceptable burden of human suffering and to a waste of precious resources in poor countries. Without the right diagnostic tools, we cannot stop the TB epidemic. Developing new diagnostics is one of the six elements of the Global Plan to Stop TB: 2006-2015. This is the first comprehensive report of its kind that identifies potential future markets for a range of diagnostics in three major testing areas developed and tested for use in resource poor settings.

World leaders, public health officials and international donors have taken action against TB and financial resources for control and research have increased dramatically in recent years. Public-private partnerships like the Foundation for Innovative New Diagnostics have emerged to bring together key players in these sectors to move research and development forward for the needs of patients. In countries, years of running DOTS control programs has built a strong basis to further develop TB detection and treatment. We have a unique opportunity to make progress in the fight against TB.

The World Health Organization encourages developers of diagnostic tests to read this report and see how they can expand their investments in this area. There is clearly a need, and governments are looking for quality-assured tests that will help them manage the TB epidemic.

We are encouraged by the potential opportunities this report has revealed, and look forward to new diagnostic tools that can result from enhanced industry engagement in this field.

Dr David L. Heymann
Acting Assistant Director-General
Communicable Diseases, and
Representative of the Director-General for Polio Eradication
World Health Organization
An industry perspective...

In industry, we are aware of the needs in developing countries and would like to do something to meet them, but we lack the basic information about which technologies would be the most useful and what the potential market for them might be.

This ground-breaking report, Diagnostics for tuberculosis: global demand and market potential, presents welcome new data on the very large global market for tuberculosis (TB) diagnostics and provides industry with a sound basis for decision-making in relation to developing better diagnostics that are suitable both for industrialized and developing countries at various levels of the health system. This report makes essential reading for all of us in industry and for public health stakeholders around the world.

In the search for new tools to fight the global burden of disease, the world’s attention has until now been focused on the need for new and better medicines. But without effective diagnostics, health workers are unable to identify the true cause of disease for most of their patients, and are therefore forced to try out various treatments in the hope of finding the right one. Such mistreatment not only inflicts a huge health and financial cost on the patient, but also results in an unnecessary waste of scarce public resources.

Simpler, more effective diagnostics that are designed for use in disease-endemic settings will be a key resource in the fight against the scourge of TB. For us in industry, this report sets out clearly the problems surrounding the existing tests and explains what kinds of improved diagnostic tools are needed and where they could have their greatest impact.

The report estimates that, every year, the world spends over US$ 1 billion on diagnostics for tuberculosis. One third of this money is spent outside the established market economies, where 73% of TB diagnostic testing takes place. In the developing world, where the vast majority of TB patients live, higher-performance but more complex and expensive tests, such as culture and nucleic acid testing, have not been widely implemented, and sputum microscopy and chest radiography remain the mainstay of diagnosis. Although relatively inexpensive on a per-test basis, these traditional methods result in considerable delay, repeat testing and misdiagnosis, with significant attendant costs. There is, therefore, an enormous demand for new and better diagnostics that are adapted to the needs of developing countries.

I hope that this report by the Special Programme for Research and Training in Tropical Diseases (TDR) and the Foundation for Innovative New Diagnostics (FIND) will receive the attention it deserves and that it will be a stepping stone to collaboration between the public and private sectors, with the aim of making real progress towards meeting global diagnostic needs.

Jean-François de Lavison
President, European Diagnostics Manufacturers Association

1 Executive Vice-President, International and Public Affairs, bioMérieux
The preparation of Diagnostics for tuberculosis: Global demand and market potential was generously financed by the Bill and Melinda Gates Foundation. The report would not have been possible without the cooperation of national tuberculosis programmes, in-country survey teams and tuberculosis diagnostic manufacturers around the world. Furthermore, the Special Programme for Research and Training in Tropical Diseases (TDR), sponsored by UNICEF/UNDP/World Bank and World Health Organization extends gratitude to the members of the WHO/TDR Tuberculosis Diagnostics Economic Working Group, their employers and other individuals who significantly contributed to the development of this report.

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**ABBREVIATIONS**

- AFB: Acid-fast bacilli
- AIDS: Acquired immunodeficiency syndrome
- AFRO: African Regional Office of the WHO
- BCG: Bacille Calmette-Guerin
- CDC: Centers for Disease Control and Prevention
- CIDA: Canadian International Development Agency
- CNPq: Conselho Nacional de Desenvolvimento Científico e Tecnológico
- COMET: Commercialising Emerging Technologies
- CPT: Clinical Procedure Terminology
- CRADA: Cooperative Research and Development Agreement
- CRAFT: Cooperative Research Action for Technology
- DNA: Deoxyribonucleic acid
- DEC: Disease-endemic country
- DFID: Department for International Development
- DOTS: Directly Observed Treatment Short-course
- DRG: Diagnosis-related group
- DST: Drug-susceptibility testing
- EDCTP: European and Developing Countries Clinical Trials Partnership
- EHTP: Essential Health Technology Package
- ELISA: Enzyme-linked immunosorbent assay
- EME: Established market economies
- EMRO: Eastern Mediterranean Regional Office of the WHO
- EU: European Union
- EURO: European Regional Office of the WHO
- FDA: U.S. Food and Drug Administration
- FIND: Foundation for Innovative New Diagnostics
- FOB: Free on board
- GATB: Global Alliance for TB Drug Development
- GDF: Global TB Drug Facility
- GFATM: Global Fund To Fight AIDS, Tuberculosis and Malaria
- GLRA: German Leprosy and Tuberculosis Relief Association
- GMP: Good Manufacturing Practice
- GTZ: German Agency for Technical Cooperation
- HIV: Human immunodeficiency virus
- HBC: High-burden country
- IC: Immunochromatographic
- ICD: International Classification of Diseases
- IEC: International Electrotechnical Commission
- IMF: International Monetary Fund
- INH+RIF: Isoniazid plus rifampicin
- IPRS: Intellectual Property Rights
- ISO: International Organization for Standardization
- IUATLD: International Union Against Tuberculosis and Lung Disease
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>IVD</td>
<td>In vitro diagnostics</td>
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<tr>
<td>JICA</td>
<td>Japan International Cooperation Agency</td>
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<td>KNCV</td>
<td>KNVC Tuberculosis Foundation</td>
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<td>LTBI</td>
<td>Latent tuberculosis infection</td>
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<td>MDG's</td>
<td>Millennium Development Goals</td>
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<tr>
<td>MDR-TB</td>
<td>Multidrug-resistant tuberculosis</td>
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<td>MGIT</td>
<td>Mycobacteria Growth Indicator Tube</td>
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<td>MIC</td>
<td>Minimum inhibitory concentration</td>
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<tr>
<td>MOH</td>
<td>Ministry of Health</td>
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<td>MSF</td>
<td>Médecins Sans Frontières</td>
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<tr>
<td>MTB</td>
<td>Mycobacterium tuberculosis</td>
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<td>NAT</td>
<td>Nucleic acid testing</td>
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<td>NAAT</td>
<td>Nucleic acid amplification test</td>
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<tr>
<td>NGO</td>
<td>Nongovernmental organization</td>
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<tr>
<td>NRC-IRAP</td>
<td>National Research Council-Industrial Research Assistance Program</td>
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<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
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<tr>
<td>PAM</td>
<td>Potential available market</td>
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<tr>
<td>PARTNERS</td>
<td>Partnership Against Resistant Tuberculosis</td>
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<tr>
<td>PATH</td>
<td>Program for Appropriate Technology in Health</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
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<tr>
<td>PhaB</td>
<td>Phage amplified biologically</td>
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<tr>
<td>POC</td>
<td>Point of care</td>
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<tr>
<td>PPD</td>
<td>Purified protein derivative</td>
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<td>ROW</td>
<td>Rest of world</td>
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<td>RT</td>
<td>Room temperature</td>
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<td>Rx</td>
<td>Treatment</td>
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<td>R&amp;D</td>
<td>Research and development</td>
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<td>SAM</td>
<td>Served available market</td>
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<td>SBIR</td>
<td>Small Business Innovation Research Program</td>
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<td>SDA</td>
<td>Strand displacement amplification</td>
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<td>SEARO</td>
<td>South East Asian Regional Office of the WHO</td>
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<td>SIDA</td>
<td>Swedish International Development Agency</td>
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<td>STTR</td>
<td>Small Business Technology Transfer Program</td>
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<tr>
<td>TAM</td>
<td>Total available market</td>
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<td>TB</td>
<td>Tuberculosis</td>
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<td>TBTC</td>
<td>Tuberculosis Trials Consortium</td>
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<td>TDR</td>
<td>UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases</td>
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<tr>
<td>TMA</td>
<td>Transcription-mediated amplification</td>
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<tr>
<td>TST</td>
<td>Tuberculin skin testing</td>
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<td>UNION</td>
<td>International Union Against Tuberculosis and Lung Disease</td>
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<td>USAID</td>
<td>US Agency for International Development</td>
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<td>WTO</td>
<td>Word Trade Organization</td>
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EXECUTIVE SUMMARY

Rapid and accurate diagnosis is critical to the care of tuberculosis (TB) patients and to the arrest of disease transmission. Despite a global strategy for diagnosing and treating TB implemented in over 182 countries worldwide, a minority of the nearly 9 million new TB sufferers each year receives a laboratory-confirmed diagnosis. Since the discovery of the TB bacillus in 1882, microscopic examination of stained sputum has remained the cornerstone of pulmonary TB diagnosis throughout most of the world. Diagnostic test manufacturers, in large part, have not invested in the development of new tests targeting the needs of developing countries, where 90% of all TB patients live. The target market is perceived to be too small, too fragmented, or too difficult to access to ensure a return on investment. For the investor, this perception of risk is compounded by anecdotes of complex regulatory policies and weak intellectual property rights protection in developing countries, ultimately resulting in a ‘no-go’ investment decision.

In Diagnostics for tuberculosis: global demand and market potential, the World Health Organization’s Special Programme for Tropical Diseases Research (WHO/TDR), in collaboration with the Foundation for Innovative New Diagnostics (FIND), has compiled existing epidemiological data and generated a wealth of new data on the availability of TB laboratory services, variations in physician diagnostic practices, workloads of national laboratory networks, and manufacturers’ sales to authoritatively document the volume and market value of TB diagnostic testing in nearly 200 countries. Customer requirements and research and development (R&D) opportunities are clarified in the document, and the major scientific, financial and market entry challenges specific to TB diagnostic development are presented alongside short-term and long-term strategies and solutions. Furthermore, the potential future TB diagnostic market is estimated for a range of hypothetical new diagnostic tests covering the three major testing indications. Fourteen countries are profiled in detail to complement the global perspective. This report, drafted with extensive input from experts in tuberculosis and public health as well as from private industry, provides essential data and knowledge to dispel common myths and inform investment decisions by industry, foundations, government organizations and world health and financial organizations.

The report comprises 7 chapters, 14 country profiles and an annex addressing global in vitro diagnostic regulatory practices and classification schemes. The key findings are summarized below. All monetary values are in United States dollars.

CHAPTER 1
Global agenda for tuberculosis control

The magnitude of the global TB problem is immense, with 8.8 million new cases annually and 2 million deaths. HIV is fuelling the epidemic in many countries and multidrug-resistance is a growing threat. Rapid and accurate diagnosis is at the core of the international strategy to control TB, but existing tests leave millions undiagnosed and untreated. World leaders, public health officials and international donors have taken action against TB, and financial resources for control and research have increased dramatically in recent years. Furthermore, several public–private partnerships to combat global health issues have emerged. Public sources of funding are available through national research institutes and through small business technology programmes around the world. There is an expanding international infrastructure and network capable of influencing national policy, clinical practice and the purchase and delivery of diagnostics, providing a gateway for manufacturers. Thus, it is an auspicious time for the development and implementation of new tools.

CHAPTER 2
Overview of current TB diagnostics

Depending on where you are in the world, the range of available TB diagnostic tools may vary, as may testing priorities. The highest priority for TB control in high-burden settings is detection of active TB cases excreting large numbers of infectious bacteria. In such settings, sputum smear microscopy is the predominant diagnostic test in use. High-tech molecular techniques and rapid culture systems, which can detect cases with many fewer organisms in clinical specimens, have penetrated markets in industrialized countries, where the TB burden is low, and where diagnostic priorities encompass all forms of active
disease (infectious and non-infectious), as well as latent infection. Such tests have not been implement-
ed in high-burden developing countries to any signif-
ificant degree, mainly because the level of sophistication and cost has, to date, made their rou-
tine application unfeasible. The advantages and limi-
tations of each of the currently available methods for diagnosing latent, active and multidrug-resistant tuberculosis are described in this chapter, as are the priority testing needs in different regions of the world. It is clear that no test is yet available that meets target specifications, and new methods that can overcome limitations and respond to the chal-
 lenges posed will be well received.

CHAPTER 3
Current TB diagnostics market

Commercial interest in TB diagnostics has been limit-
ed by a lack of detailed information on the size and character of the TB diagnostic market. An internation-
al network of contacts and investigators has, for the first time, yielded a strategic overview of the current global market for TB diagnostics, encompassing test-
ing for active disease caused by TB, as well as detecting latent infection, monitoring response to treatment, and drug-susceptibility testing (DST). This analysis indicates that annually over US$ 1 billion is spent worldwide on TB diagnostics, a figure over twice as large as the current market for TB drugs. One third (US$ 326 million) of this money is spent outside of the established market economies (EME), where 73% of TB diagnostic testing takes place. Lower labour costs primarily account for the lower cost per test performed in developing countries. Sputum smear microscopy and chest radiography for active disease are by far the most common tests performed in middle-income and low-income countries (83 mil-
ion, 47 million tests, respectively) and eclipse the use of higher performance but more complex and expen-
sive tests, such as culture and nucleic acid testing (NAT). Skin testing with purified protein derivative (PPD) is the highest volume TB diagnostic test used in the EME (40 million tests), where it makes up half the total market, reflecting the importance of detection of latent infection in those countries.

CHAPTER 4
Improving the technology

Capitalizing on market opportunities will require the development of tools that respond to the medical need at an affordable price. More than one type of new diagnostic test is needed to assist in TB care and control. The primary need is for simple confirmatory or screening tests for use in health clinics to distin-
guish active tuberculosis from all other conditions that may cause the same symptoms. Tests are also needed to monitor treatment response, to determine whether there is bacterial resistance to specific drugs and to detect latent infection in people at greatest risk for progression to active TB following exposure. New TB diagnostic tests may target different levels of the health system depending on their degree of sophistication. Two detailed customer requirement documents are included that describe the require-
ments for tests to detect active TB in peripheral clinics and for resolution testing in urban centres. By matching customer requirements to opportunities presented by emerging technologies, a set of 7 sam-
ple new products is generated that illustrates the range of tests which could be feasibly developed in the coming 3 to 10 years. The development and eval-
uation costs for several recently developed products, on different technology platforms, are included. Total R&D costs in the example products range from US$ 1 to 10 million. Opportunities for public sector partner-
ships to defray costs, accelerate development, ease evaluation and assist market entry for improved diag-
nostics are described.
CHAPTER 5
Potential market for new TB diagnostics

The persistent TB epidemic and expanding global population ensure that the total market for a range of TB diagnostic products is likely to grow over the coming decades. The portion of this market that will be accessible to new products depends on the interplay of performance and operational characteristics of the new product, end-user preferences, and the market conditions in specific geographical areas. In this chapter, the potential available markets (PAM) for seven hypothetical new TB diagnostic products (point-of-care screening, smear replacement, culture replacement, monitoring response to treatment, MDR-TB detection and latent infection replacement (with and without predictive capacity)) covering the three major TB testing indications are estimated for the year 2020.

Worldwide, we estimate that the largest potential available market for a new TB diagnostic would be for a test that both detects latent infection and predicts progression to active disease (767 million patient evaluations/year). Such a test, if widely implemented and accompanied by successful treatment, could revolutionize TB control. The infrastructure to achieve this globally is not available. Capturing 25% of the total available market (TAM) by 2020 would result in some 200 million patient evaluations/year. The next largest total available market is for a point-of-care screening test (193 million patient evaluations/year), of which 70% (137 million patient evaluations/year) is concentrated in the 22 high-burden countries. We estimate that 40% of this TAM (57 million patient evaluations/year) could be captured by 2020.

Substantial markets also exist for less revolutionary ‘replacement technologies’, for which there are already good candidates in the pipeline or for which testing platforms already exist. Specifically, the total available markets for smear, culture, monitoring and DST replacement tests are 83 million, 57 million, 40 million, and 6 million patient evaluations, respectively. Compared to the 25–40% TAM capture for the new testing approaches described above, we estimate that replacement technologies could capture greater proportions of the market by 2020: smear 59% (49 million), culture 35% (20 million), monitoring 58% (23 million) and DST 45% (3 million). Without exception, between 70–90% of the potential available markets for these replacement technologies are in the 22 high-burden countries. The continued emphasis on improving market conditions will encourage market growth in the high-burden countries and increase the accessibility to new products.

CHAPTER 6
The socioeconomic burden of TB

Investment in improved TB diagnostic tools could be life-transforming for both test developers and the ultimate end-users—TB sufferers. TB imposes a tremendous economic and social burden on societies, communities and individuals of all ages and in all social classes. Inadequate diagnostic tools perpetuate financial and opportunity losses through delays in diagnosis, and the need for repeat testing and misdiagnosis. Patients may spend between 30–40% of their annual income on TB diagnosis and treatment, and in many countries where TB is highly stigmatized, women with TB may be ineligible for marriage and/or may be forced to send their children to work. In 1999, India estimated the local economic impact of TB to be US$ 3 billion. In the 1980s, prompted by an outbreak of deadly multidrug-resistant TB particularly in HIV infected persons, New York City spent US$ 1 billion rebuilding a TB control programme. What is striking is that, world over, patients find ways to mobilize funds necessary to cover the expenses incurred by the TB diagnostic process. This fact should not diminish the importance of finding affordable tests; however, it builds confidence that new tools that are more accurate and/or require fewer clinic visits will be well received and will lead to cost savings and health benefits for TB sufferers.

CHAPTER 7
The business environment for TB diagnostics

Introducing a new product line or a new method of diagnosis to the marketplace is always a challenge. In the case of TB products, the greatest success will be won through gaining wide acceptance in both private-pay and public-tender sectors of a worldwide market. Obstacles to market entry can be reduced by (i) gaining a better understanding of how purchase
and pricing decisions are made, particularly in developing country settings, (ii) understanding current distribution mechanisms for TB commodities and trends for the future and (iii) using the extensive global Stop TB Partnership as a gateway to broad acceptance of new products.

**COUNTRY PROFILES**

National profiles are presented for 14 important or representative markets (Australia, Brazil, China, Canada, France, Germany, India, Indonesia, Japan, Russian Federation, South Africa, Uganda, United Kingdom, and the United States). They describe:
- the size and nature of the health care system and the degree of privatization;
- the local epidemiology of tuberculosis;
- the strength of the national TB control programme and the quality of the laboratory diagnostic infrastructure;
- the laboratory workload;
- the estimated in vitro diagnostics market;
- the national regulatory policies for in vitro diagnostics;
- the intellectual property rights issues (accordance with TRIPS) and
- the contact information for local industry associations.
Summary

In April 1993, the World Health Organization declared tuberculosis (TB) a global public health emergency, recognizing its enormous, rising and far-reaching burden of disease. It is a leading cause of adult deaths in the world, claiming over two million lives every year. Since that time, world leaders, public health officials and international donors have taken action against TB, and financial resources for TB control and research have increased dramatically. A global strategy for diagnosing and treating the disease has been implemented in over 182 countries worldwide. Nonetheless, millions of TB cases are either undetected or unnotified or both, and progress in controlling TB is critically constrained by the inadequacy of available diagnostic tools. The need for better diagnostics has been made even more urgent by the spread of HIV and by rising rates of resistance to anti-TB drugs. Until recently, efforts to develop diagnostic tools responsive to global needs have lacked coordination, and commercial investment has been limited. The development of public-private collaborative mechanisms that lower barriers to commercial TB diagnostic development, the existence of a strong international Stop TB partnership, and the increased purchasing power afforded to governments in high-burden countries with the advent of the Global Fund to Fight Aids, Tuberculosis and Malaria (GFATM), provide an unequalled opportunity for the successful development and deployment of new TB diagnostics.

This chapter offers an overview of the global TB problem and the strategy to control it, describing the leading actors in the fight against TB, the major constraints on TB control, and the funding opportunities for new test development and implementation.

The magnitude of the problem

Active tuberculosis

Active tuberculosis disease is divided into pulmonary (80-90% of cases) and extrapulmonary (10-20% of cases) forms of TB, and is further subdivided according to the presence (smear positive) or absence (smear negative) of stained Mycobacterium tuberculosis organisms in microscopically examined clinical specimens, i.e. sputum (Figure 1). A positive sputum smear is an indicator of infectiousness; thus, identifying these patients and promptly administering treatment is the primary focus of the internationally recommended TB control strategy known as DOTS (Directly Observed Treatment Short-course). Microbiological detection of TB, e.g. smear microscopy, is a critical element of the DOTS strategy.

DOTS control strategy (1, 2)

- Government commitment to sustained TB control
- Detecting cases early, using sputum smear microscopy among symptomatic patients reporting to the health services
- Providing effective treatment, i.e. standardized short-course chemotherapy under proper case management conditions, including direct observation of treatment
- A proper drug supply system
- A standardized recording and reporting system
- The number of countries adopting the DOTS strategy increased from 20 in 1993 to 182 in 2003. DOTS programmes now cover 77% of the world’s population
WHO’s Global TB Monitoring and Surveillance Project experts estimate the total number of cases to be 8.8 million (3.9 million sputum smear-positives) (2).

In 2003, 4.1 million cases (1.9 million sputum smear-positive) were notified to public health officials around the globe. Seven million of the estimated 8.8 million cases are concentrated in 22 high-burden countries of the developing world (Figure 2). If recent trends should continue for the rest of this decade, the projected global number of new cases will increase to 10 million cases in 2015 (3).
Despite the geographic expansion of DOTS programmes, the existing gap between the notified number and the estimated number of new TB cases – a staggering 4.4 million cases – has not narrowed significantly over the past several years. Though some of the gap may be artifactual owing to incomplete notification of public health authorities by private physicians and independent government bodies (military, prisons), inadequate case detection is a major constraint on TB control (Figures 2 and 3). Figure 4 illustrates the gap between estimated cases and notified cases.

**Drug-resistant TB**

Drug-resistant TB further complicates the task of staff working within national TB programmes, who are already struggling under the weight of heavy caseloads. Surveillance studies in over 70 countries have revealed that the annual number of new cases of multidrug-resistant TB (MDR-TB) is approaching 300,000 and that over 50 million people are latently infected with MDR strains of TB (4).

**Latent tuberculosis**

In addition to the millions living with active tuberculosis disease, population-based surveys inform us that one third of the world’s population, that is, two billion people, is infected with M. tuberculosis (5). One person is infected every second. Although no symptoms are associated with latent TB infection (LTBI), it is a necessary precursor to clinical disease. Progression to active disease is enhanced by a weakened immune
state. This has been a critical factor, particularly in Africa and in some regions in Asia, where the collision between the HIV epidemic and the high prevalence of latent TB infection (50-90%) has sparked a dramatic rise (3-10 fold in some countries) in active TB cases (6,7). Persons coinfected with HIV and TB are the most susceptible to active TB disease, followed by children less than five years of age; identifying and treating latent infection can reduce the number of active TB cases and save lives.

It is currently estimated that about 12 million adults are living with HIV-TB coinfection; less is known about the number of children at risk (6). In developed countries, the prevalence of latent infection in the general population is much lower, but can be high in certain populations such as immigrants, prisoners and contacts of new cases (8). Groups with low prevalence of TB infection but at high risk of progression if infected, such as immunocompromised individuals, intravenous drug users, and health workers, are also important foci of investigation.

Constraints on TB control
The progress of current strategies to prevent, diagnose and treat TB is hindered by the following serious technical, operational and social constraints:

i) inadequate diagnostic tools

The majority of patients are detected with advanced (smear-positive) disease, after having already transmitted the disease to their close contacts. Smear microscopy is less sensitive in HIV co-infected patients and culture is slow and too difficult to implement in many settings.

ii) long, arduous treatment regimens

Six to nine months of therapy are required using a combination of several drugs to cure TB. In the case of drug-resistant disease, treatment is even longer. With many pills, side-effects, and months of therapy, compliance guaranteeing treatment and ensuring cure is a major challenge throughout the course of treatment.

iii) ineffective vaccine

BCG, the only vaccine against TB and the most widely used vaccine worldwide, offers some protection against serious forms of TB (central nervous system, miliary) most often contracted by very young children, but is not very effective against adult pulmonary TB, the most contagious form of the disease (9).
iv) Multidrug-resistant TB

Incorrect or irregular dosing of medications on the part of the physician or patient is the cause of resistance to one or more drugs, leading to multidrug-resistant TB (MDR-TB), which is difficult to treat and more difficult to cure. Treatment of MDR-TB is much more expensive than conventional therapy and often causes significant side-effects.

v) HIV pandemic

HIV infection increases susceptibility to TB infection and disease and has caused dramatic increases in TB rates in sub-Saharan Africa, even when TB control programmes are well established (10,11). Figure 6 shows HIV as the driving force behind the rising TB incidence rates in sub-Saharan Africa.

vi) Poverty

The reach of TB extends to all continents, races, ages and economic classes. However, in settings of poverty and poorly funded general health services, TB control efforts are mostly undermined. All factors associated with poverty, including malnutrition, crowding, poor air circulation and poor sanitation, increase the probability of a person becoming infected with TB. TB is not only the result but the cause of poverty through loss of work, absence from school and payments for medical expenses.
Global agenda

Despite decades of TB control efforts, there are more cases today than ever in history. The rising global incidence rates of TB, fuelled by HIV, and the colossal gap between the notified and the estimated number of new TB cases have recently prompted global action. Tuberculosis control has begun to feature prominently on the major development agendas of the World Bank, the United Nations, the United States Government, other bilateral donors, and foundations. Numerous global partnerships and special initiatives have emerged to stimulate TB control efforts and to bring countries closer to realizing the targets of the Global Plan to Stop TB (see sidebar). Ministries of health and world leaders have also increased their commitment to fight TB, thereby securing a position for this disease on the public policy agenda (see Government pledges, page 26).

Stop TB targets

> **By 2005**: 70% of people with infectious TB will be diagnosed and 85% will be cured (World Health Assembly, 1991).

> **By 2015**: the global burden of TB disease (deaths and prevalence) will be reduced by 50% (compared with 2000 levels) (Millennium Development Goals, 2000).

> **By 2050**: the global incidence of TB disease will be less than one per million population (G8 Summit, 2000).

Flagship initiatives and partnerships that promote TB control

Global Partnership to Stop TB

This is a global movement to accelerate social and political action to stop the unnecessary spread of tuberculosis around the world. The Partnership consists of over 275 organizations and individuals committed to the short-term and long-term measures required to control and eventually eliminate TB as a public health problem worldwide.

- Founding members of Stop TB Initiative (1998):
  - American Lung Association
  - American Thoracic Society
  - Centers for Disease Control and Prevention
  - International Union Against TB and Lung Disease
  - Royal Netherlands TB Association (KNCV)
  - World Health Organization

  Now, end 2003, more than 275 partners and growing

The Partnership comprises:
- Seven Working Groups
- New Drugs, Diagnostics
- Vaccine Development, DOTS Expansion, DOTS-Plus, TB/HIV, Advocacy Communication and Social Mobilization

Global TB Drug Facility (GDF)
- The Global TB Drug Facility is a mechanism for expanding the availability of and access to existing high-quality TB drugs to facilitate global DOTS expansion.
  - The Facility provides streamlined procurement and financing services, allowing governments and non-governmental organizations to improve the coverage and quality of global TB control through the acquisition of high-quality anti-TB drugs.
  - It aims, by 2007, to provide drugs for ten million TB patients and is planning to expand to diagnostics. [http://www.stoptb.org/gdf/](http://www.stoptb.org/gdf/)

A description of the role, functions and responsibilities of the Global Partnership can be found at: [http://www.stoptb.org/stop.tb.initiative/default.asp](http://www.stoptb.org/stop.tb.initiative/default.asp)

**World Bank**

The World Bank is committed to responding to the global TB epidemic through policy dialogue and advice, country-specific lending for health-system strengthening and disease control, analytical work, and involvement in global partnerships. Tuberculosis control is among five public health priorities promoted by the Health, Nutrition and Population sector in the Bank. [www.worldbank.org](http://www.worldbank.org)

**International Union Against Tuberculosis and Lung Disease (UNION)**

The UNION is a non-profit, nongovernmental, voluntary organization, founded in 1920. It is dedicated to the...
prevention and control of TB and lung disease, the
gathering and dissemination of information about the
hazards of smoking, and the promotion of overall
community health. Its main activities are:

• technical and material support for efforts to control
tuberculosis and other lung disease in developing
countries;
• research, both operational and applied, through
cooperative, international studies and trials, with
the technical assistance of national programmes;
• education, by collecting and disseminating information
on all aspects of tuberculosis and lung diseases, and
alerting health workers, policy-makers and the general
public to their dangers; the organization works with
government and nongovernmental institutions in
health and development sectors. www.iuatld.org

Foundation for Innovative New Diagnostics (FIND)
Built on the work of the Tuberculosis Diagnostics
Initiative, which is part of TDR\(^1\), FIND is an independent,
not-for-profit organization whose mission is to accelerate
the development, evaluation and appropriate use of high-
quality yet affordable diagnostic tools for infectious dis-
eases in developing countries. It has an initial focus on
tuberculosis. Through its work with partners, the organi-
zation's mandate is to ensure that the ultimate public
health goal – improving case detection and reducing the
TB burden – can be reached. FIND launched with a
five-year US$ 30 million grant from the Bill and Melinda
Gates Foundation. www.finddiagnostics.org

Global Alliance for TB Drug Development (GATB)
This not-for-profit, public-private partnership aims to
halt the rise and reverse the spread of TB by developing
new, faster-acting and affordable medicines for tubercu-
osis. GATB will receive a grant of US$ 25 million, over
a five-year period, from the Bill and Melinda Gates
Foundation. www.tballiance.org

Partnership Against Resistant Tuberculosis (PARTNERS)
This is a network that aims to increase equity and
strengthens resources for TB control. It has an initial focus on
controlling MDR-TB in Peru by building a reproducible
model that can later be applied in other countries.
PARTNERS has received a US$ 44.7 million grant from the
Bill and Melinda Gates Foundation. Aeras Global TB Vaccine Foundation
(formerly known as the Sequella Global Tuberculosis
Foundation)
A non-profit organization working through public-private
partnerships to develop new tuberculosis vaccines.
The goal of Aeras is to develop, test, qualify, license,
manufacture and distribute a new TB vaccine within
10 years. Aeras received a grant of $82.9 million from
the Bill and Melinda Gates Foundation. www.aeras.org

Centers for Disease Control and Prevention,
USA (CDC) - TB Trials Consortium (TBTC)
Originally created to carry out a trial of once-weekly
isoniazid and rifapentine in the continuation phase of
therapy for pulmonary TB, TBTC is now an extensive
network of clinical investigators whose mission is to
conduct programmatically relevant research concerning
the diagnosis, clinical management and prevention of
TB infection and disease. Annually, CDC spends US$ 10
million in supporting a well-equipped and experi-
enced network of 28 clinical trial sites in the United
States, Canada, Brazil, Uganda, Spain and South Africa.
www.cdc.gov/nchstp/tb/tbtc

European and Developing Countries Clinical
Trials Partnership (EDCTP)
EDCTP's goal is to accelerate the development of new
clinical interventions to combat HIV/AIDS, tuberculosis
and malaria in developing countries, in particular by:
• increasing cooperation and networking among
European national programmes accelerating clinical
trials of new and improved products, particularly
drugs and vaccines, in developing countries;
• ensuring that research effectively addresses the needs
and priorities of developing countries;
• strengthening capacities in developing countries,
including the promotion of technology transfer;
• encouraging the participation of the private sector;
• mobilizing additional funds to fight these diseases.
The European Commission will provide the initial
investment by means of a US$ 200 million allocation
over five years through the Sixth Framework Programme
(2002 to 2006). European countries will contribute in
kind through their national research activities. Additional
funds may come from development programmes and
donations. However, it is foreseen that actual clinical
trials will be funded partly by industry in public-private
partnerships intended to share costs and risks.
http://europa.eu.int/comm/research/info/
conferences/edctp/edctpqa_en.html

\(^1\)UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.
Role of new diagnostics in improving TB control

The prompt and accurate diagnosis of TB among individuals reporting to health facilities is not straightforward, particularly in resource-limited environments where smear microscopy is the rule. In practice, the performance of the diagnostic technique of sputum smear microscopy is variable and, almost exclusively, bacteria are identified in sputum samples from subjects with advanced pulmonary disease. This technique requires approximately 10,000 mycobacteria per millilitre of sputum for a positive diagnosis (12). To improve sensitivity, smear microscopy is typically performed on two or three serial sputum samples, thus requiring multiple patient visits over a two-day period. Furthermore, in several important settings, including early disease, HIV coinfection, disease in organs outside the lungs, and in children, the sensitivity of smear microscopy can be between 0–20% (see Chapter 2). Ultimately, less than 20% of all TB cases are bacteriologically confirmed, and a portion of the gap between notified and estimated cases is unquestionably due to the poor performance of diagnostic tools. Industrialized countries, with lower burdens of disease, have access to advanced techniques such as culture systems and nucleic acid amplification, but these are expensive and require the skills of motivated, trained technicians and the maintenance of sophisticated equipment. The emergence of multidrug-resistant TB, outbreaks of which have occurred in the United States, and the push to
eliminate TB in high-income countries through detection and treatment of latent infection, are driving forces behind the international call for new diagnostic alternatives (13).

For any new tool to gain broad acceptance and endorsement in countries where the burden is high, it must be suitably adapted for use in resource-poor environments, and must produce reliable results. This requirement poses a considerable challenge, but a challenge that is well worth confronting.

**Opportunities**

The financial and scientific opportunities for developing new diagnostics have never been greater (Figure 7). The heightened importance of TB in governments’ public health policies and on the agendas of philanthropic foundations, combined with the emergence of several public-private partnerships to combat global health issues and the association of TB with HIV, highlighted at the XV International AIDS Conference in Bangkok in 2004, has created a significant opportunity for TB diagnostics research and development (see pages 28, 29). Public sources of funding are available through national research institutes and small business technology programmes in many areas, including the United States, Europe, Australia, Canada and Brazil. Downstream, end-users are benefiting from a boost in purchasing power through the Global Fund to Fight AIDS, Tuberculosis and Malaria. Furthermore, the work invested in expanding DOTS has resulted in an international infrastructure and network capable of influencing national policy, clinical practice, and the purchase and delivery of diagnostics and drugs. This provides a gateway for manufacturers of high-quality products into the complex health systems and markets of many developing countries. Thus, one of the chronic obstacles to deployment of effective diagnostic tools, the source of funds to purchase equipment, hire personnel and source reagents can be addressed and solved.

![Figure 7: OVERALL FINANCIAL COMMITMENTS TO TB CONTROL 1999 TO 2004 (US$ MILLIONS)](image)
Funding for tuberculosis research and control has increased dramatically in the past decade and a variety of new resources are available to support basic research, tool development, and implementation activities, including diagnostic testing. A sampling of such opportunities is provided below. This list is in no way intended to be complete, but gives an idea of the diversity of resources available. The division into three segments is somewhat arbitrary, as many of the agencies listed may fund across categories.

**Discovery science and knowledge generation**

Basic research is supported by many national research agencies, some of which have historically supported TB-related research leading to diagnostic target discovery or reagent development. Private foundations have played an increasingly large role, with the four mentioned below funding a total of nearly US$ 2 billion in health research in 2003.

**National and international research funding agencies**

- **Australia**
  National Health and Medical Research Council (NHMRC)

- **Brazil**
  Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)
  [www.cnpq.br](http://www.cnpq.br)

- **European Union**
  [www.cordis.lu](http://www.cordis.lu)

- **France**
  Pasteur Institute
  [www.pasteur.fr](http://www.pasteur.fr)

- **India**
  Indian Council of Medical Research (ICMR)
  [icmr.nic.in](http://icmr.nic.in)

- **UNICEF/UNDP/World Bank/WHO**
  Special Programme for Research and Training in Tropical Diseases (TDR)
  [www.who.int/tdr](http://www.who.int/tdr)

- **USA**
  National Institutes of Health (NIH)

**Private foundations**

- **Bill and Melinda Gates Foundation (BMGF)**
  [www.gatesfoundation.org](http://www.gatesfoundation.org)

- **Howard Hughes Medical Institute (HHMI)**
  [www.hhmi.org](http://www.hhmi.org)

- **Rockefeller Foundation**
  [www.rockfound.org](http://www.rockfound.org)

- **Wellcome Trust**
  [www.wellcome.ac.uk](http://www.wellcome.ac.uk)

**Biotechnology development**

Many countries have government programmes intended to nurture the growth of local biotechnology industry. These programmes may specify support for small businesses, start-up companies, or technology incubators. A sample of such programmes is listed below:

- **Australia**
  Commercialising Emerging Technologies (COMET)

- **Canada**
  National Research Council – Industrial Research Assistance Program (NRC-IRAP)
  [www.irap-pari.nrc-cnrc.gc.ca/main_e.html](http://www.irap-pari.nrc-cnrc.gc.ca/main_e.html)

- **European Union States**
  Cooperative Research Action for Technology (CRAFT)
  [www.sme.cordis.lu/craft/home.cfm](http://www.sme.cordis.lu/craft/home.cfm)

- **Foundation for Innovative New Diagnostics (FIND)**
  [www.finddiagnostics.org](http://www.finddiagnostics.org)

- **Israel**
  R&D support and incentive programmes
  [www.moit.gov.il](http://www.moit.gov.il)

- **Turkey**
  Small And Medium Sized Industry Development Organization

- **US NIH Cooperative Research and Development Agreement (CRADA)**

- **US Small Business Innovation Research Program (SBIR)**
  [www.sba.gov/sbir](http://www.sba.gov/sbir)
Diagnostics for tuberculosis: global demand and market potential

Programme and product implementation

Tuberculosis control activities are the ultimate responsibility of national governments, but an array of technical and financial agencies support these activities which would otherwise be severely compromised in many countries. The Global Fund (GFATM), which has so far committed US$ 3 billion to control of the leading three infectious disease killers since 2002, is a recently created innovative approach to international health financing intended to empower governments to fully implement disease control strategies that would otherwise be unaffordable.

International agencies

- Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM)
  www.theglobalfund.org
- The World Bank
  www.worldbank.org
- The World Health Organization
  www.who.int

National Aid Agencies

- Canadian International Development Agency (CIDA)
  www.acdi-cida.gc.ca
- Development for International Development (DFID)
  www.dfid.gov.uk
- German Agency for Technical Cooperation (GTZ)
  www.gtz.de/de/index.htm
- Italian Cooperation for Sustainable Development
  www.esteri.it/eng/6_40_175.asp
- Japan International Cooperation Agency (JICA)
  www.jica.go.jp/english/index.html
- Swedish International Development Agency (SIDA)
  www.sida.se
- US Agency for International Development (USAID)
  www.usaid.gov

NGOs

- BRAC
  www.brac.net
- Damian Foundation
  www.damiaanactie.be
- German Leprosy and TB Relief Association (GLRA)
  www.glra.de
- International Union Against Tuberculosis and Lung Disease (IUATLD) and Fidelis
  www.fidelistb.org
  www.iuatld.org
- KNCV
  www.tuberculose.nl
- Médecins Sans Frontières (MSF)
  www.msf.org
- Philippine Coalition Against Tuberculosis
  email: philcat@pacific.net.ph
- Project Hope
  www.projecthope.org

From a scientific viewpoint, recent technological advances in genetics, microelectronics, materials science, cell and phage biology, and nanotechnology have sparked a revolution in diagnostics for infectious diseases and an array of promising new diagnostic approaches has been developed for TB. These include nucleic acid amplification, phage replication, antibody detection, liquid culture, cellular immune recognition, antigen capture, and chemical or physical detection (see Chapters 2 and 4).

Ultimately, new diagnostic tests have the potential to revolutionize TB control by improving the speed and ease of detection, permitting the diagnosis of difficult non-pulmonary cases, and bringing the diagnosis closer to the patient. The expected results are improved case detection rates, reduced morbidity, fewer early deaths in dually infected HIV subjects, and reduced transmission.

Conclusions

In conclusion, the following points are important to consider:

- TB, in its various forms, is a growing health problem.
- Diagnosis is a key element in the plan to control TB.
- TB control has gained the attention of health-care providers and governments around the world.
- Economic conditions for improving current TB testing and introducing market-appropriate technologies, have never been better.

A survey of currently available TB tests is presented in the next chapter.
Transmission, latent infection and progression to active disease

TB is a bacterial disease caused by Mycobacterium tuberculosis. The family mycobacteriaceae has over 60 members or species. Some species, including those in the M. tuberculosis complex, cause human disease, but most are not pathogenic to humans. Many of the non-pathogenic mycobacteria are found in the environment, e.g. in water and soil.

M. tuberculosis transmission commences when a person with active pulmonary TB coughs, sneezes or spits, launching TB bacteria into the air. Inhalation of these bacteria is the most common mode of infection. The risk of infection following exposure depends on several factors, including the concentration of bacteria in the air, the duration of exposure, the virulence of the organism (debatable), and the immunocompetence of the exposed individual.

Approximately one third of the world’s population is infected with the TB bacillus, but the majority of infected people never develop active disease (1). Even in the absence of a competent immune system (i.e. in children) or under conditions that suppress immunity (HIV, diabetes, kidney failure, etc.), most humans contain the bacilli and never become ill. This condition is referred to as latent TB infection (LTBI). Overall, there is only a 10% lifetime chance of a person with LTBI developing an active form of the disease (2). When TB does outstrip the body’s immune defences, active tuberculosis disease develops. Disease of the lungs (pulmonary TB) is the most common form of active TB and is the infectious form of the disease. A highly infectious person can transmit disease to 10–15 persons in a year, with household members being particularly at risk (3). TB, however, is not limited to the lungs but can affect virtually any organ of the body. Persons with extrapulmonary tuberculosis make up about 10–20% of all those with active TB. These forms of the disease are not infectious and are seen more commonly in children and persons coinfected with HIV.

Diagnostic priorities

The most important priority for TB control is the accurate diagnosis and prompt treatment of persons with active, infectious TB. Doing this both interrupts TB transmission and cures patients. In the absence of effective treatment, TB mortality is 50% or more (4).

Since the discovery of TB, the basis for its definitive diagnosis has been detection of the bacillus in clinical specimens. Following microscopic detection of the organism in 1882, technical advances have allowed us to detect fewer and fewer organisms in a specimen. Unfortunately, however, the level of sophistication and cost associated with more sensitive techniques has, to date, made their general application unfeasible in developing countries. Therefore, the basis for TB diagnosis in developing countries has continued to be the stained smear of expectorated sputum. Fortunately,
this technique detects the most infectious patients and those most in need of treatment. In contrast, in developed countries with lower rates of TB and greater human and financial resources, advanced techniques to complement sputum smear microscopy have been adopted and other tests to detect additional forms of disease, such as extrapulmonary and latent infection, have been applied. Thus,

#### Figure 1

**Diagnostic Priorities in Developing and Developed Countries: Where, Who, Why?**

**Developed Country**
- High income
- Low prevalence
- Goal: elimination of TB

- **All forms of active TB disease**
- **Detection of multidrug-resistant TB**
- **Latent infection in high-risk groups**

Targeted at detecting and treating people with any form of tuberculosis (active or latent), with attention paid to:
1. High prevalence groups: socially marginalized / People born in high-prevalence countries and
2. High-risk groups: HIV infected / Close contacts of an active case / Immuno-compromised / Children under 5 years.

**Developing Country**
- Low income
- High prevalence
- Goal: identify and treat cases

- **Pulmonary tuberculosis highly contagious patients**

Target the reservoir of highly contagious patients to interrupt transmission by early diagnosis and treatment.

- **Latent infection in lower risk groups**

Identification of individuals found to be infected, or likely to be infected, including recent tuberculin skin test converters and individuals with certain medical conditions (diabetes, kidney failure).

- **Pulmonary tuberculosis: less contagious patients (pulmonary smear-negative)**
- **TB in other organs (extrapulmonary TB)**
- **Latent infection: surveillance purposes**
- **Multidrug-resistant TB: surveillance purposes**
the quantity of financial and human resources has a direct impact on access to diagnostic tools and in part shapes a country’s diagnostic priorities (as explained in Figure 1).

**Making the diagnosis**

In developing countries, screening for active disease is rarely conducted and case finding is therefore dependent on patients seeking care at a health facility (passive case finding). Those with active disease will present with a broad range of clinical manifestations, influenced by age, comorbidity, affected site (i.e. lungs, bones, lymph nodes, central nervous system), and severity of disease. Unfortunately, none of these manifestations points directly to TB as the definitive cause. And syndromic management is rarely recommended owing to the long, arduous treatment regimens and the social stigma associated with TB.

At best, the history and clinical examination of a patient can establish “clinical suspicion,” and laboratory and radiographic tests therefore play a critical role in therapeutic decision-making. TB patients coinfected with HIV, children, and those with extrapulmonary forms of the disease, pose special challenges, and often a presumptive diagnosis based on clinical findings is justifiable owing to the limited availability and performance of the available diagnostic techniques (see Table 1: Special situations). The emergence of drug resistance to standard anti-tuberculosis therapy has further challenged the limits of clinical diagnosis and heightened the importance of drug-susceptibility testing. The general approach to diagnosis and the current armamentarium of commercially available tools for screening and detecting active and latent TB infection are reviewed below. Of the tests described, conventional smear microscopy and chest X-ray are the most commonly used in both developing and developed countries.

### Table 1. Special Situations

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Impact on Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>+ Infants and pre-school children</td>
<td>• At elevated risk of developing active disease after primary infection, often rapidly progressive, life-threatening disseminated disease.</td>
</tr>
<tr>
<td>+ The elderly</td>
<td>• Children are often asymptomatic or have ill-defined symptoms in the early stages of illness.</td>
</tr>
<tr>
<td>+ From the age of 65-70 years, people are at heightened risk for either reactivation or rapid progression of recent infection to disease.</td>
<td></td>
</tr>
<tr>
<td><strong>Concurrent disease</strong></td>
<td></td>
</tr>
<tr>
<td>+ Diabetes, cancer, drug abuse, nutritional status, alcoholism, other conditions causing immunosuppression</td>
<td>• Symptoms and findings of the baseline disease state can obscure and delay the diagnosis of TB or result in misdiagnosis.</td>
</tr>
<tr>
<td><strong>HIV</strong></td>
<td></td>
</tr>
</tbody>
</table>
Radiographic methods

Advantages:
> Convenient
> High sensitivity in those uninfected by HIV
> Fast

Limitations:
> Nonspecific, resulting in over-diagnosis when used alone
> Relatively expensive
> Limited availability of equipment in most high-burden countries
> Requires specialized equipment and power source
> Particularly unreliable in settings of HIV

Radiographic methods for detection of active disease

It is still widely believed that tuberculosis of the lung can be diagnosed by chest X-ray alone (Figure 2). However, practical experience and numerous studies have shown that no radiographic pattern is diagnostic of tuberculosis (5). Many diseases of the lung have a similar radiographic appearance that can easily mimic tuberculosis (6). Similarly, the lesions of pulmonary tuberculosis can take almost any form on a radiographic picture (7). In developed countries and other settings where facilities and resources permit, patients with signs and symptoms of pulmonary TB are screened by chest X-ray. Films can be very helpful in localizing abnormalities in the lung. However, to establish the tubercular aetiology of an abnormality, further examination is necessary, and only bacteriology can provide the necessary proof.
Diagnostic laboratory methods for detection and confirmation of active M. tuberculosis disease

Smear microscopy

Worldwide, the most common diagnostic test used to detect tuberculosis is microscopic examination of stained sputum or other clinical material smeared on a glass slide. When present in sufficiently high concentrations, the bacteria can be readily identified by a trained technician using this technique, which has changed little since it was invented over 100 years ago. Microscopy is cheap to perform, specific enough to indicate treatment in countries where TB is prevalent, and can be completed within hours if necessary (Figure 3). Microscopy requires a large number of bacilli to be present in order for the result to be positive (5000–10,000 per ml of sputum), and identifies the most infectious subset of patients (8). However, this requirement limits its sensitivity, especially for less advanced disease. Certain groups of patients, such as those with advanced HIV coinfection, people with tuberculosis outside the lungs, and children, are usually sputum smear-negative. The inherent low sensitivity of the test is compounded by the conditions under which it is commonly performed: poor equipment, heavy workload, and inexpert or unmotivated staff. The proportion of cases detected by microscopy is often as low as 20–30% of all cases (9). Duplicate or triplicate sputum examinations are requested to help overcome this problem. This need for multiple tests, each of which requires sputum collection, drying, staining and meticulous examination, results in delays in reporting and a relatively large number of patients do not complete the testing or are lost to the health care system despite having a positive test. Several methods are in use that may increase the speed or sensitivity of microscopy somewhat, including the use of fluorescence microscopes (10).

Because of the greater cost of the necessary equipment, fluorescence microscopes are used primarily in industrialized countries.

Smear microscopy

Advantages:
- Detects the most infectious cases
- Highly specific in high-prevalence settings
- Inexpensive
- Widely established

Limitations:
- Difficult to maintain in the field
- Requires well-trained, motivated technicians
- Insensitive (35–70%) especially in HIV infection, children and extrapulmonary disease (11-13).
- Cannot distinguish between drug-resistant and drug-sensitive MTB
- Requires repeat visits (2-3)
**Culture**

**Advantages:**
- More sensitive than smear microscopy, requires fewer bacilli (10–100 bacilli per ml versus 5000–10,000/ml of sputum)
- Semi-quantitative
- Allows species identification – important in developed countries
- Allows drug susceptibility testing

**Limitations:**
- Requires 2–6 weeks rather than days for results
- Requires specialized personnel and equipment and a dependable supply of water and electricity

**Culture**

Bacteriological culture, considered the diagnostic gold standard, can identify the *M. tuberculosis* organism in over 80% of TB cases with a specificity of over 98% (14–16). As few as 10–100 viable bacilli per ml may be detected, although the sensitivity of cultures varies substantially depending on the specimen-processing method and the culture medium used. Compared to smear microscopy, culture is more expensive and requires more highly trained personnel but allows detection of more forms of disease, including less advanced cases.

Although bacterial culture is routinely applied in industrialized countries, access to culture facilities is limited in countries with fewer resources (see Chapter 3) and its use in the public sector is restricted to smear-negative TB and to cases of suspected drug resistance. As *M. tuberculosis* grows slowly, conventional culture with visual detection of bacterial colony formation usually requires 2–6 weeks. Recently, a number of growth indicators have been used, often involving liquid media and automated systems that shorten the detection period to 1–3 weeks in most cases. See Table 2 for the advantages and limitations of different culture media.

---

**Figure 4**

Mycobacterial culture

1. Sputum collection / 2. Sputum decontamination / 3. Inoculation on solid media (top) and on liquid media (bottom) / 4. Incubation on solid and liquid media / 5. Reading culture results / 6. Mycobacteria species identification (molecular or biochemical methods) / 7. Reporting results.

**Table 2**

<table>
<thead>
<tr>
<th>Culture Media</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid media</td>
<td>High specificity, easy to interpret</td>
<td>Requires specialized personnel and equipment, labor-intensive, slow detection</td>
</tr>
<tr>
<td>Liquid media</td>
<td>High sensitivity, rapid detection</td>
<td>Requires specialized equipment, labor-intensive, may require technical expertise</td>
</tr>
</tbody>
</table>

**Notes:**
- Total time: 2–6 weeks
- Patient visits: 2 or 3
TABLE 2.ADVANTAGES AND LIMITATIONS OF DIFFERENT CULTURE MEDIA

<table>
<thead>
<tr>
<th>MEDIA</th>
<th>ADVANTAGES</th>
<th>LIMITATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manual</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid:</td>
<td>• Egg-based or agar-based(^a)(^b)</td>
<td>• 2–6 weeks detection time</td>
</tr>
<tr>
<td>Liquid:</td>
<td>• Synthetic(^c)</td>
<td>• Less sensitive than liquid</td>
</tr>
<tr>
<td><strong>Automated</strong></td>
<td></td>
<td>• Labour-intensive read-out</td>
</tr>
<tr>
<td>Solid:</td>
<td>• TK MEDIA (SALUBRIS, Inc.)</td>
<td></td>
</tr>
<tr>
<td>Liquid:</td>
<td>• Bactec 460 (Becton Dickinson)</td>
<td>• Expensive</td>
</tr>
<tr>
<td></td>
<td>• MGIT(^{TM}) 960 (Becton Dickinson)</td>
<td>• Requires more infrastructure</td>
</tr>
<tr>
<td></td>
<td>• MB/BacT (bioMérieux)</td>
<td>• Equipment purchase and maintenance needed</td>
</tr>
<tr>
<td></td>
<td>• SeptiChek-AFB(^{TM}) (Becton Dickinson)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ESP Culture II System (Trek Diagnostics)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 1–4 weeks detection time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Speeds drug-susceptibility testing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Speeds species identification</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Decreases workload</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Löwenstein–Jensen.  
\(^b\) Middlebrook 7H10 or 7H11.  
\(^c\) Middlebrook 7H9 broth, locally prepared or commercial with growth indicators (MGIT, MBRedox\(^{®}\)).
Nucleic acid amplification

**Advantages:**
- Results available in several hours
- Specificity 98–100% (17).
- Sensitivity is greater than 95% in sputum that is acid-fast bacilli (AFB) smear-positive and 60–70% in smear-negative, culture-positive specimens (18–20).
- Recently developed amplification tests may have better sensitivity in smear-negative specimens while retaining the same high degree of specificity (16,21,22).
- Shows promise for materials other than sputum (blood, lymph, bone marrow, gastric aspirate, cerebrospinal fluid, urine, bronchial aspirate and lavage), although results have considerable variability (23-24).

**Limitations:**
- Cost
- Complexity
- Lower specificity (higher proportion of false-positives) under field conditions
- In-house tests may be less expensive but are more time-consuming

Nucleic acid amplification constitutes a rapidly evolving improvement in the detection and identification of M. tuberculosis. Bacterial DNA (or ribosomal RNA transcribed into DNA) is enzymatically amplified and detected with an appropriate reading system via a signal-generating probe. Several enzymatic amplification processes have been developed and introduced into commercial products; the most widely used are PCR (polymerase chain reaction), TMA (transcription mediated amplification) and SDA (strand displacement amplification).

Tests based on nucleic acid amplification are usually highly specific for M. tuberculosis (close to 100%), although some commercial products require a 2-step diagnostic procedure (initial test for mycobacteria genus, followed by tests which differentiate M. tuberculosis from non-tuberculous mycobacteria). Positive results can be obtained with less than 10 bacteria/ml; therefore sensitivity is much better than smear microscopy, but slightly less than culture. Currently, nucleic acid tests are used primarily for confirmation of smear-positive results or for primary case finding in combination with other methods.

The most outstanding feature of nucleic acid amplification methods is the short time-to-result (between a half and one working day, including sample preparation) paired with a high level of diagnostic accuracy. Because of their price and complexity the use of these methods is still limited to developed countries.

**Test steps for Gen-Probe’s MTD Test**

1. Test kit
2. Lysis of cells and release of the nucleic acid target. Subsequently, a specific sequence of the mycobacterial nucleic acid is amplified, resulting in million-fold increased target DNA concentration
3. Labelled DNA probe is added, resulting in a concentration-dependent complex of labelled DNA probe and DNA
Serology
In contrast to many infectious diseases for which serodiagnosis (detection of antibodies or antigens in blood – Figure 6) is used, technology has so far largely failed to provide an adequately sensitive, specific and practical method as a first-line screening tool for clinical use in TB (25, 26). Specificity is hampered by antibodies in the sample that cross-react with environmental mycobacteria, leading to false-positive results. Also, the lack of reproducible methods for purifying antigens means that results are variable. Currently available serological tests, therefore, offer little compared to standard smear microscopy, but their superior operational characteristics hold some promise. Since none of the assays is yet approved by regulators in North America or Europe, or recommended by the international TB community, their use is restricted to the private sectors of countries lacking diagnostic regulatory bodies.

Serology

**Advantages:**

- More convenient when obtaining specimens from extrapulmonary cases and children suspected of having pulmonary disease
- Simpler to use than smear microscopy
- High negative predictive value
- Results available within 1 hour
- Involves simple technology
- Relatively inexpensive

**Limitations:**

- Sensitivity is highest in patients with smear-positive disease, but much lower in children, patients with extrapulmonary disease, human immunodeficiency virus (HIV)-infected individuals, and smear-negative cases
- Cannot reliably distinguish active tuberculosis disease from latent infection with *M. tuberculosis*
- Cannot distinguish *M. tuberculosis* from other species of mycobacteria

*Figure 6*

Serological detection of TB

1. Preparation of supplies / 2. Sample collection / 3. Application of blood sample to immunochromatographic (IC) strip / 4. Reading the IC strip / 5. Positive results (control and patient bars bars visible).
Phage assay

Advantages:
- Rapid results obtained from sputum (48–72 hours)
- No dedicated equipment required
- High sensitivity in smear-positive specimens [27].
- Semiquantitative results
- May be most useful in high-burden countries; in a study conducted in South Africa, sensitivity was 70.3% and specificity 99% in previously untreated TB patients [28].

Limitations:
- Low sensitivity in smear-negative culture-positive specimens
- Requires technical expertise
- Evaluated only on sputum specimens

Mycobacteriophage assay

FASTPlaqueTB is the only commercial phage assay and is a method based on a technology that utilizes mycobacteriophages (viruses that infect mycobacteria) as indicators of the presence of viable \( M. \) tuberculosis in a clinical specimen (Figure 7). Some groups have developed home-based methods.

Test steps for FastPlaque TB\textsuperscript{TM}
1. Sputum sample / 2. Mycobacteriophage added to sputum sample. Phages recognize and attack \( M. \) tuberculosis cell and release DNA / 3. New phage particles produced and virucide added to inactivate phages outside the cell / 4. Virucide neutralized and specimen mixed with Mycobacteria smegmatis and agar, which are poured into Petri dish / 5. Phages replicate and lyse MTB and then repeatedly infect Mycobacteria smegmatis cells. This appears as clear zones on the agar plate.
Detection of latent infection

**Tuberculin skin test**

Purified protein derivative (PPD), or tuberculin, is composed of a witch’s brew of proteins from heat-killed *M. tuberculosis*. Injection of PPD under the forearm skin precipitates a hypersensitivity reaction in people with prior TB infection. This reaction presents as skin thickening at the site of injection after 24–48 hours. (Figure 8). This method has been in clinical use for more than 90 years and its primary role has been in the detection of latent infection, although it has also been applied inappropriately for detecting active disease in adults. Unfortunately, its application is problematic due to the frequency of false-positive and false-negative skin reaction (Table 3). Despite these shortcomings, the test is manufactured around the globe and applied broadly in almost all countries. Applications range from screening health care workers to conducting prevalence surveys.

**TABLE 3. CAUSES OF FALSE-POSITIVE AND FALSE-NEGATIVE PPD REACTIONS**

<table>
<thead>
<tr>
<th>FALSE-POSITIVE REACTION</th>
<th>FALSE-NEGATIVE REACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter-observer variability can cause errors in reading of tuberculin skin test(^\text{29})</td>
<td>* Technical factors (poor preparation, storage or administration)</td>
</tr>
<tr>
<td>• BCG vaccination</td>
<td>• Immunocompromised conditions</td>
</tr>
<tr>
<td>• Infection with non-tuberculous mycobacteria (overlapping proteins with other species of acid-fast bacilli)</td>
<td>• Age (newborns, adults &gt; 65 years)</td>
</tr>
<tr>
<td></td>
<td>• Cancer</td>
</tr>
<tr>
<td></td>
<td>• Immunosuppressive drugs, i.e. steroids</td>
</tr>
<tr>
<td></td>
<td>• Bacterial, viral or fungal infections</td>
</tr>
<tr>
<td></td>
<td>• Advanced HIV disease</td>
</tr>
<tr>
<td></td>
<td>• Active tuberculosis</td>
</tr>
</tbody>
</table>

**Advantages:**

> A positive test can support a diagnosis of tuberculosis infection or disease in children
> Has a role in monitoring for recent infection in certain high-risk groups

**Limitations:**

> Sensitivity and specificity vary depending on the population tested and reaction cut-off points (7, 38).
> Requires follow-up visit at 48–72 hours
> Confounded by HIV, BCG and other forms of mycobacteria
> False-negative rates can occur in up to 50% of those with advanced HIV infection (31, 32).
> About 25% of those with active TB may have negative skin tests (33, 34).

**Mantoux test**

**Advantages:**

> A positive test can support a diagnosis of tuberculosis infection or disease in children
> Has a role in monitoring for recent infection in certain high-risk groups

**Limitations:**

> Sensitivity and specificity vary depending on the population tested and reaction cut-off points (7, 38).
> Requires follow-up visit at 48–72 hours
> Confounded by HIV, BCG and other forms of mycobacteria
> False-negative rates can occur in up to 50% of those with advanced HIV infection (31, 32).
> About 25% of those with active TB may have negative skin tests (33, 34).
CHAPTER 2

Cytokine detection assay

Advantages:
> Single visit required
> Less subject to reader objectivity in comparison to tuberculin skin test
> Assesses response to multiple antigens simultaneously
> Can distinguish between exposure to Mycobacterium tuberculosis and environmental mycobacteria

Limitations:
> Requires blood drawing and use of fresh samples
> Additional tests are required in order to exclude TB disease and confirm diagnosis of latent infection
> Not recommended for evaluation of patients with suspected TB disease
> Expensive

Cytokine detection

Molecular biological advances in the past decade have allowed the development of tests to estimate cell-mediated immune response against M. tuberculosis. Circulating lymphocytes are extracted from samples of venous blood, exposed to purified mycobacterial antigens, and incubated for 6 to 24 hours. If the patient is infected with M. tuberculosis, the blood cells will recognize the tuberculin and produce cytokines (most commonly interferon-gamma), which are measured (Figure 9). In 2001, the FDA approved a commercial assay of this nature, called “QuantiFERON®-TB” (Cellestis Ltd.), to detect latent tuberculosis infection. This assay has evolved into QuantiFERON®-TB Gold (Cellestis Ltd), which incorporates TB-specific antigens ESAT-6 and CFP-10 and is approved for diagnostic use in Europe, Japan and the USA. Use of specific MTB antigens reduces cross-reactivity to the BCG vaccine and many environmental mycobacteria. T SPOT-TB (Oxford Immunotec Ltd.) is a similar assay that has been approved for use in Europe. The test captures IFN-gamma released from peripheral blood mononuclear cells in response to stimulation with MTB-specific antigens.

Test steps for Quantiferon-Gold™ assay
Detection of drug resistance

Drug-resistant TB and drug-susceptibility testing

Mutations of the M. tuberculosis bacterial chromosome confer reduced susceptibility to chemotherapy agents, leading to drug resistance. In the early 1990s, resistance to anti-tuberculosis drugs was acknowledged as an emerging global threat to tuberculosis control. Multidrug-resistant tuberculosis (MDR-TB) is characterized as resistance to at least isoniazid and rifampicin, which are the mainstay of anti-tuberculosis treatment. Drug resistance can be acquired in two ways, either through infection with a resistant strain of M. tuberculosis or as a result of inappropriate anti-TB drug use by the patient or the clinician.

The rising rates of MDR-TB worldwide and epidemics of MDR-TB in the United States, coupled with increased threats of bioterrorist attacks, highlight the importance of drug-susceptibility testing to identify drug-resistant strains, and have spawned research into the molecular mechanisms of resistance and the development of new tools. Nonetheless, it is estimated that only a small fraction of total MDR cases are microbiologically confirmed. Susceptibility testing is routine in industrialized countries, but is beyond the financial and technical means of laboratories in most developing countries, which rely on their national reference laboratories or international laboratory networks for drug-susceptibility testing. When, and if, results arrive, many months may have passed. Therefore, in most areas, drug resistance is inevitably clinically defined by repeated treatment failure. The result of this, even where second-line drugs are available, is a prolonged period of contagious illness and opportunity for the spread of MDR-TB. A strategy for treating MDR-TB – DOTS-Plus – has been developed to ensure effective treatment protocols and management of MDR-TB, but the timing and most cost-effective approaches for diagnosing MDR-TB are still unknown.

The conventional as well as some new methods for drug-susceptibility testing are described briefly below.

Solid media

Proportions method

The reference standard is the proportions method, in which the growth (culture) of organisms on an anti-tuberculosis drug-containing medium is compared with growth on a drug-free, control medium. The proportion of growth on both media is compared. Results are generally not available for 2–3 months after the sample is received. In the meantime, patients are put on standard anti-tuberculosis therapy.

Resistance ratio method

In the same experiment, the ratio of minimum inhibitory concentration (MIC) for the patient’s strain to the MIC of the drug-susceptible, reference strain is measured.

Absolute concentration method

Media containing several sequential dilutions of each drug are used and resistance is indicated by the lowest concentration of the drug that will inhibit growth.

Most newly developed commercial methods reduce waiting times, but are extremely costly, and require skilled operators and an advanced infrastructure.

Liquid media

Automated BACTEC 460 TB radiometric method

In this method, a liquid medium containing anti-tuberculous drugs at different concentrations is used to cultivate resistant bacilli. Results (including identification) are available within 10–12 days. The major disadvantages are the problems associated with a large volume of radioactive materials and the high cost.

BD BACTEC™ MGIT™ 960 SIRE Susceptibility testing of Mycobacterium tuberculosis (MGIT - Mycobacteria Growth Indicator Tube)

Nonradiometric, patented media and sensors are used, making efficient use of advanced fluorometric technology which permits highly accurate detection of O2 consumption without sharps.
Other commercially developed drug-susceptibility testing methods in limited use

Molecular amplification
Drug resistance is conferred by changes in the organism’s DNA. Numerous molecular methods that detect a limited number of mutations in genes associated with resistance to anti-tuberculous drugs have been described. Resistance to the most effective of anti-tuberculous drugs, rifampicin, is associated with a mutation in the rpoB gene and highly predictive of MDR-TB in most settings (35–37). Commercial methods have been developed that detect, amplify and probe this region to confirm or rule out resistance. Molecular amplification has the same advantages and disadvantages as those associated with nucleic acid amplification for case detection (see page 38).

Phage amplified biological (PhaB) assay
Phages, clinical specimens and anti-tuberculosis drugs are incubated together. The phage replication system detects living cells, and, therefore, drug-resistant mycobacteria will only infect and replicate in drug-resistant mycobacterial cells. Noninfecting, exogenous phages are inactivated by chemical treatment.

Diagnostic limitations in special settings

Diagnosis of TB in HIV-seropositive individuals, in children, and in persons with extrapulmonary forms of TB, remains an unmet challenge in both high-prevalence and low-prevalence settings. Persons with extrapulmonary TB do not transmit disease and those immunocompromised by HIV and/or of paediatric age generally transmit less owing to the lower frequency of cavitary disease and/or expectoration (children). While this makes them less of a public health threat, they remain a dilemma of nightmare proportions for physicians in clinical practice, for the reasons outlined in Table 4 (see next page).
### TABLE 4. THE CHALLENGES OF DIAGNOSIS

<table>
<thead>
<tr>
<th>Diagnostic Approach</th>
<th>TB-HIV</th>
<th>Paediatric TB</th>
<th>Extrapulmonary TB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Onset can be acute rather than chronic. Less likely to have copious sputum production or haemoptysis.</td>
<td>• &lt; 6 years – acute onset and dissemination common.</td>
<td>• Nonspecific swelling, pain, with or without loss of function, at one or more of the following sites: - Pleural space - Lymph node - Peritoneum - Kidney/bladder - Uterus - Central nervous system - Bone, joint space. Fever, weight loss and appetite loss may or may not be present.</td>
<td></td>
</tr>
<tr>
<td>• Coinfection with other bacterial, viral or parasitic pathogens adds complexity.</td>
<td>• Non-specific constitutional symptoms, with up to 50% asymptomatic during the initial stages.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Extrapulmonary and disseminated forms of TB more common.</td>
<td>• Diagnosis often confused with pneumonia, asthma or congenital pulmonary abnormalities.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Does not distinguish between infection and disease. HIV+ individuals are often anergic.</td>
<td>• Extrapulmonary forms common (25%).</td>
<td>• Generally nonspecific findings with the exception of advanced spinal or vertebral TB (Pott’s disease).</td>
<td></td>
</tr>
<tr>
<td><strong>Radiographic</strong></td>
<td>Variable; cavities less common.</td>
<td>Hilar adenopathy is the hallmark of primary TB. However, abnormalities are often subtle and easily missed.</td>
<td>Cannot distinguish between infection and disease.</td>
</tr>
<tr>
<td><strong>Tuberculin skin test</strong></td>
<td>Does not distinguish between infection and disease. HIV+ individuals are often anergic.</td>
<td>May take up to three months to develop a positive test following exposure.</td>
<td></td>
</tr>
<tr>
<td>• Requires sputum induction, bronchoscopy and/or culture to confirm diagnosis.</td>
<td>• False-positives (BCG vaccination, environmental mycobacteria) and false-negatives (serious viral, bacterial or tuberculous infection, immunosuppression) occur.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Low bacillary load in clinical specimens leads to negative acid-fast stain and culture.</td>
<td>• Generally nonspecific findings with the exception of advanced spinal or vertebral TB (Pott’s disease).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td>Unlikely to expectorate, therefore swallow bacilli – this is the rationale for testing gastric contents for acid-fast bacilli. However, sensitivity is notoriously low, i.e. &lt; 10% (38). Furthermore, optimal sputum and gastric aspirate cultures are sensitive in &lt; 50% of cases. (39, 40)</td>
<td>Invasive procedure required to obtain clinical specimen (fluid or biopsy).</td>
<td></td>
</tr>
<tr>
<td>• Requires sputum induction, bronchoscopy and/or culture to confirm diagnosis.</td>
<td></td>
<td>Low bacillary load in clinical specimens leads to negative acid-fast stain and culture.</td>
<td></td>
</tr>
<tr>
<td>• Low bacillary load in clinical specimens leads to negative acid-fast stain and culture.</td>
<td></td>
<td>Chemical analysis of pleural or peritoneal fluid inconclusive (exudate, lymphocytic, high protein, very low glucose) (41, 42).</td>
<td></td>
</tr>
<tr>
<td>• Adenosine deaminase in pleural fluid – variable results (43).</td>
<td></td>
<td>Adenosine deaminase in pleural fluid – variable results (43).</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 4. THE CHALLENGES OF DIAGNOSIS (CONTINUED)

<table>
<thead>
<tr>
<th>DIAGNOSTIC APPROACH</th>
<th>TB-HIV</th>
<th>PAEDIATRIC TB</th>
<th>EXTRAPULMONARY TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scoring systems – attempt to produce diagnostic standardization</td>
<td>* Research under way.</td>
<td>* Seventeen different scoring systems published. No one method adaptable for general use in all settings. Modifications required in areas of high HIV prevalence, limited resources, malnutrition and high burden. Diagnosis continues to rely primarily on clinical findings and in association with an adult source. Failure to thrive may still be the best available predictor (44,45).</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

In conclusion, the advantages and limitations of each available TB diagnostic method are evident and no test is yet available that meets target specification (Figure 10). Furthermore, the quality of the test results with existing methods are dependent on the availability of sufficient human and financial resources, training of laboratory personnel and monitoring of performance. New methods that overcome limitations and respond to the challenges posed by special populations will be well received.

Figure 10

CHARACTERISTICS OF CURRENT TB DIAGNOSTICS

<table>
<thead>
<tr>
<th>Performance</th>
<th>Ease to use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serology</td>
<td>Microscopy</td>
</tr>
<tr>
<td>X-ray</td>
<td>Culture</td>
</tr>
<tr>
<td>NAAT</td>
<td>Desired</td>
</tr>
</tbody>
</table>

1. **Performance** is a compilation of sensitivity, specificity and speed.
2. **Ease to use** is a compilation of safety, number of steps, cost, robustness and training simplicity.
Chapter 3
Summary
The market for diagnostic technologies has been expanding over the past decades and developing world markets are a key growth area. Commercial interest in TB diagnostics has been limited by a lack of detailed information on the size and character of the TB diagnostic market. This chapter provides a strategic overview of the current global market for TB diagnostic testing encompassing testing for active disease caused by tuberculosis as well as latent infection, monitoring response to treatment, and drug susceptibility testing (DST). Our analysis indicates that annually, over US$ 1 billion is spent worldwide on TB diagnostics. One third (US$ 326 million) of this money is spent outside of the established market economies (EMEs), where 73% of TB diagnostic testing takes place. Lower labour costs primarily account for the lower cost per test performed in developing countries. Sputum smear microscopy and chest radiography for active disease are by far the most common tests performed in developing countries, and eclipse the use of higher performance but more complex and expensive tests, such as culture and nucleic acid testing (NAT). Skin testing with PPD is the highest volume TB test used in the EMEs, where it makes up half the total market, reflecting the importance of detection of latent infection in those countries.

Introduction
The biotechnology revolution of the past decades is now bearing fruit, yielding a range of diagnostic technologies that have found receptive markets both in developed and developing countries. The market for these products has markedly expanded over the past decades, and the global in vitro diagnostic (IVD) market was valued at US$ 28.7 billion in 2004. Molecular diagnostics and point-of-care testing are the fastest growing segments of that market (1). Geographically, developing world markets are expected to provide the most important areas of growth in the coming decade. Worldwide, the diagnostics industry is composed of hundreds of small companies, but just ten companies have over two-thirds of the IVD market share. Only three of these ten leading IVD companies have included tuberculosis diagnostics in their product portfolios (Figure 1), (2). Similarly, only a fraction of smaller companies include TB diagnostics in their portfolios, in part owing to the difficulty in raising investment capital for development of tests for a disease that is popularly perceived to be under control or to affect only the poorest of the developing world.
The lack of commercial interest in TB diagnostics is discordant with the need for such tests, defined both by the size of the global TB epidemic and the inadequacy of the available test methods (Chapter 2). Until now, detailed information on the size and character of the TB diagnostic market has not existed, and in the face of this uncertainty, commercial investors have considered this to be a high risk area for research and development investment.

Published commercial analyses have focused on the fraction of the TB diagnostic market that exists in EMEs, and little work has been done to gain primary information about the size and nature of the market in countries where tuberculosis is endemic, and where 99% of all cases of the disease occur.

Accurate estimates of current market demand for TB diagnostics (or served available market-SAM) are challenging to generate because of the global distribution of disease, the wide regional variations in physician diagnostic test practices and costs per test result, and the predominance of current testing that is not commercially packaged and distributed as test kits, but instead assembled from raw materials acquired from multiple suppliers.

In order to clarify the global market for tuberculosis diagnostic testing, the UNICEF/UNDP/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases (TDR) and the Foundation for Innovative New Diagnostics (FIND), a non-profit foundation developing diagnostics for poverty-associated diseases, carried out a detailed market analysis.

The report addresses testing for active disease caused by tuberculosis as well as latent infection, monitoring response to treatment, and drug susceptibility testing (DST).

Information on the global epidemiology of TB was compiled from existing sources such as the WHO Reports of 2004 to 2006 on Global tuberculosis control surveillance, planning, financing (3), the Euro TB reports on Surveillance of Tuberculosis in Europe (4), the country mission reports of WHO Stop TB Department, national TB control programme statistics and the published literature. Data on the distribution of TB laboratory services (availability and workload), the volume of test manufacturers’ sales, retail and reimbursement diagnostic test fees, and physician test usage practices, were gathered through primary research carried out for the purposes of the report (5, 6).

Market size estimates are disaggre-
Epidemiology of tuberculosis

Mycobacterium tuberculosis is a ubiquitous human pathogen, reaching populations stretching from the Amazon rain forest to the outer reaches of Siberia. A total of 8.8 million people develop active tuberculosis disease each year (incident cases), adding to a similar number of already existing untreated (prevalent) cases. Figure 2 illustrates the magnitude and distribution of the global burden of incident cases of TB disease. As apparent, TB is concentrated in the developing world, and over 80% of active cases of disease are reported from just 22 countries, defined for convenience by WHO as high burden countries (HBCs)\(^1\). The mortality from tuberculosis is striking, and 1.8 million people are estimated to die each year, or nearly 5,000 a day.

The map in Figure 2 represents the distribution of disease, but not the distribution of testing. Because symptoms of TB, whether pulmonary or extrapulmonary, can mimic other medical conditions, millions of symptomatic people without the disease are screened. The ratio of the number of patients screened to the number found positive varies significantly between and within countries. For sputum microscopy, the most commonly performed test to detect active tuberculosis, that ratio is inversely proportional to the TB incidence (see Figure 3). For example, in Japan\(^2\), where TB is relatively uncommon, for every TB case detected, approximately 45 coughing patients are screened. In high burden settings such as India\(^3\) and South Africa\(^4\), for every TB case detected, on average 7 and 4 coughing patients are screened, respectively.

---

1 The 22 high-burden countries accounting for 80% of TB cases globally are Afghanistan, Bangladesh, Brazil, Cambodia, China, DR Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, Philippines, Russian Federation, South Africa, Thailand, Uganda, Uf Tanzania, Viet Nam, Zimbabwe

2 Data by courtesy of Satoshi Mitarai and based on survey responses from 242 hospital and 135 commercial laboratories.

3 [http://www.tbchina.org](http://www.tbchina.org) - based on results from 72 districts in first quarters of 2000, 2001 and 2002

4 Republic of South Africa, National TB Contol Programme, Executive action document Sept. 2001
In addition to the millions living with active tuberculosis, approximately one third of the world’s population, or approximately 2 billion people, is infected with the TB bacillus, a condition referred to as latent TB infection (LTBI). These individuals are asymptomatic, and may remain so for the rest of their lives. Most humans contain the bacilli following infection and never become ill, except in the absence of a competent immune system (i.e. in children) or under conditions that suppress immunity (HIV, diabetes, kidney failure, etc.). A fraction of individuals with LTBI, however, develop active disease in the years following infection. Detection and treatment of LTBI is an important part of the disease control strategy in industrialized countries.

Incorrect or irregular dosing of medications on the part of the physician or patient may cause the development of resistance to one or more drugs. Resistance to multiple drugs, including the two most important anti-TB medications, isoniazid and rifampin, is called multidrug-resistant TB (MDR-TB). MDR-TB requires prolonged and expensive treatment and is difficult to cure. Though globally only 4.3% of incident cases of TB are multidrug-
resistant, it is estimated that over 400,000 people fall ill with MDR-TB each year, and that over 50 million people are latently infected with MDR strains of TB (7). The regional distribution of MDR-TB is illustrated in Figure 4. Two thirds of MDR-TB cases occur in just three countries, China, India and the Russian Federation.

Another serious threat underlying the need for improved diagnostics is the HIV pandemic, which greatly increases susceptibility to TB infection and disease, and decreases the effectiveness of conventional diagnostic approaches. Globally, 12% of new adult cases of TB are HIV co-infected, but the burden of dual disease is concentrated in Africa and in some regions in Asia (see Figure 5), where the collision between HIV and high prevalence of latent TB infection (50-90%) has sparked a dramatic rise (3-10 fold in some countries) in active TB cases.

In summary, tuberculosis is a global epidemic concentrated in the developing world, in close association with poverty and, increasingly, HIV. Testing for tuberculosis remains common in industrialized countries, where immigrants make up a large and growing fraction of all cases. MDR-TB and HIV are both substantial threats to TB control, and have prompted significant increases in expenditure on TB diagnosis and treatment in developed countries since the mid-1980s, when TB was declared to be in the elimination phase in the United States.

**Global availability of TB laboratory services**

Little information has been accessible on the availability of TB diagnostic services in developing countries or the volume of testing. To this end, we carried out a global survey of TB laboratory services. Surveys were distributed to 207 WHO Member States to gather information on the number of public and private laboratory facilities performing sputum smear microscopy, mycobacterial culture and drug susceptibility testing (DST). Information was also collected on the volume of testing in the public sector. Each survey of the 116 survey responses was screened and respondents were contacted directly to explain errors and/or unexpected information. Raw data on the number of testing centres for TB microscopy, culture and DST are shown in Table 1.
### TABLE 1. GLOBAL ESTIMATES FOR TB DIAGNOSTIC FACILITIES AND SERVICES

<table>
<thead>
<tr>
<th>Region</th>
<th>Population (Millions)</th>
<th>No. Public DST Labs</th>
<th>No. Private DST Labs</th>
<th>No. Public Culture Labs</th>
<th>No. Private Culture Labs</th>
<th>No. Public Microscopy Centres</th>
<th>No. Private Microscopy Centres</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>327.813</td>
<td>71</td>
<td>253</td>
<td>130</td>
<td>1,013</td>
<td>600</td>
<td>2,279</td>
</tr>
<tr>
<td>Europe</td>
<td>459.088</td>
<td>713</td>
<td>1,998</td>
<td>252</td>
<td>2,333</td>
<td>39,198</td>
<td>5,912</td>
</tr>
<tr>
<td>Japan</td>
<td>127.417</td>
<td>24</td>
<td>9</td>
<td>62</td>
<td>42</td>
<td>160</td>
<td>124</td>
</tr>
<tr>
<td>Other high income</td>
<td>29.552</td>
<td>24</td>
<td>9</td>
<td>62</td>
<td>42</td>
<td>160</td>
<td>124</td>
</tr>
<tr>
<td><strong>Total 22 HBC</strong></td>
<td>3,892.273</td>
<td>629</td>
<td>57</td>
<td>2,135</td>
<td>299</td>
<td>39,198</td>
<td>5,912</td>
</tr>
<tr>
<td>Rest of world</td>
<td>1,382.869</td>
<td>691</td>
<td>138</td>
<td>785</td>
<td>383</td>
<td>15,340</td>
<td>3,663</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>6,219.011</td>
<td>2,128</td>
<td>457</td>
<td>5,110</td>
<td>1,737</td>
<td>57,528</td>
<td>11,978</td>
</tr>
</tbody>
</table>

**22 HBCs**

- Afghanistan: 22.930
- Bangladesh: 143.809
- Brazil: 176.257
- Cambodia: 13.810
- China: 1,294.867
- DR Congo: 51.201
- Ethiopia: 68.961
- India: 1,049.549
- Indonesia: 217.131
- Kenya: 31.540
- Mozambique: 18.537
- Myanmar: 48.852
- Nigeria: 120.911
- Pakistan: 149.911
- Philippines: 78.580
- Russian Fed.: 144.082
- South Africa: 44.759
- Thailand: 62.193
- Uganda: 25.004
- Tanzania: 36.276
- Viet Nam: 80.278
- Zimbabwe: 12.835

*No. = number*
The global availability of TB diagnostic services for each of these types of tests are illustrated in Figures 6, 7 and 8 as the number of testing centres per 100,000 or 1,000,000 inhabitants. The findings demonstrate a wide variability in the availability of TB diagnostic services around the globe. Microscopy facilities, the backbone of laboratory detection in disease-endemic countries, are available at a similar frequency overall in North America and in the 22 countries with the highest TB burden, at around 1 laboratory per 100,000 population (0.88/100,000 population in North America and 1.37/100,000 population in the 22 HBCs). Although there are over 45,000 microscopy centres in the 22 HBCs, these cover a population of nearly 4 billion people. For culture and DST, however, there are striking differences in the availability of testing. In the endemic countries, there are 0.63 and 0.18 testing facilities for culture and DST, respectively, per million in the population. As seen in Table 1, 13 of the 22 countries with the greatest number of TB cases have less than 10 culture laboratories in the country, and several countries in Africa have only one such facility. In Europe, by contrast, there are nearly 2,000 culture laboratories and some 700 DST laboratories, or 4.4 and 1.6 such laboratories, respectively, per million in the population.

When compared with the burden of disease, these disparities in laboratory services are even more conspicuous. In the high-burden countries, there are 35 culture laboratories and 10 DST laboratories per 100,000 incident TB cases. For North America, there are, by comparison, over 20 times as many higher-level testing facilities per case, with 7,000 culture laboratories and 2,000 DST laboratories per 100,000 incident TB cases (data not tabulated).
Volume and value of TB testing in the served available market

Segmentation approach
The volume of current diagnostic testing for tuberculosis, estimated from market research data collected between 2003-2004, was determined for three diagnostic indications. These are listed below, along with the type of testing currently used for each indication.

Indication 1
Detection of active tuberculosis and treatment monitoring
- Smear microscopy
- Commercial (liquid) and non-commercial culture
- Molecular testing
- Chest radiography
- Other (phage-based and serologic assays)

Indication 2
Drug susceptibility testing
- Commercial and non-commercial drug susceptibility testing

Indication 3
Detection of latent TB infection
- Skin testing with purified protein derivative (PPD)
- Interferon-gamma release assays

The served available market for TB diagnostics representing the current volume and value of testing performed in each market segment, was segmented by test indication as above, and also into commercial TB test types (i.e. ready-to-use kits that can be purchased from a commercial organization) and non-commercial TB test types (i.e. “home brew” reagents, including smear microscopy, conventional culture and drug susceptibility testing).

For commercial test kits (i.e. commercial liquid culture tubes, purified protein derivative (PPD), nucleic acid testing) data sourced directly from the companies are given on the distribution of sales and unit volumes as a function of geography. For commercial test kits, the fraction of sales to the public versus the private sector was not available. For non-commercial tests, the market can be further segmented into public and private sectors. For non-commercial tests, the SAM is described as the number of test requests and number of test units. For sputum smear microscopy, 1 test request generates 1 test unit, while for culture and DST, 1 test request generates 1.4 and 8-12 test units, respectively. For a more detailed description, see the “More on methods” section at the end of this chapter.

Dollar value approach
The dollar value assigned to non-commercial tests was based on the sum of disposable supplies/reagents purchased on the international market and regionally specific labour costs. The cost of disposables can vary several fold depending on the volume purchased and the suppliers. Local distributors may charge an additional 50% to 100% over the manufacturer’s price or that of a nongovernmental organization (NGO) supplier. In this analysis, conservative costs for disposables were calculated using price quotes from the last two suppliers. For commercial test kits, the disposable supply/reagent costs are based on manufacturer sales and labour costs are estimated by subtraction from the average of reimbursement fees in the United States, Germany and Japan. The latter method was applied because over 90% of commercial kits are sold and used in high-income settings. It is important to be aware that reimbursement fees can differ from private insurance claims and laboratory fees by orders of magnitude. For example, a US health care insurance claims data warehouse reports a mean claim charge for tuberculin skin testing of US$ 17, smear microscopy of US$ 35 and for culture US$ 75.

1 Volumes reported for commercial culture tubes includes test units used for performing drug susceptibility testing, as manufacturers were not able to determine final use of the product. Commercial culture does not include pre prepared solid media sales.
2 Market data for these recently developed assays were not collected as part of this analysis.
3 In high income countries approximately 2 test units are generated per culture request (1 solid and 1 liquid)
4 Vendors on the international market include nongovernmental organization suppliers, and therefore may not reflect prices from manufacturers or commercial distributors.
5 Sales represent sales to distributors and direct to end-users.
6 Based on Solucient’s database of health care claims information for more than 2.5 million covered lives annually from self insured employers, health maintenance organizations and other managed care organizations. For more information, see http://www.solucient.com/
However, Texas Medicaid reimbursement for these same tests are US$ 6.94, US$ 7.42 and US$ 15.43, respectively.

To compare our principal costing approaches with retail prices, we conducted surveys of laboratories offering TB diagnostic tests in two cities each of seven high-burden countries. The following table illustrates how calculated dollar values used in this analysis compare with retail survey prices.

US Medicaid reimbursement values for each of these tests is presented as an illustrative comparison for the developed world. In general, retail prices are substantially higher, accounting for non-disposables (ie. equipment, laboratory infrastructure/overhead) and a profit margin.

Results

The global market for TB diagnostic testing is an estimated US$ 1 billion. This is composed of US$ 395 million for disposable materials and US$ 638 million for labour. As our cost calculations assumed that disposables were purchased directly from manufacturers or NGO suppliers, the true market value could be significantly larger than that. Furthermore, inclusion of the costs of equipment (microscopes, incubators) and other reusable supply costs and facility maintenance costs could as much as triple our estimates of expenditures on TB diagnostic testing.

Table 3 summarizes the worldwide TB diagnostic testing market for each of three test indications. For simplicity, the markets are segmented into established market economies (EMEs)(North America, Europe, Japan, Australia/New Zealand and the Rest of the World (ROW)).

Globally, diagnostics for detection and monitoring of active TB comprise 65% (US$ 677 million) of the market share value and 76% of testing volume, followed by detection of latent infection and drug susceptibility testing with 34% (US$ 352 million), and 1% (US$ 4 million) of market share value, respectively. In the EMEs, the market value for tests that detect active disease and tests that detect latent infection is equivalent (50:50), whereas in the ROW, 95% of all testing is for active TB disease. (Table 3; Figure 9).

Smear microscopy, the internationally recommended first method for TB diagnosis, is the most common-

### Table 2. Private Sector Retail Prices and Reimbursement Fees for Commercial and Non-Commercial Tests in a Selection of Markets (US$)

<table>
<thead>
<tr>
<th>TEST</th>
<th>INDIA Retail survey</th>
<th>Calculated valuea</th>
<th>CHINA Retail survey</th>
<th>Calculated value</th>
<th>BRAZIL Retail survey</th>
<th>Calculated value</th>
<th>INDONESIA Retail survey</th>
<th>Calculated value</th>
<th>UGANDA Retail survey</th>
<th>Calculated value</th>
<th>SOUTH AFRICA Retail survey</th>
<th>Calculated value</th>
<th>USA Average reimbursementb</th>
<th>Calculated value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear</td>
<td>1.62</td>
<td>1.21</td>
<td>1.81</td>
<td>1.33</td>
<td>12.07</td>
<td>1.83</td>
<td>2.38</td>
<td>1.17</td>
<td>2.55</td>
<td>1.33</td>
<td>5.96</td>
<td>2.55</td>
<td>20.03</td>
<td>8.75</td>
</tr>
<tr>
<td>Culture</td>
<td>3.61</td>
<td>3.30</td>
<td>3.67</td>
<td>3.63</td>
<td>13.79</td>
<td>5.28</td>
<td>10.42</td>
<td>3.20</td>
<td>7.68</td>
<td>3.67</td>
<td>12.04</td>
<td>7.40</td>
<td>46.79</td>
<td>25.33</td>
</tr>
<tr>
<td>X-ray</td>
<td>2.08</td>
<td>2.32</td>
<td>18.62</td>
<td>3.86</td>
<td>5.90</td>
<td>2.05</td>
<td>6.01</td>
<td>2.37</td>
<td>16.08</td>
<td>5.45</td>
<td>44.78</td>
<td>21.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DST (2 drugs &amp; includes culture)</td>
<td>3.68</td>
<td>5.48</td>
<td>20.40</td>
<td>6.05</td>
<td>69.25</td>
<td>8.96</td>
<td>10.59</td>
<td>5.34</td>
<td>62.25</td>
<td>6.11</td>
<td>178.83</td>
<td>12.56</td>
<td>74.75</td>
<td>47.41</td>
</tr>
<tr>
<td>TST</td>
<td>1.28</td>
<td>0.49</td>
<td>0.74</td>
<td>0.55</td>
<td>2.73</td>
<td>0.97</td>
<td>0.49</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.37</td>
<td>12.18</td>
<td>5.55</td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>106.21</td>
<td>NA</td>
<td>23.00</td>
<td>NA</td>
<td>NA</td>
<td>75.67</td>
<td>NA</td>
<td>172.57</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

---

ly requested test, with 87 million tests requested annually worldwide. 94% of all sputum smears and chest X-rays are performed outside the EMEs. The number of smear requests is matched by the number of culture requests in the EMEs, but outside of Russia and South Africa, culture is rarely used.

### TABLE 3. SUMMARY TABLE OF SERVED AVAILABLE MARKET FOR TB DIAGNOSTIC TESTING: COMMERCIAL AND NON-COMMERCIAL TEST METHODS COMBINED

<table>
<thead>
<tr>
<th>EMEs</th>
<th>Test</th>
<th>Requests</th>
<th>Units</th>
<th>Disposables (US$)</th>
<th>Laboura (US$)</th>
<th>Total (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB detection and monitoring</strong></td>
<td>Sputum smear</td>
<td>5,036,334</td>
<td>5,036,334</td>
<td>4,551,644</td>
<td>30,868,675</td>
<td>35,420,319</td>
</tr>
<tr>
<td></td>
<td>Non-commercial cultureb</td>
<td>5,107,879</td>
<td>10,309,928</td>
<td>5,107,879</td>
<td>140,295,047</td>
<td>168,157,435</td>
</tr>
<tr>
<td></td>
<td>Commercial liquid cultureb</td>
<td>5,202,049</td>
<td>22,754,509</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chest radiography</td>
<td>2,988,084</td>
<td>2,988,084</td>
<td>4,118,022</td>
<td>44,330,555</td>
<td>48,448,577</td>
</tr>
<tr>
<td></td>
<td>Nucleic acid testing</td>
<td>2,279,579</td>
<td>2,279,579</td>
<td>32,742,306</td>
<td>81,236,644</td>
<td>113,978,950</td>
</tr>
<tr>
<td><strong>Drug susceptibility testing</strong></td>
<td>Non-commercial DST</td>
<td>125,708</td>
<td>1,005,667</td>
<td>1,517,182</td>
<td>846,295</td>
<td>2,363,478</td>
</tr>
<tr>
<td><strong>Detection of latent infection</strong></td>
<td>PPD skin testingd</td>
<td>40,963,012</td>
<td>81,926,023</td>
<td>129,796,246</td>
<td>208,823,648</td>
<td>338,619,894</td>
</tr>
<tr>
<td><strong>EMEs subtotal</strong></td>
<td></td>
<td>56,594,766</td>
<td>103,545,615</td>
<td>200,587,788</td>
<td>506,400,864</td>
<td>706,988,652</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ROW/NON-EMEs</th>
<th>Test</th>
<th>Requests</th>
<th>Units</th>
<th>Disposables (US$)</th>
<th>Laboura (US$)</th>
<th>Total (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Detection and monitoring of active TB</strong></td>
<td>Sputum smear</td>
<td>82,937,722</td>
<td>82,937,722</td>
<td>79,011,209</td>
<td>41,260,577</td>
<td>120,271,786</td>
</tr>
<tr>
<td></td>
<td>Non-commercial culturec</td>
<td>11,924,181</td>
<td>16,693,853</td>
<td>28,705,701</td>
<td>26,532,326</td>
<td>55,238,027</td>
</tr>
<tr>
<td></td>
<td>Commercial liquid culturec</td>
<td>1,499,157</td>
<td>1,499,157</td>
<td>7,753,583</td>
<td></td>
<td>7,753,583</td>
</tr>
<tr>
<td></td>
<td>Chest radiography</td>
<td>47,164,728</td>
<td>47,164,728</td>
<td>68,851,087</td>
<td>50,253,251</td>
<td>119,104,337</td>
</tr>
<tr>
<td></td>
<td>Nucleic acid testing</td>
<td>166,274</td>
<td>166,274</td>
<td>2,377,233</td>
<td>5,936,467</td>
<td>8,313,700</td>
</tr>
<tr>
<td><strong>Drug susceptibility testing</strong></td>
<td>Non-commercial DST</td>
<td>630,825</td>
<td>5,046,603</td>
<td>989,899</td>
<td>966,165</td>
<td>1,956,064</td>
</tr>
<tr>
<td><strong>Detection of latent infection</strong></td>
<td>PPD skin testingd</td>
<td>8,646,972</td>
<td>17,293,943</td>
<td>6,970,592</td>
<td>6,870,019</td>
<td>13,840,611</td>
</tr>
<tr>
<td><strong>ROW/non-EMEs subtotal</strong></td>
<td></td>
<td>152,969,858</td>
<td>170,802,280</td>
<td>194,659,303</td>
<td>131,818,805</td>
<td>326,478,108</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td>209,564,624</td>
<td>274,347,895</td>
<td>395,247,091</td>
<td>638,219,669</td>
<td>1,033,466,760</td>
</tr>
</tbody>
</table>

* Labour costs, expressed in US$, were estimated for sputum microscopy, noncommercial culture, indirect drug susceptibility testing (2 drugs) with noncommercial media and chest radiography using economic costing analyses. For commercial tests, (PPD skin testing, commercial culture, and nucleic acid testing) labour costs were estimated based on averaged EME reimbursement fees from USA, Germany, Japan minus disposables costs (manufacturer unit sales). However, labour costs for PPD in the ROW category, were estimated to be 10% of EME values. See details in “More on methods” section at the end of the chapter.

b In the EME, it is assumed that mycobacterial culture utilizes 1 solid (non commercial) tube and 1 liquid tube per request. It is further assumed that sold media tubes are purchased for US $1 per unit.

c Costs are based on indirect Löwenstein-Jensen proportion method, 2 drugs (8 tubes inoculated). Estimate does not include cost of culture/primary isolation on solid media.

d Assume 50% wastage of PPD units. Therefore, request are 50% of units.

e In the ROW, it is assumed that mycobacterial culture utilizes 1.4 solid tubes (units) per request. The cost of 1,499,157 million commercial, liquid culture tubes (ROW average cost US$ 5.17) is added to the total disposable costs.
in the ROW (5 million requests in a population of 5 billion), reflecting poor laboratory infrastructure and restricted financial resources (Figure 9). Similarly, less than 10% of nucleic acid testing (NAT) is performed outside the EMEs.

The SAM for commercial TB diagnostic testing is presented in greater detail in Table 4 and Figure 10. The types of tests currently in use are tightly linked to geography and economy. Commercially manufactured test kits have the greatest share of their markets in established market economies. Overall, 94% of sales of commercial products for purified protein derivative (PPD) skin testing, culture, and nucleic acid testing is in established market economies. The predominance of EME markets for commercialized tests is particularly prominent for PPD skin testing and nucleic acid testing, for which roughly 95% of market value is in industrialized countries. In contrast, fully 25% of the sales of commercial culture tubes are to countries outside the EMEs. South Africa accounted for over 500,000 units and Latin America for over 200,000 units. No price differential for culture tubes is seen between EMEs and ROW, which probably reflects the predominance in the developing world, of private sector purchasing of these systems.

Manufacturers’ sales data for commercial tests also reveal striking differences in diagnostic practices, as indicated by the frequent use of culture in North America and Europe compared to Japan. NAT is used most widely in Japan and twice as often in Europe as in North America. North America accounts for 50% of the PPD sales volumes, followed by Japan and the ROW countries which accounts for 20% each. The last group has not included data from large domestic manufacturers in China and the Russian Federation; therefore, this is an underestimate for the ROW market share. Overall, however, sales volumes for commercial tests to the ROW are uniformly less than one-fifth that to the EMEs.
### TABLE 4. SERVED AVAILABLE MARKET FOR COMMERCIAL TESTS, BY AREA OF SALE

#### PPD SKIN TESTING

<table>
<thead>
<tr>
<th>Region</th>
<th>Requests</th>
<th>Units</th>
<th>Test kit sales (US$)</th>
<th>Labour (US$)</th>
<th>Total (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>23,130,878</td>
<td>46,261,755</td>
<td>76,746,716</td>
<td>45,401,464</td>
<td>222,148,180</td>
</tr>
<tr>
<td>Europe</td>
<td>7,371,193</td>
<td>14,742,385</td>
<td>19,608,079</td>
<td>48,760,085</td>
<td>68,368,164</td>
</tr>
<tr>
<td>Japan</td>
<td>10,460,942</td>
<td>20,921,883</td>
<td>33,441,451</td>
<td>14,662,099</td>
<td>48,103,550</td>
</tr>
<tr>
<td>ROW</td>
<td>8,646,972</td>
<td>17,293,943</td>
<td>6,970,592</td>
<td>6,870,019</td>
<td>13,840,611</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>49,609,983</td>
<td>99,219,967</td>
<td>136,766,839</td>
<td>215,693,667</td>
<td>352,460,505</td>
</tr>
</tbody>
</table>

#### NUCLEIC ACID TESTING

<table>
<thead>
<tr>
<th>Region</th>
<th>Requests</th>
<th>Units</th>
<th>Test kit sales (US$)</th>
<th>Labour (US$)</th>
<th>Total (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>240,347</td>
<td>240,347</td>
<td>3,722,701</td>
<td>8,294,649</td>
<td>12,017,350</td>
</tr>
<tr>
<td>Australia/NZ</td>
<td>10,187</td>
<td>10,187</td>
<td>127,347</td>
<td>382,003</td>
<td>509,350</td>
</tr>
<tr>
<td>Europe</td>
<td>478,261</td>
<td>478,261</td>
<td>8,575,806</td>
<td>15,337,244</td>
<td>23,913,050</td>
</tr>
<tr>
<td>Japan</td>
<td>1,550,784</td>
<td>1,550,784</td>
<td>20,316,452</td>
<td>57,222,748</td>
<td>77,539,200</td>
</tr>
<tr>
<td>ROW</td>
<td>166,274</td>
<td>166,274</td>
<td>2,377,233</td>
<td>5,936,467</td>
<td>8,313,700</td>
</tr>
</tbody>
</table>

#### LIQUID CULTURE TUBES

<table>
<thead>
<tr>
<th>Region</th>
<th>Requests</th>
<th>Units</th>
<th>Test kit sales (US$)</th>
<th>Labour (US$)</th>
<th>Total (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>2,101,098</td>
<td>2,101,098</td>
<td>9,454,942</td>
<td>56,400,473</td>
<td>65,855,415</td>
</tr>
<tr>
<td>Australia/NZ</td>
<td>381,658</td>
<td>381,658</td>
<td>1,776,462</td>
<td>10,244,972</td>
<td>11,962,344</td>
</tr>
<tr>
<td>Europe</td>
<td>2,324,585</td>
<td>2,324,585</td>
<td>9,805,918</td>
<td>63,054,325</td>
<td>72,860,243</td>
</tr>
<tr>
<td>Japan</td>
<td>394,708</td>
<td>394,708</td>
<td>1,776,187</td>
<td>10,595,277</td>
<td>12,371,464</td>
</tr>
<tr>
<td>ROW</td>
<td>1,499,157</td>
<td>1,499,157</td>
<td>7,753,583</td>
<td>39,234,995</td>
<td>46,988,578</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>6,701,207</td>
<td>6,701,207</td>
<td>30,508,094</td>
<td>179,530,041</td>
<td>210,038,135</td>
</tr>
</tbody>
</table>

#### Other

- Based on reports from 15 companies, test volumes of other commercial kits, including phage-based and serological assays, range from 3,000 to 300,000 tests sold annually.

---

a. We assume 50% product wastage, therefore, requests equal one-half of units sold; 1 unit is equivalent to 1 test dose.

b. Based on a mixture of the manufacturer’s transfer price to the distributors and sales to the end-user.

c. Labour costs for commercial test kits = average reimbursement fee [US (Texas Medicaid), Germany (Official Private Fee Schedule) and Japan (public sector)] - average manufacturer sale per test kit/dose. Two exceptions: i) labour costs for Mantoux testing in Japan are based on the Japanese reimbursement fee schedule; ii) labour costs for Mantoux testing in the ROW are 10% of the average reimbursement fee - average manufacturer sale per test dose.
The vast majority of TB testing performed in the developing world uses methods not distributed as commercial kits, as reflected in Table 5. 94% of microscopy, 55% of solid culture, 82% of chest radiography, and 68% of conventional DST are performed in middle- and low-income countries, primarily in the public sector. Despite the relatively weak penetration of commercial culture and NAT kits into developing countries, these areas still represent a market of over US$ 16 million per annum.

The volume of testing done in high-burden countries is tremendous, with over 66 million microscopy examinations, 8.5 million cultures, and 39 million chest X-rays performed for evaluation of tuberculosis suspects. Three countries account for the 91% of TB cultures performed in the high-burden countries - the Russian Federation (6.5 million), India (0.8 million) and South Africa (0.6M). After smear microscopy, chest radiography is the most frequently employed diagnostic test for TB. Endemic countries in Asia account for 68% of the global chest X-ray market for TB. While the vast majority of microscopy examinations are performed in public sector facilities, there is a large private sector, particularly in Asia, where a substantial fraction of TB culture and chest radiography is performed.
TABLE 5. NON-COMMERCIAL TEST MARKET FOR DETECTION OF ACTIVE TB, BY REGION OF SALE AND HEALTH SECTOR

<table>
<thead>
<tr>
<th></th>
<th>Requests</th>
<th>Units</th>
<th>Disposables (US$)</th>
<th>Labour (US$)</th>
<th>Total (US$)</th>
<th>Average cost per request</th>
<th>% public sector</th>
</tr>
</thead>
<tbody>
<tr>
<td>High income</td>
<td>5,036,334</td>
<td>5,036,334</td>
<td>54,551,644</td>
<td>30,868,675</td>
<td>35,420,319</td>
<td>7.03</td>
<td>NA</td>
</tr>
<tr>
<td>Endemic Asia</td>
<td>43,101,861</td>
<td>43,101,861</td>
<td>42,296,184</td>
<td>11,977,625</td>
<td>54,273,809</td>
<td>1.26</td>
<td>66.4%</td>
</tr>
<tr>
<td>Endemic Africa</td>
<td>5,708,821</td>
<td>5,708,821</td>
<td>55,723,700</td>
<td>3,954,346</td>
<td>96,678,046</td>
<td>1.70</td>
<td>80.1%</td>
</tr>
<tr>
<td>Russian Federation and Brazil</td>
<td>17,009,878</td>
<td>17,009,878</td>
<td>15,801,249</td>
<td>11,418,135</td>
<td>27,219,383</td>
<td>1.60</td>
<td>93.5%</td>
</tr>
<tr>
<td>ROW</td>
<td>17,117,161</td>
<td>17,117,161</td>
<td>15,190,076</td>
<td>13,910,471</td>
<td>29,100,547</td>
<td>1.70</td>
<td>67.0%</td>
</tr>
<tr>
<td>Total</td>
<td>87,974,055</td>
<td>87,974,055</td>
<td>83,562,853</td>
<td>72,129,252</td>
<td>155,692,105</td>
<td>1.77</td>
<td>69.9%</td>
</tr>
</tbody>
</table>

**CULTURE**

<table>
<thead>
<tr>
<th></th>
<th>Requests</th>
<th>Units</th>
<th>Disposables (US$)</th>
<th>Labour (US$)</th>
<th>Total (US$)</th>
<th>Average cost per request</th>
<th>% public sector</th>
</tr>
</thead>
<tbody>
<tr>
<td>High income</td>
<td>5,107,879</td>
<td>10,309,928</td>
<td>27,862,388</td>
<td>140,295,047</td>
<td>168,157,435</td>
<td>32.92</td>
<td>NA</td>
</tr>
<tr>
<td>Endemic Asia</td>
<td>33,895,556</td>
<td>33,895,556</td>
<td>50,279,203</td>
<td>23,735,830</td>
<td>74,015,032</td>
<td>2.18</td>
<td>52.5%</td>
</tr>
<tr>
<td>Endemic Africa</td>
<td>2,821,267</td>
<td>2,821,267</td>
<td>4,312,063</td>
<td>5,586,682</td>
<td>9,989,745</td>
<td>3.51</td>
<td>63.0%</td>
</tr>
<tr>
<td>Russian Federation and Brazil</td>
<td>2,065,829</td>
<td>2,065,829</td>
<td>2,812,230</td>
<td>3,910,990</td>
<td>6,723,220</td>
<td>3.25</td>
<td>93.3%</td>
</tr>
<tr>
<td>ROW</td>
<td>3,334,964</td>
<td>4,668,949</td>
<td>57,297,416</td>
<td>9,122,438</td>
<td>16,419,854</td>
<td>4.92</td>
<td>93.7%</td>
</tr>
<tr>
<td>Total</td>
<td>17,032,059</td>
<td>26,909,610</td>
<td>56,568,089</td>
<td>166,827,373</td>
<td>223,395,462</td>
<td>13.12</td>
<td>90.5%</td>
</tr>
</tbody>
</table>

**X-RAY**

<table>
<thead>
<tr>
<th></th>
<th>Requests</th>
<th>Units</th>
<th>Disposables (US$)</th>
<th>Labour (US$)</th>
<th>Total (US$)</th>
<th>Average cost per request</th>
<th>% public sector</th>
</tr>
</thead>
<tbody>
<tr>
<td>High income</td>
<td>2,988,084</td>
<td>2,988,084</td>
<td>4,118,022</td>
<td>44,330,555</td>
<td>48,448,577</td>
<td>16.21</td>
<td>NA</td>
</tr>
<tr>
<td>Endemic Asia</td>
<td>33,895,556</td>
<td>33,895,556</td>
<td>50,279,203</td>
<td>23,735,830</td>
<td>74,015,032</td>
<td>2.18</td>
<td>52.5%</td>
</tr>
<tr>
<td>Endemic Africa</td>
<td>2,821,267</td>
<td>2,821,267</td>
<td>4,312,063</td>
<td>5,586,682</td>
<td>9,989,745</td>
<td>3.51</td>
<td>63.0%</td>
</tr>
<tr>
<td>Russian Federation and Brazil</td>
<td>2,065,829</td>
<td>2,065,829</td>
<td>2,812,230</td>
<td>3,910,990</td>
<td>6,723,220</td>
<td>3.25</td>
<td>93.3%</td>
</tr>
<tr>
<td>ROW</td>
<td>8,382,076</td>
<td>8,382,076</td>
<td>11,447,590</td>
<td>17,019,749</td>
<td>28,467,339</td>
<td>3.40</td>
<td>69.9%</td>
</tr>
<tr>
<td>Total</td>
<td>50,152,812</td>
<td>50,152,812</td>
<td>72,969,108</td>
<td>94,583,805</td>
<td>167,552,914</td>
<td>3.34</td>
<td>59.9%</td>
</tr>
</tbody>
</table>

**DST**

<table>
<thead>
<tr>
<th></th>
<th>Requests</th>
<th>Units</th>
<th>Disposables (US$)</th>
<th>Labour (US$)</th>
<th>Total (US$)</th>
<th>Average cost per request</th>
<th>% public sector</th>
</tr>
</thead>
<tbody>
<tr>
<td>High income</td>
<td>125,708</td>
<td>1,005,667</td>
<td>2,159,927</td>
<td>2,666,181</td>
<td>4,806,108</td>
<td>38.23</td>
<td>100.0%</td>
</tr>
<tr>
<td>Endemic Asia</td>
<td>135,467</td>
<td>1,083,735</td>
<td>568,749</td>
<td>188,574</td>
<td>757,323</td>
<td>5.59</td>
<td>79.7%</td>
</tr>
<tr>
<td>Endemic Africa</td>
<td>54,134</td>
<td>433,071</td>
<td>234,302</td>
<td>420,838</td>
<td>655,140</td>
<td>12.10</td>
<td>93.2%</td>
</tr>
<tr>
<td>Russian Federation and Brazil</td>
<td>322,689</td>
<td>2,581,583</td>
<td>1,297,565</td>
<td>1,162,950</td>
<td>2,460,515</td>
<td>7.62</td>
<td>97.8%</td>
</tr>
<tr>
<td>ROW</td>
<td>118,527</td>
<td>948,214</td>
<td>426,896</td>
<td>520,843</td>
<td>947,739</td>
<td>8.00</td>
<td>97.4%</td>
</tr>
<tr>
<td>Total</td>
<td>756,534</td>
<td>6,052,271</td>
<td>4,687,439</td>
<td>4,939,386</td>
<td>9,626,825</td>
<td>12.72</td>
<td>94.4%</td>
</tr>
</tbody>
</table>

| Overall total  | 155,915,461| 120,935,936| 144,918,381       | 338,479,816  | 556,267,305| 12.72                    | 94.4%           |

**Notes:**
- **ROA**: Afghanistan, Bangladesh, Cambodia, China, India, Myanmar, Pakistan, Philippines, Thailand, Viet Nam.
- **ROB**: DR Congo, Ethiopia, Kenya, Mozambique, Nigeria, South Africa, Uganda, UR Tanzania, Zimbabwe.
Conclusion

For the first time, a comprehensive analysis of the global market for TB diagnostics is now available. That market, at over US$ 1 billion, is large, over twice as large as the current market for TB drugs (8). In the developing world, where the vast majority of TB cases occur, and where most TB testing takes place, non-commercial test methods are most commonly used. This reflects, in part, the dominant role of the public sector in TB control in these countries, and its need to minimize cost and complexity of testing, and to follow international guidelines. There is nonetheless a significant private sector market in countries with a high volume of TB diagnostic testing, particularly in South-East Asia. Information on the amount of testing done in this segment of the market, including the volume of commercial test use, is the most difficult to assess.

The high volume of testing carried out in developing countries is a credit to the decades of effort at national and international levels to build infrastructure and ensure the provision of diagnostic services for patients with tuberculosis symptoms. The existence of that infrastructure will be critical to the introduction of newer, better technologies, and its emphasis on low cost and lack of sophisticated automation should inform their design. These topics are covered in detail in Chapters 4 and 5.
More on methods...

General approaches
The methods for determining test volume in the SAM depended upon the sourcing of the most accurate information regarding each test method. As described below, a “top down” approach was used for commercial test kits for which industry sales data were available. Conversely, a “bottom up” approach was used for testing with non-commercial methods in the public sector when data on actual testing volume could be determined from direct contact with national laboratories worldwide. A “middle out” approach was used, primarily for estimates of private sector testing with non-commercial methods, when direct information on testing volume was not available.

The primary sources of information were:
- WHO TB Laboratory Assessment Missions (Bangladesh, Kenya, Pakistan, Uganda)
- TDR Survey of TB diagnostic test prices, practices and physician preferences in Brazil, China, India, Indonesia, Uganda, Russian Federation, South Africa (6).
- Sales information provided by TB diagnostic test manufacturers, under a confidentiality agreement with WHO/TDR

Top down
Data from manufacturers
Over 60 manufacturers of TB diagnostic tests falling into the following 4 categories were contacted for information. These companies, primarily mid-sized to large companies and market leaders, kindly provided data regarding sales (number of test units, in United States dollar value and regional distribution) over a 3-year period (2001-2003). All the major manufacturers agreed to provide data.

Testing indications are in brackets.

1. Purified protein derivative (PPD) [LTBI]
2. Nucleic acid testing (NAT) [case detection]
3. Liquid culture [case detection, DST, and treatment monitoring]
4. Other: serological and phage assays [case detection]
Middle out

To determine the number of non-commercial tests performed in the private sector, and the number of X-rays done in the public sector, two sets of data were collated.

Survey of diagnostic practices

216 public and private practicing physicians and TB experts were interviewed in 7 countries (Brazil, China, India, Indonesia, Russian Federation, South Africa and Uganda) regarding their TB diagnostic test practices. Responses were used to model test usage in the private sector population for smear microscopy, chest radiography (X-ray), mycobacterial culture and drug susceptibility testing (DST) and in the public sector for X-ray. Test practices and preferences were extrapolated to other countries in the same region of similar economic status.

Distribution of testing in the public and private health sectors

The size of the populations accessing TB diagnostic services in the public versus private sectors was derived from WHO surveillance estimates of incident TB cases, the fraction of cases notified by the public sector, and estimates of the number of untreated (and undetected) TB cases. The public sector pool was comprised of all case notifications to public health authorities and a portion of cases detected but not notified (not reported to public health authorities). The magnitude of the underreporting problem in the public sector was estimated to be inversely proportional to the case detection rate. Therefore, if the national case detection rate is <75%, 66–75%, 56–65%, 46–55%, 36–45%, 26–35%, 16–25%, <16%, then the predicted underreporting is 0, 2.5%, 5%, 10%, 15%, 20%, 25%, 30%, respectively.

We estimated the number of cases detected in the private sector as the difference between all estimated treated/detected cases minus the cases that are treated/detected in the public sector. A few country estimates were then adjusted to reflect knowledge of the private sector utilization from specific studies (9) or based on personal communication. The ratio of suspects to cases was assumed to be equivalent in the public and private sectors.

It is well known that before and after a diagnosis of tuberculosis, patients crossover between public and private health sectors and may undergo repeat testing (10, 11). This analysis assumed no crossover between public and private sectors and therefore estimates are conservative.

---

m Estimates provided by C Watt, Epidemiologist, WHO Tuberculosis Monitoring and Evaluation Unit.
**Bottom up**

Estimates of test usage, including smear microscopy, non-commercial mycobacterial culture (solid media) and DST, were based on one of three levels of evidence, in descending priority.

1. Direct information on the number of tests performed, based on survey responses from 116 countries accounting for 99% of the global TB burden.

2. The estimated number of suspects being tested based on the incidence of tuberculosis per country and the expected ratio of smear tests performed per case detected, as obtained from large population-based studies and laboratory record surveys (12, 16).\(^1\)

3. Regression equations were used to estimate the volume of testing in countries for which information was missing, based on data from countries with similar epidemiology and testing patterns. In exceptional circumstances, the regional average or regression prediction for a specific country was overridden because alternative reliable data sources, including the number of testing facilities, test volumes from regional laboratories and expert opinion, clearly indicated that the calculated value was grossly overestimating or underestimating the testing volume.

Global totals are based on data from 181 countries representing 99.6% of the global TB burden.

Of the approaches described above, the methodology applied to determine the served available market for each test type in each segment is represented in tabular form below.

**TABLE 6: SUMMARY OF TB DIAGNOSTIC MARKET SIZING APPROACHES**

<table>
<thead>
<tr>
<th>Private sector</th>
<th>Public sector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear</td>
<td>B</td>
</tr>
<tr>
<td>Commercial liquid culture</td>
<td>A</td>
</tr>
<tr>
<td>Non commercial culture</td>
<td>B</td>
</tr>
<tr>
<td>NAT</td>
<td>A</td>
</tr>
<tr>
<td>Other</td>
<td>A</td>
</tr>
<tr>
<td>X-ray</td>
<td>B</td>
</tr>
<tr>
<td>DST (non commercial)</td>
<td>B</td>
</tr>
<tr>
<td>PPD</td>
<td>A</td>
</tr>
</tbody>
</table>

A – top down
B – middle out
C – bottom up

---

1. WHO mission reports for Bangladesh, Cambodia, Kenya and Pakistan.
2. WHO Adult Lung Health Initiative studies of case management in primary health facilities for Côte d’Ivoire, Guinee, Morocco, Nepal and Thailand.
3. National disease control programme data from China, India, Indonesia, Myanmar, Philippines and Viet Nam.
4. Personal correspondence with directors of representative laboratories in Australia, Canada, South Africa, Uganda and the United States.
Dollar value calculations

Disposable cost estimates of commercial test methods (PPD, liquid culture, NAT, and other), are based only on the cost of the pharmaceuticals, vials, or test kits. The price is based on a mixture of the manufacturer’s transfer price to the distributors, and sales to the end-user. The former is likely to be substantially lower (20–50%) than the cost to the end-user. Labour costs for commercial test kits are calculated as the average reimbursement fee (US (Texas Medicaid), Germany (Official Private Fee Schedule) and Japan (public sector)) – average manufacturer sale per test kit. Two exceptions include:

i. labour costs for PPD skin testing in Japan are based on the Japanese reimbursement fee schedule.

ii. labour costs for PPD skin testing in ROW are calculated as 10% of the (average reimbursement fee - average manufacturer sale per test dose).

Other costs associated with performing the test have not been included in the estimates.

For non-commercial testing methods (smear microscopy, chest radiography), we used the Essential Healthcare Technology Planning (EHTP) method (17) of WHO, and for culture and drug susceptibility testing, data was extrapolated from a TDR-sponsored economic cost analysis of drug susceptibility method in Lima, Peru (18). To adjust correctly for culture and DST media costs, we assumed that high income countries purchased ready-made media, and that middle and low income countries prepared media from raw materials. In all cases, it is assumed that supplies for non-commercial tests are purchased on the international market and labour costs are based on WHO-CHOICE (Choosing interventions that are cost-effective) which reports the costs and effects of a wide range of health interventions.

Retail pricing is based on survey data from a TDR sponsored study of TB diagnostic test prices, practices and physician preferences in 7 high-burden countries (6).

Detailed methods and key assumptions for volume calculations

The basic methods and key assumptions that underlie estimates of volume estimates in the SAM are described on a test-by-test basis below.

Smear microscopy

Test unit estimates were based on four tiers of evidence, in order of descending preference.

1. TDR global survey of TB laboratory services: national volume of smears performed. Includes public sector and private sector laboratory testing in established market economies. For all other countries, these data applied to public sector laboratories only. It was assumed 75% of total smears were performed for diagnosis and 25% for monitoring of treatment (16).

2. Ratio of the number of TB suspects (or 33–50% of smears examined) to the number of TB cases multiplied by the predicted incidence. The ratios were derived from large population-based surveys in developing countries or high volume laboratory surveys in developed countries. We assumed 2 smears per suspect in developing countries, 3 smears per suspect in developed countries, and 4 smears per suspect in the Russian Federation.

---

1 Costs of enrichment, antibiotic supplements and species identification not included in cost of liquid culture vials.

2 Vendors on the international market include non-governmental organization suppliers, and therefore may not reflect prices from manufacturers or commercial distributors.

3 http://www.who.int/choice/en/
3. Using the laboratory survey data on the number of smears performed provided by 85 countries, we extrapolated values for smears performed in countries where we did not receive survey responses. The extrapolation was based on factors correlated with the number of smears performed in a country (e.g., number of laboratory facilities, economic status, health conditions, DOTS coverage and TB incidence). The analysis technique was regression.¹

4. Usage predictions were modelled on physician diagnostic practices as determined in a physician survey (6). Physicians in 7 countries were asked how often they used various diagnostic tests to investigate TB suspects. The allowed responses were never, rarely, sometimes, frequently and always. We translated these qualitative responses into percentages as shown below:

<table>
<thead>
<tr>
<th>Response</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>0</td>
</tr>
<tr>
<td>Rarely</td>
<td>.25</td>
</tr>
<tr>
<td>Sometimes</td>
<td>.5</td>
</tr>
<tr>
<td>Frequently</td>
<td>.75</td>
</tr>
<tr>
<td>Always</td>
<td>1.00</td>
</tr>
</tbody>
</table>

The values for responses to each of the questions were then averaged. The handling of extrapulmonary TB suspects was divided into the following 3 proportions: lymph node TB (0.5), pleural TB (0.4) and meningeal TB (0.1).

These figures were adjusted for strength of infrastructure as represented by gross national income (estimated total number of sputum smears = predicted number from survey of physician practices x GNI/1200).

**Non-commercial culture**

The volume of non commercial culture (solid media) is expressed as the number of test units (or inoculated culture vials) which is equivalent to 1.4 times the number of requests in all countries except in high-income countries. In the latter case, it is assumed that 1 request comprises 1 solid media vial (non-commercial) and 1 liquid culture vial (commercial). Test unit estimates for non-commercial culture were based on four tiers of evidence in order of descending preference.

For the private sector:

1. TDR global survey of TB laboratory services: national volume of cultures performed. Includes public sector and private sector laboratory volumes in established market economies. For all other countries, this data applied to public sector laboratories only.

2. In low-income and middle-income countries, the number of cultures is estimated as the ratio of the number of public sector cultures to he number of public sector DST multiplied by the number of DSTs done in the public sector (5).

3. In high-income countries it is assumed that the number of cultures is equal to the number of smear microscopy examinations.

4. In 17 European countries the estimate was based on special information provided by EuroTB survey reports (4).

¹The regression equation used the provided number of sputum smear examinations performed per smear-positive case notified as the dependent variable. The independent variables were the percent of the country covered by DOTS, the inverse of national TB incidence, the economic status of the country, and the regional dummy variables. The regression equation explained about 50 percent of the variance in the observed number of smears examined per notified smear positive case detected.
For the private sector:

The number of cultures is equal to the sum of the cultures done in the private sector for pulmonary TB and extrapulmonary TB. The number of cultures done for pulmonary TB in the private sector is equal to:

1. Zero if the country reported that no private labs performed cultures.
2. The number of smears for diagnosis for pulmonary TB in the private sector, times the ratio of cultures to smears for pulmonary TB, divided by the number of smears per suspect (5). If the gross national income (GNI) of a country was less than US$ 2400, the number derived with the equation above was multiplied by the GNI of the country divided by 2400.

The number of cultures done for extrapulmonary TB in the private sector is equal to:

1. Zero, if the country reported that no private laboratories performed culture.
2. The number of smears for diagnosis for extrapulmonary TB (EPTB) in the private sector, times the ratio of cultures to smears for extrapulmonary TB, (5, 18) divided by the number of smears per suspect. If the GNI of a country was less than US$ 2400, the number derived with the equation above was multiplied by the GNI of the country divided by 2400.

Commercial liquid culture

Test unit estimates were based on industry survey reports of the average number of units sold over a 3-year period (2001–2003 or 2002–2004).

Drug susceptibility testing (non-commercial methods only)

Non-commercial DST volumes were expressed as the number of testing units (or inoculated tubes), which is based on the economic variation of the proportion method (19) and is equivalent to 8 tubes (2 drugs) or 12 tubes (4 drugs) times the total number of requests. Volume estimates were based on four tiers of evidence, in order of descending preference.

For the private sector:

1. WHO/TDR global survey of TB laboratory services: national volumes of DST performed. This includes both public sector and private sector laboratory volumes in established market economies. For all other countries, these data applied to public sector laboratories only.
2. In low-income and middle-income countries, the number of DSTs performed was assumed to be equal to the number of retreatment cases treated each year multiplied by regional estimates of the frequency of drug-susceptibility testing in re-treatment (3–5).
3. In high-income countries, the number of DSTs is estimated as the sum of the following elements:
   i. 0.85 times the number of smear-positive cases plus
   ii. 0.7 times the number of smear-negative cases plus
   iii. 0.4 times the number of EPTB cases
For the private sector:

The number of DSTs performed in the private sector was assumed to be equal to the sum of the volume of DST for pulmonary TB and extrapulmonary TB. Using data from the physician survey, the number of DST for pulmonary TB was calculated as the number of pulmonary TB cases in the private sector multiplied by the percent of pulmonary TB suspects evaluated with culture (6) multiplied by the percentage of pulmonary TB patients with positive cultures evaluated with DST (6). Similarly, the number of DST for extrapulmonary TB in the private sector was calculated as the number of extrapulmonary TB cases in the private sector multiplied by the percentage of extrapulmonary TB suspects evaluated with culture (6) multiplied by the percentage of culture-positive extrapulmonary TB patients that are evaluated with DST (6).

**Chest radiography (X-ray)**

Estimated volume of chest X-rays was modelled on physician diagnostic practices from the physician survey (6). These figures were adjusted for strength of infrastructure as represented by gross national income (total chest X-rays = estimated number of chest X-rays x GNI/600).

**Molecular testing**

The estimated volume of test units used was based on industry survey reports of the average number of units sold over a 3-year period (2001–2003 or 2002–2004).

**Skin testing with purified protein derivative (PPD)**

Volume of test units used were based on industry survey reports of the average number of doses sold over 3-year period (2001–2003 or 2002–2004). If tuberculin units (TU) were provided, these were converted to doses based on manufacturers’ recommendations (i.e. 1 dose = 2TU or 5TU). For consistency, it was assumed that 1 dose = 1 test unit. We assumed 50% product wastage; therefore, the total number of requests equals one-half of units sold.

**Other**

Test unit estimates based on industry survey reports of average number of tests sold over a 3-year period (2001–2003 or 2002–2004). Due to poor response from manufacturers, it was not possible to generate a credible global estimate, therefore a range of average units sold is presented.
Summary

For the majority of people living in countries where tuberculosis (TB) is endemic, diagnostic services are limited and the existing technologies are poorly adapted for the task. More than one type of new diagnostic test is needed to assist in TB care and control. This chapter describes the priority indications for new diagnostic tests and customer requirements from the perspective of different stakeholders, and ultimately presents a set of sample product specifications. The technical, financial and logistical challenges and opportunities for TB diagnostic development are addressed and the evolving field of public–private collaborations for product development is described.

Significance of current test limitations

As amply demonstrated in the previous chapter, for the majority of people living in countries where tuberculosis is endemic, diagnostic services are limited and the existing technologies are poorly adapted for the task.

The majority of high-burden countries are currently detecting and notifying just over 40% of the estimated number of newly arising smear-positive cases each year, a fraction that is rising relatively slowly despite impressive progress in the expansion of DOTS (directly observed therapy short-course) programmes, the disease control strategy recommended by the WHO (1). Globally, TB control efforts are still falling short of the WHO target of detecting 70% of all new smear-positive cases.

Furthermore, this case detection target is based on the available technology, and does not address the majority of TB patients, those who have pulmonary disease that is not advanced enough to be detected by microscopy or who have disease outside the lung (extrapulmonary tuberculosis).

Unfortunately, HIV coinfection, the single greatest factor influencing susceptibility to disease, disproportionately increases smear-negative and extrapulmonary disease, further eroding the utility of sputum microscopy (2, 3).

Priority indications for new TB diagnostics

More than one type of diagnostic test is needed to assist in TB care and control. The primary need is for either confirmatory or screening tests to distinguish active pulmonary (and extrapulmonary) tuberculosis from all of the other conditions that may cause the same symptoms. Also needed are tests to monitor treatment response in TB patients, to determine whether there is bacterial resistance to specific drugs, and to detect latent infection in people at greatest risk for progression to active TB following exposure. These five test types, described in Table 1, may have different formats, and will be used in entirely different populations.
The diagnostic priorities for tuberculosis control, which concentrate on the needs as defined by the countries with the highest burden of tuberculosis, are summarized in Table 2. The order of these priorities is based on (a) the number of individuals that would directly benefit by an improved tool, (b) the importance of specific populations (such as smear-positive patients) to disease control efforts, and (c) the degree of medical benefit that new technologies could offer over existing tools. For example, detection of pulmonary disease, which makes up some 80% of all cases, gets the highest priority. Extrapulmonary and paediatric tuberculosis, though less common, are both lethal and especially difficult to diagnose using the technologies currently available in disease-endemic countries, and are therefore ranked third in the list of diagnostic priorities.

Similarly, the need for improved drug-susceptibility testing (DST) methods, which could be used to direct drug therapy (using more expensive and more toxic second-line drugs for multidrug-resistant cases), is ranked above the need for DST surveillance tools, not because the latter application is not important, but because existing DST technologies, although slow, are generally adequate for this purpose.

### Table 1. TB Diagnostic Test Indications

<table>
<thead>
<tr>
<th>Test Indication</th>
<th>Condition or Event</th>
<th>Test Population</th>
<th>Prevalence of Target</th>
<th>Currently Available Tests</th>
<th>Target of Current Dominant Methodologies</th>
<th>Clinical Decision Informed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of active tuberculosis</td>
<td>Tuberculosis</td>
<td>Symptomatic individuals</td>
<td>1–30%</td>
<td>Sputum microscopy; culture; NAAT; serology; phage</td>
<td>Whole bacteria or bacterial fragments</td>
<td>Whether to start treatment</td>
</tr>
<tr>
<td>Screening for active disease</td>
<td>Tuberculosis</td>
<td>Symptomatic individuals</td>
<td>1–30%</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Referral for specific test to determine treatment need</td>
</tr>
<tr>
<td>Treatment monitoring</td>
<td>Response to therapy</td>
<td>TB patients</td>
<td>100%</td>
<td>Sputum microscopy</td>
<td>Whole bacteria</td>
<td>When to stop or alter treatment</td>
</tr>
<tr>
<td>Drug-susceptibility testing</td>
<td>Drug resistance</td>
<td>TB patients</td>
<td>1–75%</td>
<td>Culture; phage; NAAT</td>
<td>Live bacteria or bacterial DNA</td>
<td>Which treatment to select</td>
</tr>
<tr>
<td>Exposure screening</td>
<td>Latent infection</td>
<td>Healthy exposed individuals</td>
<td>1–80%</td>
<td>PPD skin test; cytokine assays for immune response</td>
<td>Cellular immune responses</td>
<td>When to offer preventive therapy</td>
</tr>
</tbody>
</table>

NAAT = nucleic acid amplification test; PPD = purified protein derivative.
The scale of the problem and the size of the target populations for tests to detect disease and drug resistance are reflected in Table 2. Detecting active tuberculosis, the highest priority, means differentiating the nearly 9 million new cases of TB from over 10 times that many individuals who have similar symptoms to those of active TB but of a different cause (1). For simplicity, these calculations are generally based on the annual number of incident (i.e. new) cases, and not the number of prevalent (i.e. new and pre-existing) cases, although clinics will obviously see a mixture of both types. The number of prevalent cases, which includes those already diagnosed and currently on therapy, those with chronic untreatable disease, and those with undetected disease, may be twice as large as the number of incident cases.

**Customer requirements**

Although the call for better TB diagnostics is decades old, product specifications and priorities have only recently been established. In a 1996 WHO consultation with industry, companies pointed to the lack of clear customer requirements for test performance as one of the important obstacles to focused commercial development efforts. In 1997, the WHO convened a group of experts to develop target test specifications. These specifications were published in a report that was circulated to interested commercial developers and posted on TDR’s website (4). The target product profiles, or customer requirements, for different TB diagnostic applications have since been defined through a series of more sophisticated approaches, including field studies examining the causes of missed or delayed diagnosis in TB-endemic countries. To some degree, customer requirements depend on the specific customer. Public-sector agencies, for example, may value cost or accuracy over speed. Private physicians and individual patients may, on the other hand, place greater value on convenience features. This variation in preferences, which may be geographic as well, is illustrated in the conjoint analysis included in Chapter 5.

**TABLE 2. TB DIAGNOSTIC PRIORITIES**

<table>
<thead>
<tr>
<th>PURPOSE</th>
<th>PRIORITY TEST INDICATIONS</th>
<th>TEST INDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of active tuberculosis</td>
<td>1. Detect pulmonary TB with high bacterial load (ss+)</td>
<td>100–200 million</td>
</tr>
<tr>
<td></td>
<td>2. Detect pulmonary TB with low bacterial load (ss-, Cx+)</td>
<td>100–200 million</td>
</tr>
<tr>
<td></td>
<td>3. Detect extrapulmonary and paediatric TB</td>
<td>5–50 million</td>
</tr>
<tr>
<td>Drug-susceptibility testing</td>
<td>4. Detect MDR-TB for treatment</td>
<td>10 million</td>
</tr>
<tr>
<td></td>
<td>5. Detect MDR-TB for surveillance</td>
<td>100 000</td>
</tr>
<tr>
<td>Latent TB infection</td>
<td>6. Detect LTBI for surveillance</td>
<td>unknown</td>
</tr>
<tr>
<td></td>
<td>7. Detect LTBI for treatment</td>
<td>test-dependent</td>
</tr>
<tr>
<td>Ancillary tests</td>
<td>8. Screening to rule out TB</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9. Monitoring response to treatment</td>
<td></td>
</tr>
</tbody>
</table>

ss+ = smear-positive; ss- = smear-negative; Cx+ = culture-positive; MDR-TB = multidrug-resistant tuberculosis; LTBI = latent tuberculosis infection.
The customer requirements for a specific indication will also depend largely on what infrastructure is available. In rural settings and smaller clinics, human and financial resource limitations render the implementation of sophisticated technologies impossible, even if they are otherwise attractive. These smaller clinics on the periphery of the health system are, however, where the vast majority of TB suspects initially seek care. Laboratory diagnostic services for TB in such settings are currently either nonexistent or are limited to microscopy. Thus, tests that offer the capability of point-of-care testing on the periphery of the health system would have the greatest impact and the largest potential market. In Chapter 5, urban versus rural habitation is used as a surrogate to estimate the degree of access to laboratory services, and thus the market size, for a range of hypothetical products, depending on their complexity of use.

In the public sector, the laboratory capacity to perform different types of testing can usefully be divided into levels of the health system, as depicted in Figure 1 below. In this idealized model, the national laboratory network serving the public sector is divided into four levels. At the top of the pyramid, the national reference laboratory (usually one per country) is responsible for supervision of the laboratory network, surveillance for drug resistance and provision of reference methods. Though such a laboratory may be relatively sophisticated and capable of implementing complex technologies, the number of such testing centres is low, and the fraction of all TB patients getting diagnosed at this level is very small. More numerous are TB referral laboratories at the regional or, sometimes, the district level. Ideally, such laboratories would provide resolution testing for patients not detected by screening methods at more peripheral clinics and laboratories, and for patients at risk for drug-resistant disease.

The current technology used for such resolution testing is mycobacterial culture. Unfortunately, as demonstrated in Chapter 3, culture capability in many countries with a high burden of tuberculosis is limited to one or two reference centres, and is not otherwise available. Below the level of the referral laboratory is the microscopy centre, where most sputum examinations are currently performed.

![Figure 1](image-url)
Although the sophistication of the health services infrastructure varies widely, not only from country to country, but also within a given country, peripheral health clinics, where most patients first seek care, generally have a very limited infrastructure and in many cases severely restricted human resources. For such settings, the term ASSURED has been coined to describe the ideal characteristics of a diagnostic test (Figure 2) (6).

Not all of these characteristics are equally weighted, nor may all be possible in a single test. In many cases, a sacrifice in performance that allows a test to be used as a point-of-care device will result in more patients being appropriately treated than a device of superior performance that requires laboratory infrastructure or necessitates a return clinic visit (7).

These general, somewhat idealized characteristics have been translated into customer requirements documents to guide the development of new diagnostic tests for tuberculosis. The two customer requirements documents below describe the requirements for tests to detect active tuberculosis in peripheral clinics or rural areas (Table 3) and for resolution testing in urban centres or at referral laboratories (Table 4).

![IDEAL CHARACTERISTICS OF A DIAGNOSTIC TEST](image)
Detection of active TB in rural area or peripheral health centre.

Primary intended use:
Detection of disease caused by M. tuberculosis. This is currently accomplished via sputum smear microscopy, which is relatively insensitive even for pulmonary disease, and (more rarely) via culture, which takes from four to six weeks to complete. The primary goal is to provide a test system that has the sensitivity and specificity equal to or better than microscopy, but that has a much reduced time to results. To be widely useful, the test must work properly regardless of the prevalence of HIV or other coinfection in the test population.

### TABLE 3. CUSTOMER REQUIREMENTS DOCUMENT FOR TEST TO REPLACE SPUTUM SMEAR MICROSCOPY

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>DESIRED</th>
<th>MINIMUM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Workflow</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1. Sample type</td>
<td>Sputum, skin, breath, urine</td>
<td>As under Desired plus blood or serum</td>
</tr>
<tr>
<td>1.2. Sample preparation</td>
<td>None</td>
<td>Simple 1-step or 2-step procedure &lt; 30 min</td>
</tr>
<tr>
<td>2. Time to results</td>
<td>&lt; 10 min</td>
<td>&lt; 1 week, if performance = culture</td>
</tr>
<tr>
<td>3. Instrumentation</td>
<td>None</td>
<td>None, or maintenance-free single device; only sample addition needed</td>
</tr>
<tr>
<td>4. Additional equipment required</td>
<td>None</td>
<td>Only robust equipment with minimal maintenance needs (&gt; 3 monthly). No balance, HEPA filter or equipment of similar complexity needed.</td>
</tr>
<tr>
<td>5. Biosafety</td>
<td>No need for biosafety cabinet Disposal without further treatment</td>
<td>No need for biosafety cabinet</td>
</tr>
<tr>
<td><strong>B. Performance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Diagnostic sensitivity&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt; 95% in smear-positive patients &gt; 60% in smear-negative patients</td>
<td>&gt; 90% in smear-positive patients &gt; 0% in smear-negative patients</td>
</tr>
<tr>
<td>2. Diagnostic specificity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&gt; 98%</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td><strong>C. Product design</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Stability/storage requirements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1. Kit stability</td>
<td>12 months storage at 35 °C, 70% humidity, incl. transport stress (48 h at 50 °C)</td>
<td>12 months storage at 4 °C, incl. transport stress (48 h at 50 °C)</td>
</tr>
<tr>
<td>1.2. Reconstituted reagents stability</td>
<td>Ready-to-use reagents, no reconstitution</td>
<td>8 h at 4 °C</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined in symptomatic adults with culture-confirmed TB, with and without HIV or parasitic coinfection.

<sup>b</sup> Determined in ill TB suspects confirmed not to have TB by negative cultures (X2) and negative microscopy (X2) and either by improvement on treatment other than for TB or confirmation of an alternative cause of symptoms. The cohort should include patients with a history of BCG-vaccination and TB exposure or some patients with prior cured TB.
Detection of active TB in urban area or referral laboratory.

Primary intended use: Detection of symptomatic cases of tuberculosis not identified during primary diagnostic testing at the clinic level (commonly smear-negative, paucibacillary or extrapulmonary cases). This is currently accomplished via culture, which is slow and cumbersome and results in low patient return rates, or by chest X-ray, which is relatively nonspecific. The goal is to provide a test system that has a sensitivity and specificity similar to those of culture, but with a much reduced time to results. To be widely useful, the test must work properly regardless of the prevalence of HIV or other coinfection in the test population.

### TABLE 3. CUSTOMER REQUIREMENTS DOCUMENT FOR TEST TO REPLACE SPUTUM SMEAR MICROSCOPY (continued)

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>DESIRED</th>
<th>MINIMUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Calibrators</td>
<td>Fixed cut-off</td>
<td>No more than 1 calibrator</td>
</tr>
<tr>
<td>3. Controls</td>
<td>Full-process positive and negative control</td>
<td>Positive control, negative control</td>
</tr>
<tr>
<td>4. Determinations per “reconstituted reagent unit”</td>
<td>Ready-to-use units, no reconstitution</td>
<td>Opened package lasts for 2 weeks</td>
</tr>
<tr>
<td>5. Results capturing and documentation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6. Instrument design</td>
<td>Option for battery operation</td>
<td>115/220 V AC operates at 35 °C</td>
</tr>
<tr>
<td></td>
<td>(if electricity is required). Instrument platform can be used also for testing of other relevant infections.</td>
<td></td>
</tr>
<tr>
<td>7. Training and education needs</td>
<td>&lt; 1 hour, nurse level</td>
<td>&lt; 2 days, high school education</td>
</tr>
</tbody>
</table>

Source: reference 5.

### TABLE 4. CUSTOMER REQUIREMENTS DOCUMENT FOR TEST TO REPLACE CULTURE

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>DESIRED</th>
<th>MINIMUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Workflow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1. Sample type</td>
<td>Sputum, urine, blood, pleural fluid, CSF, etc.</td>
<td>Sputum or alternative</td>
</tr>
<tr>
<td>1.2. Sample preparation</td>
<td>1-step procedures &lt; 1/2 h</td>
<td>Comparable to NaOH + centrifugation</td>
</tr>
<tr>
<td>2. Time to results, including sample preparation</td>
<td>&lt; 6 h</td>
<td>&lt; 1 week, if performance = culture</td>
</tr>
</tbody>
</table>
### TABLE 4. CUSTOMER REQUIREMENTS DOCUMENT FOR TEST TO REPLACE CULTURE (continued)

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>DESIRED</th>
<th>MINIMUM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3. Instrumentation needs</strong></td>
<td>Single device, only sample input</td>
<td>Comparable to solid culture</td>
</tr>
<tr>
<td><strong>4. Biosafety</strong></td>
<td>No need for biosafety cabinet. Processing (if required) should disinfect sample. No open handling of cultured infectious material.</td>
<td>Comparable to present solid culture methods. No handling of open tubes with enriched/infected material.</td>
</tr>
<tr>
<td><strong>B. Performance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1. Sensitivity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1. Diagnostic sensitivity&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt; 95% in smear-positive patients</td>
<td>&gt; 90% in smear-positive patients</td>
</tr>
<tr>
<td></td>
<td>&gt; 85% in smear-negative patients</td>
<td>&gt; 50% in smear-negative patients</td>
</tr>
<tr>
<td><strong>2. Specificity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.1. Diagnostic specificity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&gt; 98%</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td><strong>C. Product design</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1. Stability/storage requirements</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1. Kit stability</td>
<td>12 months storage at 35 °C, 70% humidity, incl. transport stress (48 h at 50 °C)</td>
<td>12 months storage at 4 °C, incl. transport stress (48 h at 50 °C)</td>
</tr>
<tr>
<td>1.2. Reconstituted reagents stability</td>
<td>Ready-to-use reagents, no reconstitution</td>
<td>8 h at 4 °C</td>
</tr>
<tr>
<td><strong>2. Calibrators</strong></td>
<td>Fixed cut-off</td>
<td>As required</td>
</tr>
<tr>
<td><strong>3. Controls</strong></td>
<td>Full-process internal positive and negative control</td>
<td>Positive control, negative control</td>
</tr>
<tr>
<td><strong>4. Determinations per “reconstituted reagent unit”</strong></td>
<td>Ready-to-use units, no reconstitution</td>
<td>For 25 patient samples/day x days of reconstituted reagent stability</td>
</tr>
<tr>
<td><strong>5. Results capturing and documentation</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>6. Instrument design</strong></td>
<td>Option for battery operation (if no electricity). Can test other parameters (e.g. HIV, STD, etc.)</td>
<td>115/220 V AC operates at 35 °C</td>
</tr>
<tr>
<td><strong>7. Training and education needs</strong></td>
<td>&lt; 1 day training time, nurse level</td>
<td>&lt; 1 week training, high school education</td>
</tr>
<tr>
<td><strong>D. Additional features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1. Resistance testing</strong></td>
<td>Simultaneous detection of rifampin resistance</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 5. CHARACTERISTICS OF 7 SAMPLE NEW PRODUCTS COMPARED WITH CURRENT TEST BENCHMARKS

<table>
<thead>
<tr>
<th>Dimension</th>
<th>SPUTUM MICROSCOPY</th>
<th>SPUTUM CULTURE</th>
<th>DRUG-SUSCEPTIBILITY TESTING</th>
<th>SCREENING TEST</th>
<th>MONITORING RX RESPONSE</th>
<th>TUBERCULIN SKIN TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intended use</td>
<td>Detect advanced, contagious TB</td>
<td>Detect early or extrapulmonary TB</td>
<td>Detect resistance to treatment</td>
<td>Rule out TB in suspects</td>
<td>Detect response to treatment</td>
<td>Detect asymptomatic, latent MTB infection</td>
</tr>
<tr>
<td>Specimen type</td>
<td>sputum</td>
<td>blood, urine, saliva, sputum, breath</td>
<td>culture isolate</td>
<td>sputum</td>
<td>blood, urine, saliva, sputum, breath</td>
<td>skin, blood</td>
</tr>
<tr>
<td>Specimen number</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>40–70% sputum; &lt;20% other</td>
<td>80–90%</td>
<td>90–95%</td>
<td>90%</td>
<td>95%</td>
<td>0–70%</td>
</tr>
<tr>
<td>Specificity</td>
<td>&gt; 95% culture</td>
<td>&gt; 95%</td>
<td>&gt; 95% (INH+RIF)</td>
<td>&gt; 95% (INH+RIF)</td>
<td>90–95%</td>
<td>&gt; 85%</td>
</tr>
<tr>
<td>Performance reduced in HIV+ cases</td>
<td>yes</td>
<td>yes/no</td>
<td>yes</td>
<td>yes/no</td>
<td>no</td>
<td>yes/no</td>
</tr>
<tr>
<td>Speed</td>
<td>2 hours–7 days</td>
<td>&lt; 3 hours</td>
<td>4 weeks</td>
<td>&lt; 7 days</td>
<td>8 weeks</td>
<td>2 days</td>
</tr>
<tr>
<td>Infrastructure needs</td>
<td>minimal use of microscope</td>
<td>simpler than microscopy</td>
<td>multi-step processing + incubation</td>
<td>minimal processing, electricity</td>
<td>as culture</td>
<td>as culture</td>
</tr>
<tr>
<td>Technician requirements</td>
<td>moderate</td>
<td>minor</td>
<td>moderate</td>
<td>minor</td>
<td>extensive</td>
<td>none</td>
</tr>
<tr>
<td>Stability</td>
<td>3 months–1 year</td>
<td>1–2 years at RT</td>
<td>3 months</td>
<td>1–2 years at 4°C</td>
<td>2 months</td>
<td>1 year</td>
</tr>
</tbody>
</table>

INH+RIF = isoniazid plus rifampicin; ELISA = enzyme-linked immunosorbent assay; RT = room temperature.

*Characteristics of a test for LTBI that has the capacity to predict future TB disease.*
Getting new products developed: challenges and opportunities

Traditionally, many of the health technologies used for diagnostics in the developing world, such as sputum smear microscopy and culture, were developed in publicly funded research institutes and disseminated as generic products, or rather, techniques. More recently, a burgeoning diagnostics and biotechnology industry has proved its capacity to develop and distribute sophisticated and reliable technologies that far outperform conventional methods. This shift from a public-sector, needs-driven model for technology development to a private-sector, market-driven model has resulted in a rapid rise in the range of diagnostic products available for major markets, but in a dearth of products for detection of diseases that are not prevalent in industrialized countries.

Despite the growth of the diagnostics industry, and the technical advances that underpin it, many diagnostic needs still go unmet, especially in developing countries. The markets of the United States, Europe and Japan account for the vast majority of in vitro diagnostics (IVD) sales. Given the distribution of the markets, the vast majority of diagnostic tests target needs and conditions prevalent in industrialized countries and are built on platforms developed to serve the sophisticated laboratories of developed countries. Many have limited relevance for most of the world’s population. For example, in the last decade, new tests have been developed for the rapid detection of uncommon genetic conditions or predispositions (e.g. cystic fibrosis and breast cancer), for continuous glucose monitoring in diabetes, and for the speciation and subspeciation of mycobacteria and other organisms. Many of these technologies have been adopted by clinical laboratories in industrialized countries and put to widespread use. At the same time, the vast majority of the world’s population continues to have access only to diagnostic methods developed decades and sometimes centuries ago.

This technology gap between developed and developing countries has been well described. More than US$ 70 billion is spent annually by public- and private-sector agencies on health-related research and development. It is estimated that only 10% of these funds goes toward researching health problems that cause 90% of global morbidity. Despite the existence of a sizeable, although poorly characterized, market for new diagnostics for TB, and the compelling need for better tests to support global disease control efforts, relatively few such tests have been developed recently. Most of these, especially molecular tests and automated culture systems, have been developed for markets in developed countries and are not readily implemented in resource-constrained settings. The primary reason given by diagnostics companies in 2001 for not developing broadly applicable tests for TB was lack of a readily apparent market for return on investment. Since that time, several large public-sector initiatives have emerged that have altered that picture. The Global Fund to Fight AIDS, Tuberculosis and Malaria has created public-sector markets where none previously existed. At the same time, the Foundation for Innovative New Diagnostics (FIND) has been launched, defraying R&D costs for test development and allowing new technologies to be harnessed for TB. The current business environment for developing TB diagnostics, further examined in Chapter 7, has never been more auspicious.

The launch at the 2006 Annual Meeting of the World Economic Forum in Davos, Switzerland of a US$ 50 billion plan prepared by the Stop TB Partnership to control tuberculosis globally and the declaration by Bill Gates at the same event that the Bill and Melinda Gates Foundation would triple its funding for TB-related tool development, spending US$ 900 million during the next 10 years, are symptomatic of this changed environment.

Technical considerations

Beyond the purely financial considerations, technical issues also contribute to the dearth of new test methods for TB. The dark cloud of these technical challenges, as well as the silver lining of associated opportunities, are outlined in Table 6.
Diagnostics for tuberculosis: global demand and market potential

Slow growth

The TB bacillus replicates approximately once every 24 hours, versus every 15 minutes for common bacteria. This makes mycobacterial culture, yielding results only after 4–8 weeks of incubation, impractical in many settings. Early disease, HIV coinfection and extrapulmonary disease further complicate detection. Bacilli are rarely found in blood or urine.

Biohazard risk

Aerosolized organisms, especially in high concentration in culture, pose a biohazard risk to laboratory workers. In many countries, regulations mandate high levels of biosafety in laboratories handling TB, driving up cost and staff training requirements. In the USA, multidrug-resistant \( M. tuberculosis \) has been named a Category C biological weapon, with implications for transport of TB culture isolates.

Many alternatives to whole cell detection with microscopy and/or culture may target bacterial products such as DNA and RNA or cellular antigens which may be present in tens to thousands of copies per cell.

Low bacterial number

The TB bacillus is present in low concentrations in most clinical samples. Roughly half of pulmonary TB patients have < 10,000 AFB/ml needed for detection with microscopy. Early disease, HIV coinfection and extrapulmonary disease further complicate detection. Bacilli are rarely found in blood or urine.

Biohazard risk

Aerosolized organisms, especially in high concentration in culture, pose a biohazard risk to laboratory workers. In many countries, regulations mandate high levels of biosafety in laboratories handling TB, driving up cost and staff training requirements. In the USA, multidrug-resistant \( M. tuberculosis \) has been named a Category C biological weapon, with implications for transport of TB culture isolates.

Much research and development work can be carried out using avirulent strains in the TB complex, such as H37Ra and M. bovis BCG (bacille Calmette-Guerin). Also, new regulations have reduced the complexity of international shipment of clinical specimens potentially containing TB.

Waxy cell wall

\( M. tuberculosis \) has a thick, waxy cell wall, which complicates the liberation and detection of nucleic acids (DNA and RNA) or other intracellular material.

The complex and highly antigenic TB cell wall contains abundant mycolic acids and a number of novel structures as potential targets.

Difficult test matrix

Sputum, the most common specimen, is inhomogeneous, difficult and sometimes dangerous to collect, disagreeable to handle and highly contaminated with other microbes and compounds that can interfere with test performance. Sample preparation, which is critical, usually relies on alkaline digestion, buffered wash and centrifugal concentration. These methods which kill most \( M. tuberculosis \) in the sample, are complex to perform and may not remove some inhibitors.

Most sputum processing R&D has supported culture methods, limiting the breadth of technical approaches used. For non-culture methods, a variety of alternative processing methods might be used that would be both simpler and more effective in liberating diagnostic targets (e.g. DNA, antigens).

### TABLE 6. TECHNICAL CHALLENGES TO AND OPPORTUNITIES FOR TB TEST DEVELOPMENT

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>TECHNICAL CHALLENGE</th>
<th>SILVER LINING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low bacterial number</td>
<td>The TB bacillus is present in low concentrations in most clinical samples. Roughly half of pulmonary TB patients have &lt; 10,000 AFB/ml needed for detection with microscopy. Early disease, HIV coinfection and extrapulmonary disease further complicate detection. Bacilli are rarely found in blood or urine.</td>
<td>Many alternatives to whole cell detection with microscopy and/or culture may target bacterial products such as DNA and RNA or cellular antigens which may be present in tens to thousands of copies per cell.</td>
</tr>
<tr>
<td>Biohazard risk</td>
<td>Aerosolized organisms, especially in high concentration in culture, pose a biohazard risk to laboratory workers. In many countries, regulations mandate high levels of biosafety in laboratories handling TB, driving up cost and staff training requirements. In the USA, multidrug-resistant ( M. tuberculosis ) has been named a Category C biological weapon, with implications for transport of TB culture isolates.</td>
<td>Much research and development work can be carried out using avirulent strains in the TB complex, such as H37Ra and M. bovis BCG (bacille Calmette-Guerin). Also, new regulations have reduced the complexity of international shipment of clinical specimens potentially containing TB.</td>
</tr>
<tr>
<td>Slow growth</td>
<td>The TB bacillus replicates approximately once every 24 hours, versus every 15 minutes for common bacteria. This makes mycobacterial culture, yielding results only after 4–8 weeks of incubation, impractical in many settings.</td>
<td>Mycobacterial culture, which is slow and complex, remains the reference standard. This sets a low threshold for tests to show improved performance.</td>
</tr>
<tr>
<td>Waxy cell wall</td>
<td>( M. tuberculosis ) has a thick, waxy cell wall, which complicates the liberation and detection of nucleic acids (DNA and RNA) or other intracellular material.</td>
<td>The complex and highly antigenic TB cell wall contains abundant mycolic acids and a number of novel structures as potential targets.</td>
</tr>
<tr>
<td>Difficult test matrix</td>
<td>Sputum, the most common specimen, is inhomogeneous, difficult and sometimes dangerous to collect, disagreeable to handle and highly contaminated with other microbes and compounds that can interfere with test performance. Sample preparation, which is critical, usually relies on alkaline digestion, buffered wash and centrifugal concentration. These methods which kill most ( M. tuberculosis ) in the sample, are complex to perform and may not remove some inhibitors.</td>
<td>Most sputum processing R&amp;D has supported culture methods, limiting the breadth of technical approaches used. For non-culture methods, a variety of alternative processing methods might be used that would be both simpler and more effective in liberating diagnostic targets (e.g. DNA, antigens).</td>
</tr>
</tbody>
</table>
Incomplete understanding of pathogen

The mechanisms of bacterial virulence, persistence and latency are largely unknown, and the complex interaction between infection and immunity is incompletely understood.

Most of the antigens evaluated as targets for immunodiagnostic tests are those present in culture filtrate, and the bulk of the TB proteome remains unexplored for diagnostics potential. The broad nature of the immune response may lead to tests which can discriminate between stages of disease.

Complex immune response

TB exposure is common in endemic areas, and in most individuals induces a strong immune response which abrogates development of disease. Assays that detect cellular or humoral immunity to TB must differentiate active disease from latent infection, BCG vaccination and exposure to environmental mycobacteria. HIV coinfection compromises the effectiveness of many immunologically related tests for TB.

The TB genome is now sequenced. The molecular mechanism of most drug resistance has been identified. Homologous recombination and other techniques have uncovered novel metabolic pathways and potential drug, vaccine and diagnostic targets.

Incomplete understanding of pathogen

The mechanisms of bacterial virulence, persistence and latency are largely unknown, and the complex interaction between infection and immunity is incompletely understood.

Most of the antigens evaluated as targets for immunodiagnostic tests are those present in culture filtrate, and the bulk of the TB proteome remains unexplored for diagnostics potential. The broad nature of the immune response may lead to tests which can discriminate between stages of disease.

Financial considerations

The modern cost of the development of a new drug has been estimated variously at between US$ 115–240 million (13), US$ 897 million (14), and US$ 1.7 billion (15). Similarly, cost estimates for vaccine development range from US$ 120–400 million (16) to over US$ 800 million (17). Both drug and vaccine development have extended timelines of from 10 to 25 years, and clinical trials are increasingly lengthy and expensive for both. Diagnostics development is relatively inexpensive by comparison, and timelines are substantially shorter. The cost and complexity of diagnostics R&D vary dramatically depending on the complexity of the format and the status of reagent science. Many companies have developed lateral flow (dipstick) tests for malaria, for example, exploiting the relative ease of immunodetection of parasite antigen in peripheral blood. Given the low cost of clinical trials, the lack of strict regulatory oversight of diagnostics in most target countries, the existence of standard reagents for malaria antigen detection, and the simplicity of the lateral flow format, total development costs may be less than US$ 500,000. On the other hand, for diseases with more challenging technical requirements or for which a novel testing platform needs to be developed, costs may be more than a magnitude higher. As the development of a technology platform to serve only a single disease may not be financially viable, companies often look to recover their R&D investment, or at least to share the risk, across a number of indications.

As a concrete example, the development and evaluation costs for five different diagnostic products for tuberculosis that have come to market within the last 10 to 15 years are shown in Table 7. Unique identifiers have been removed as this information has been kindly supplied in confidence by the test developers. Costing information for some later stages of development is not available for all of the technologies listed, but, in general, development costs ranged from US$ 1 to US$ 10 million, with several technology platforms represented. The development costs of new technologies will also be affected by the locations in which they are developed, evaluated and registered. Regulatory requirements for new TB diagnostics will vary depending on the national regulatory authorities’ classification schemes for in vitro diagnostics (see the annex and the Country Profiles).
TABLE 7. R & D COSTS FOR NEW TB TESTS (US$)

<table>
<thead>
<tr>
<th>TYPE OF TEST</th>
<th>SOLID CULTURE</th>
<th>AUTOMATED LIQUID CULTURE</th>
<th>NUCLEIC ACID AMPLIFICATION</th>
<th>SCREENING TEST</th>
<th>DRUG-SUSCEPTIBILITY TESTING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of company</td>
<td>ROW</td>
<td>USA/EU</td>
<td>USA/EU</td>
<td>USA/EU</td>
<td>USA/EU</td>
</tr>
<tr>
<td>1. Market research costs</td>
<td>10,000</td>
<td>100,000</td>
<td>50,000</td>
<td>500,000</td>
<td>500,000</td>
</tr>
<tr>
<td>2. Total product development costs</td>
<td>575,000</td>
<td>5,625,000</td>
<td>4,850,000</td>
<td>4,987,000</td>
<td>3,375,000</td>
</tr>
<tr>
<td>Technology acquisition and patent fees</td>
<td>275,000</td>
<td>250,000</td>
<td>50,000</td>
<td>200,000</td>
<td>2,000,000</td>
</tr>
<tr>
<td>Development of prototype</td>
<td>3,775,000</td>
<td>4,000,000</td>
<td>4,662,000</td>
<td>75,000</td>
<td>150,000</td>
</tr>
<tr>
<td>Consumable costs during development</td>
<td>1,575,000</td>
<td>600,000</td>
<td>200,000</td>
<td>200,000</td>
<td></td>
</tr>
<tr>
<td>Scale-up and validation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Total cost of clinical trial(s)</td>
<td>180,000</td>
<td>1,450,000</td>
<td>2,000,000</td>
<td>294,000</td>
<td></td>
</tr>
<tr>
<td>Location of study site(s)</td>
<td>DEC</td>
<td>USA/EU</td>
<td>USA/EU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Regulatory approval costs</td>
<td>100,000</td>
<td>800,000</td>
<td>454,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agencies</td>
<td>FDA, EU</td>
<td>USA, Japan</td>
<td>FDA, France</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Marketing and launch support costs</td>
<td>80,000</td>
<td>1,500,000</td>
<td>200,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Product support (1 year) costs</td>
<td>50,000</td>
<td>1,125,000</td>
<td>200,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>995,000</td>
<td>10,600,000</td>
<td>7,754,000</td>
<td>5,781,000</td>
<td>3,875,000</td>
</tr>
</tbody>
</table>

ROW = rest of world; EU = European Union; DEC = disease-endemic country; FDA = Food & Drug Administration (USA).

Logistic considerations

As product validation must be done in the setting of the end-user, TB, along with other tropical diseases, poses a number of research and development challenges related to logistics and location. TB cases are found in the most significant numbers in places where the medical infrastructure is suboptimal and where it is often difficult to collect and transport specimens, as well as to provide the necessary supporting information for the patient. This difficulty is even more acute when fresh samples are required for a test or when particular variants, such as suspected multidrug-resistant TB, need to be identified and collected. There are a limited number of locations in TB-endemic settings where capacity for test evaluation is high, and there is sometimes competition for these sites among diagnostics, drug and vaccine developers.

The maturation of ethical procedures for clinical trials of all types has both strengthened and lengthened the now formalized processes for protocol development, submission and approval. The spread of the HIV pandemic has increased the complexity of clinical studies, especially where HIV testing is necessary, and has increased the sensitivity of communities appropriately guarding themselves against exploitation or involvement in unethical research.

Performing diagnostic evaluations in countries in North America and Europe where TB prevalence is low can be slow and expensive, and may yield limited insight into the performance of the test in populations with higher disease prevalence. The efficient field evaluation of TB diagnostics in developing countries clearly requires a detailed understanding of clinical trial capacity, not only in terms of clinical enrolment, but also of laboratory testing and ethical and institutional review. Local, trusting relationships are critical. Few biotechnology or diagnostics companies in industrialized countries have this knowledge or these relationships, and the prospect of gathering regulatory quality performance data on products in the developing world may be a serious deterrent.
Partnership with the public sector

Taken together, the technical, financial and logistic challenges to developing and evaluating new TB diagnostics can appear commercially daunting, especially as markets have not been well understood or easily accessible. These apparent risks have limited private-sector investment in this area by larger biotechnology companies. The relative failure of market forces to drive the speedy development of public goods is not limited to TB diagnostics, and has sponsored the growth of public–private partnerships for product development that address a range of health issues (Table 8) (18).

According to Science magazine, by 2004, these initiatives had become a “formidable force” to change the way health products are developed and delivered to developing countries (19). Public–private partnerships for health-product development are intended to take advantage of the focused, milestone-driven approach of the commercial sector, together with its intellectual property management and its manufacturing and distribution capacity, while serving the public interest in a manner driven by health needs rather than potential profits (Figure 3).
Public–private development partnerships work in partnership with industry and provide the financial, technical, and managerial means to drive the development of new tools. The extent and the type of support depend on the nature of the target health product, the size and strength of industry partners, and the apparent profitable market. For tuberculosis diagnostics, given the large public- and private-sector markets for testing, direct funding is less critical to accelerating test development than logistical and technical assistance to overcome some of the hurdles described above. Figure 4 lists some of the obstacles that companies may face along the pathway towards the development and delivery of diagnostics for diseases prevalent outside the industrialized world. The figure also describes the types of public-sector support, beyond the provision of funding, that can have the most impact.

Figure 3

**EvoluTheion of Technology Development for Diseases Prevalent in Developing Countries**

**Public sector** -
- Needs-driven
- Altruism
- Partnership

**Private sector** -
- Market driven
- Product focus
- IP management
- Goal-directed R&D
- Complex project
- Financing
- Manufacture and distribution
- Rigid targets/milestones
- Marketing

**Public-private partnership** -
- Industry model
- Needs-driven
- Partnership

1900 1950 2000
**Chapter 4**

**PUBLIC-SECTOR ASSISTANCE TO OVERCOME OBSTACLES TO COMMERCIAL DIAGNOSTIC DEVELOPMENT FOR DISEASES OF POVERTY**

**Product development path**

<table>
<thead>
<tr>
<th>STAGE OF DEVELOPMENT</th>
<th>CONCEPTUALIZATION</th>
<th>PROJECT PLANNING</th>
<th>DEVELOPMENT</th>
<th>EVALUATION</th>
<th>REGULATORY</th>
<th>MARKETING</th>
<th>POST MARKETING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obstacle to development</strong></td>
<td>Lack of visible market; needs not expressed by the public sector; no perceived return on investment.</td>
<td>Basic science incomplete, lack of proven reagents, intellectual property (IP) risk.</td>
<td>Lack of access to clinical samples, reference materials, and disease-specific expertise.</td>
<td>No access to patients near manufacturer and limited contacts or experience in developing world trials.</td>
<td>Diverse, non-rationalized regulatory requirement; lack of agreed performance goals for high-burden countries.</td>
<td>Public sector suspicion of industry; wide diversity in settings of use.</td>
<td>Poor infrastructure in widely distributed market.</td>
</tr>
<tr>
<td><strong>Public sector input needed</strong></td>
<td>Clarify medical need, settings of use and desired specifications; describe public sector market.</td>
<td>Define biology; identify targets and reagents; provide financing; manage IP and craft contracts that protect public and commercial partners.</td>
<td>Provide reference clinical materials for assay development, and reduce investment risk with technical support and reagent access.</td>
<td>Offer experienced clinical trials sites in high-prevalence settings; carry out high-quality trials proving efficacy in target populations.</td>
<td>Clarify criteria for success with ministries of health and technical agencies; interact with regulatory agencies in high-burden countries.</td>
<td>Develop public sector access strategy; demonstrate effectiveness of test in programmatic settings; provide evidence to normative agencies and donors.</td>
<td>Assist in scale-up in national disease control programmes; perform post-marketing performance surveillance, and provide training and infrastructure support.</td>
</tr>
</tbody>
</table>

The Foundation for Innovative New Diagnostics (FIND) and the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) are two public-sector organizations that are cooperating to assist in the development of new TB diagnostics. FIND, which is dedicated wholly to the development of diagnostic tests for infectious diseases, was launched at the World Health Assembly in 2003 and works closely with WHO and TDR on TB diagnostics. Created to overcome the obstacles that have blocked technologies from moving from proof of concept to implementation in national disease control programmes, FIND invests in the development, evaluation and demonstration of new tools with the final goal of ensuring their appropriate uptake by public health systems in order to decrease global health inequities. More information about FIND is available at: [www.finddiagnostics.org](http://www.finddiagnostics.org).

TDR, a Special Programme created by United Nations agencies over 30 years ago to support basic and applied research on neglected diseases, added tuberculosis to its portfolio in 1999. By creating TB specimen and strain banks to support development work and by coordinating laboratory-based evaluations and diagnostic trials, the TDR has made substantial progress in...
facilitating access to samples, strains and clinical trials sites. For more information on how to access specimens from the bank, visit: www.who.int/tdr/diseases/tb/specimen.htm. Working under the umbrella of the Stop TB Partnership, TDR and FIND have hosted a number of forums with representatives of industry and academia and with control managers to improve communication regarding needs and ongoing projects.

Conclusion

Despite global expenditures of over US$ 1 billion on TB diagnostic testing, outlined in Chapter 3, large numbers of tuberculosis cases are detected late or not at all. The need for improved diagnostic tools to simplify and speed diagnosis is clear and urgent. The pandemic of HIV, the rising levels of drug resistance and the growth in human migration and in population density can all be expected to increase that need over the coming decade. The highest priority is for tests to detect cases of active tuberculosis among people with cough and other symptoms who are seeking medical attention. Tests that could be used at the point of care to indicate rapidly the need for treatment could revolutionize the care and control of this disease.

Tests for drug resistance to replace the slow and tedious current methods are also increasingly needed, and would be likely to capture significant markets in the expanding European Union and other industrialized countries, as well as in countries where tuberculosis is endemic. The existence of a strong and growing diagnostics industry, together with the impressive advances in basic and applied science, create an opportunity for rapid progress in the development of innovative new approaches to attack this age-old problem. The costs of diagnostic test development are small in relation to the costs of many other health products, and a number of testing platforms that are being developed for other applications could be harnessed for TB diagnostics. While significant technical and logistic challenges exist to the development of the types of tools that are needed most, new public-sector mechanisms are available that can defray costs, accelerate development, ease evaluation, and assist market entry for improved diagnostics. The potential market for several hypothetical products, listed in Table 5, is described in Chapter 5.
Summary

The persistent TB epidemic and expanding global population ensure that the total market for a range of TB diagnostic products is likely to grow over the coming decades. The portion of this market that will be accessible to new products depends on the interplay of performance and operational characteristics of the new product, end-user preferences, and the market conditions in specific geographical areas. In this chapter, the potential available markets (PAM) for 7 hypothetical new TB diagnostic products point-of-care (POC) screening, smear replacement, culture replacement, monitoring response to treatment, MDR-TB detection and latent infection replacement (with and without predictive capacity) covering the three major TB testing indications are estimated for the year 2020.

The potential markets for improved tests to detect active disease are large: 80 million, 50 million, 20 million tests per year for point-of-care, smear replacement and culture replacement tests, respectively. A test to rapidly detect drug resistance has more modest potential of around 3 million tests per year. The largest potential market is for a test capable of detecting latent TB infection and predicting the risk of progression to active disease. Such a test could generate between 200 and nearly 800 million patient evaluations per year. The huge improvement in infrastructure required to implement testing and treatment based on such a test makes it less likely that the calculated PAM could be reached for this test than for the tests to detect TB disease. For all the testing indications, between 70-90% of the potential available markets for new TB diagnostic technologies are concentrated in the 22 high-burden countries.

Introduction

The previous chapters demonstrated the unmet need for improved TB diagnostic testing and the size and complexity of the global markets. The market for new technologies to enter this space depends on the performance of the technology, the importance that local end-users put on the specific characteristics of the test, the capacity of public and private markets to respond to new technical opportunities, and the future size of the medical problem being addressed.

In order to make estimates of future market size more concrete, in this chapter the potential market for a series of hypothetical TB diagnostic products, as described in Chapter 4, are presented. The information contained in this section was collected from a number of sources (1–17), and represents the best prediction of future markets for TB diagnostics that are available.

Market definitions and key assumptions

Conventionally, markets are defined in relative terms such as the total available market (TAM, all potential users of a test for a given indication), with its sub-sets the served available market (SAM) comprising current users of such diagnostic services (see Chapter 3),
CHAPTER 5

Diagnostics for tuberculosis: global demand and market potential

and the potential available market (PAM), made up of all potential users who might be reached by a specific new technology, either through takeover of existing market segments or by creation of new users.

In Chapter 4, the global public health priorities for TB testing were presented as i) the detection of active TB, including complementary testing; ii) detection of multidrug-resistant TB; and iii) detection of latent infection. Based on these test indications, 7 hypothetical new TB tests which could feasibly be developed in the coming 3–10 years were developed in concept, and the SAM, TAM and PAM calculated for each. These tests, outlined below, are described in greater detail in Table 5 of Chapter 4.

- **POC screening test.** Similar to chest X-ray, sensitive and non-specific, but simple and rapid
- **Sputum smear replacement.** A test with performance similar to microscopy but simpler
- **Culture replacement.** Similar to culture, highly sensitive and moderately complex, but faster
- **Monitoring treatment response.** Similar to microscopy, but with greater sensitivity
- **Drug-susceptibility testing.** A moderately complex but very rapid susceptibility test
- **Non-predictive PPD replacement.** Similar to PPD skin testing, but non-invasive
- **Predictive PPD replacement.** Moderately complex but predictive of incipient active TB

For each hypothetical product our market estimates are dependent upon several key assumptions.

1. The SAM for smear, culture and DST, monitoring and PPD skin test replacement is based on the results presented in Chapter 3 and corresponds to the number of patient evaluations as opposed to the number of test requests or units as presented in Chapter 3.1

2. In cases for which there is no current product specifically fulfilling a hypothetical test’s function (screening test, and PPD skin test replacement with predictive capacity), then the SAM is assumed to be zero.

3. A test with poor performance on samples from HIV+ patients would have no PAM in countries where the prevalence of HIV+ in the adult population is equal to or exceeds 5%. In countries where HIV prevalence is less than five percent, the PAM for such tests would be reduced by 10%.

4. For the hypothetical products that could not be feasibly introduced outside of urban settings (culture replacement, DST replacement, and PPD skin test with predictive capacity), the PAM in 2020 excludes the population of rural TB suspects/cases from the market estimate.

5. Product-dependent assumptions are listed in the accompanying product description.

For clarity, the PAM estimates for 2020 are presented first in this chapter, and more detailed information on current and potential markets for each of the hypothetical tests follows. A summary table is included at the end of the chapter.

**Potential available market for TB diagnostics in 2020**

This chapter presents estimates of the potential available market for each of these tests based on product performance and customer requirements. It is assumed in these calculations that each test is introduced in isolation. The PAM in each case is expressed as units of patient evaluations. The approach to estimating the PAM for a new test comprises a two-part process:

1. Estimation of the portion of the served available market that can be captured by the new TB diagnostic (replacing or augmenting current methods).
2. Estimation of the incremental market share that can be captured by the new TB diagnostic (testing individuals not served with current methods).

Key factors driving estimates of future markets include epidemiologic trends, the fit between test performance characteristics and end-user requirements, the strength of the local TB control programme, and country economic

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1 For smear, the number of patient evaluations is between one half and one third the number of test requests. For culture, we assume  that in high-income countries each patient evaluation generates on average two cultures requests, and that in the Russian Federation a patient evaluation generates on average three requests. For DST, we assume each patient evaluation generates one request; however, in the Russian Federation, each patient evaluation generates on average three sputum smears during the treatment phase. Therefore, the number of patient evaluations for a monitoring test is a third the number of smears done for monitoring. For PPD skin test replacement, the number of patient evaluations is equivalent to the number of test requests (which is 50% of test doses sold, assuming 50% wastage).
indicators. These factors were addressed in the regression equations used to calculate the PAM for 2020. For a more detailed explanation, see the “More on methods” section at the end of this chapter.

The target markets were segmented by geography as follows:

- High-income countries (as defined by the World Bank)
- Disease-endemic countries (DEC) with a high burden of TB (the 22 countries bearing 80% of the global disease burden for TB)

**Rest of the world**

The DEC were further stratified by geography into TB-endemic countries in Asia and TB-endemic countries in Africa, Brazil and the Russian Federation were analysed separately owing to distinctive test usage practices.

In the summary below (Table 1), PAM is expressed as annual patient evaluations in millions in the year 2020, as a function of the geographical segmentation and product type. Each of the hypothetical new diagnostic products generates one test unit per patient evaluation, except monitoring replacement, which generates two test units. A more detailed analysis comparing PAM 2020 with SAM and TAM, along with an analysis of market size if the products fail to work in HIV-infected individuals or require infrastructure associated with urban settings, is presented in the tables that follow.

**TABLE 1. POTENTIAL AVAILABLE MARKET FOR 7 HYPOTHETICAL NEW TB DIAGNOSTIC PRODUCTS (IN MILLIONS OF PATIENTS EVALUATED)**

<table>
<thead>
<tr>
<th>Product</th>
<th>High income countries</th>
<th>Endemic Asia</th>
<th>Russian Fed. and Brazil</th>
<th>Endemic Africa</th>
<th>Rest of world</th>
<th>DEC totals</th>
<th>Global total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DISEASE-ENDEMIC COUNTRIES</td>
<td></td>
<td></td>
<td>Rest of world</td>
<td>DEC totals</td>
<td>Global total</td>
</tr>
<tr>
<td>POC screening test</td>
<td>3.6</td>
<td>25.7</td>
<td>2.5</td>
<td>28.4</td>
<td>19.0</td>
<td>56.6</td>
<td>79.1</td>
</tr>
<tr>
<td>Sputum smear replacement</td>
<td>2.7</td>
<td>27.0</td>
<td>1.6</td>
<td>7.9</td>
<td>9.7</td>
<td>36.6</td>
<td>49.0</td>
</tr>
<tr>
<td>Culture replacement</td>
<td>3.0</td>
<td>9.8</td>
<td>0.9</td>
<td>3.1</td>
<td>3.6</td>
<td>13.7</td>
<td>20.3</td>
</tr>
<tr>
<td>Monitoring treatment response</td>
<td>0.4</td>
<td>12.4</td>
<td>0.4</td>
<td>5.1</td>
<td>5.1</td>
<td>18.0</td>
<td>23.5</td>
</tr>
<tr>
<td>Drug-susceptibility testing</td>
<td>0.1</td>
<td>2.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.3</td>
<td>2.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Non-predictive PPD replacement</td>
<td>14.0</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>17.8</td>
<td>ND</td>
<td>31.7</td>
</tr>
<tr>
<td>Predictive PPD replacement</td>
<td>9.6</td>
<td>143.4</td>
<td>4.6</td>
<td>14.1</td>
<td>32.9</td>
<td>162.1</td>
<td>204.6</td>
</tr>
</tbody>
</table>
Hypothetical product descriptions and SAM, PAM 2020 and TAM 2020 estimates

Point-of-care screening test
The primary intended use is to rule out tuberculosis in patients with respiratory symptoms. Those testing positive with a screening test would require confirmatory testing with smear microscopy or an alternative test with high specificity. The screening test is fast (<3 hours) and can be delivered at the point of care because of minimal infrastructure and technical requirements. The test will be of greatest utility in health clinics with high volumes of coughing patients and overloaded microscopy laboratories. Relative to current practices for TB screening (clinical history, physical examination +/- X-ray), the hypothetical test fitness assessment is rated “Good”. In six out of seven country surveys of physician preferences, the characteristics of the hypothetical screening test ranked moderately well. In the seventh country (China), the characteristics ranked high.

### Figure 1
SAM, PAM 2020 AND TAM 2020 REGIONAL ESTIMATES FOR A HYPOTHETICAL POINT-OF-CARE SCREENING TEST

<table>
<thead>
<tr>
<th></th>
<th>High income</th>
<th>High-burden Asia</th>
<th>High-burden Africa</th>
<th>Rest of world</th>
<th>Global total</th>
<th>High-burden total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAM</td>
<td>2.98</td>
<td>34.00</td>
<td>3.44</td>
<td>34.07</td>
<td>24.25</td>
<td>98.75</td>
</tr>
<tr>
<td>TAM 2020</td>
<td>7.57</td>
<td>65.93</td>
<td>6.31</td>
<td>64.51</td>
<td>49.03</td>
<td>193.36</td>
</tr>
<tr>
<td>PAM 2020</td>
<td>3.56</td>
<td>25.67</td>
<td>2.51</td>
<td>28.44</td>
<td>19.00</td>
<td>79.17</td>
</tr>
<tr>
<td>PAM 2020 no utility in presence of HIV</td>
<td>3.20</td>
<td>23.10</td>
<td>2.26</td>
<td>1.63</td>
<td>12.43</td>
<td>42.64</td>
</tr>
<tr>
<td>PAM 2020 no utility in presence of HIV</td>
<td>3.20</td>
<td>23.10</td>
<td>2.26</td>
<td>1.63</td>
<td>12.43</td>
<td>42.64</td>
</tr>
</tbody>
</table>
Smear replacement test
The primary intended use of this test is the detection of disease caused by M. tuberculosis in pulmonary and extrapulmonary forms, in populations of all ages. The test has a sensitivity and specificity equal to or better than microscopy, but with a much faster time-to-result (< 3 hours) and reduced infrastructure and technical requirements. It could be applied at the lowest level (peripheral health clinic) of the health system, as well as at the level of the microscopy centre. To be used most widely, the test must work properly regardless of the prevalence of HIV or other co-infection in the test population. Relative to current practices for detection of active TB by smear microscopy, the hypothetical test fitness assessment is rated “Excellent”. In six out of seven country surveys of physician preferences, the characteristics of the hypothetical smear replacement test ranked moderately well. In the seventh country (China), the characteristics ranked high.
Culture replacement test

The primary intended use of this test is detection of symptomatic cases of tuberculosis not identified during primary diagnostic testing at the clinic level (commonly smear-negative, paucibacillary or extrapulmonary cases). This test provides a sensitivity and specificity similar to culture, but with a faster time-to-result (<7 days). The test requires minimal sample processing/preparation and minor technical expertise, but the system does require electricity and is dependent on a laboratory infrastructure, thereby restricting its implementation to urban areas in low-income and middle-income countries. To be widely useful, the test must work properly regardless of the prevalence of HIV or other co-infection in the test population. Relative to culture, the hypothetical test rated “Excellent” in the fitness assessment. In six out of seven country surveys of physician preferences, the characteristics of the hypothetical culture replacement test ranked low. In the seventh country (China), the characteristics ranked moderate.

![Figure 3](image-url)
Test for monitoring response to treatment
The primary intended use is to monitor the response to anti-tuberculosis treatment. The test is more sensitive than smear microscopy and can be applied in the setting of either pulmonary or extrapulmonary disease. Technical and infrastructure requirements are similar to microscopy. Relative to current practices for monitoring, the hypothetical test fitness assessment is rated “Very Good”. In seven out of seven country surveys of physician preferences, the characteristics of the hypothetical monitoring tool ranked high.
Drug-susceptibility test replacement

The primary intended use is detection of *M. tuberculosis* resistance to the drugs isoniazid and rifampicin directly from sputum. The test has similar performance characteristics and infrastructure needs as the current standard but provides much faster time-to-result (<3 hours) and requires minimal technical expertise. Infrastructure requirements that are similar to MTB culture restrict its implementation to referral centres in urban areas in low-income and middle-income countries. Relative to current practices for drug-susceptibility testing, the hypothetical DST fitness assessment is rated “Excellent”. In four out of seven country surveys of physician preferences, the characteristics of the hypothetical drug-susceptibility test ranked moderate. In the remaining three countries the characteristics of the hypothetical drug-susceptibility test ranked low.

### Figure 5
SAM, PAM 2020 AND TAM 2020 REGIONAL ESTIMATES FOR A HYPOTHETICAL DRUG-SUSCEPTIBILITY TEST REPLACEMENT

<table>
<thead>
<tr>
<th>Region</th>
<th>SAM 2020</th>
<th>PAM 2020</th>
<th>TAM 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>High income</td>
<td>0.67</td>
<td>0.51</td>
<td>0.39</td>
</tr>
<tr>
<td>High-burden Asia</td>
<td>12.80</td>
<td>19.75</td>
<td>12.43</td>
</tr>
<tr>
<td>High-burden Russian Fed. and Brazil</td>
<td>0.40</td>
<td>0.69</td>
<td>0.35</td>
</tr>
<tr>
<td>High-burden Africa</td>
<td>2.33</td>
<td>11.12</td>
<td>5.10</td>
</tr>
<tr>
<td>Rest of world</td>
<td>4.92</td>
<td>8.29</td>
<td>5.09</td>
</tr>
<tr>
<td>Global total</td>
<td>21.12</td>
<td>19.75</td>
<td>12.82</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>SAM 2020</th>
<th>PAM 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-burden total</td>
<td>15.53</td>
<td>31.56</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>SAM 2020</th>
<th>PAM 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-burden total</td>
<td>15.53</td>
<td>31.56</td>
</tr>
</tbody>
</table>

Millions of patients evaluated

<table>
<thead>
<tr>
<th>Region</th>
<th>0.40</th>
<th>0.69</th>
<th>0.39</th>
<th>1.24</th>
<th>3.33</th>
<th>16.50</th>
<th>12.82</th>
</tr>
</thead>
<tbody>
<tr>
<td>High income</td>
<td>0.67</td>
<td>0.51</td>
<td>0.39</td>
<td>0.40</td>
<td>1.24</td>
<td>3.33</td>
<td>12.82</td>
</tr>
<tr>
<td>High-burden Asia</td>
<td>12.80</td>
<td>19.75</td>
<td>12.43</td>
<td>0.43</td>
<td>5.10</td>
<td>5.09</td>
<td>17.97</td>
</tr>
<tr>
<td>High-burden Russian Fed. and Brazil</td>
<td>0.40</td>
<td>0.69</td>
<td>0.39</td>
<td>1.24</td>
<td>3.33</td>
<td>16.50</td>
<td>12.82</td>
</tr>
<tr>
<td>High-burden Africa</td>
<td>2.33</td>
<td>11.12</td>
<td>5.10</td>
<td>5.10</td>
<td>5.09</td>
<td>23.45</td>
<td>17.97</td>
</tr>
<tr>
<td>Rest of world</td>
<td>4.92</td>
<td>8.29</td>
<td>5.09</td>
<td>5.09</td>
<td>5.09</td>
<td>23.45</td>
<td>17.97</td>
</tr>
<tr>
<td>Global total</td>
<td>21.12</td>
<td>19.75</td>
<td>12.82</td>
<td>12.82</td>
<td>12.82</td>
<td>60.35</td>
<td>43.82</td>
</tr>
</tbody>
</table>
PPD skin test replacement for detection of latent infection

The primary intended use of this test is detection of latent M. tuberculosis infection. The test has performance characteristics and time-to-result similar to the current test (PPD skin testing) but is non-invasive (skin patch or urine test). Performance of the hypothetical test would not be reduced in the setting of HIV co-infection that is seen with PPD skin testing.

Relative to current practices for monitoring, the hypothetical test fitness assessment is rated "Very Good". In seven out of seven county surveys of physician preferences, the characteristics of the hypothetical monitoring tool ranked high.

### Figure 8

**SAM, PAM 2020 AND TAM 2020 REGIONAL ESTIMATES FOR A HYPOTHETICAL PPD SKIN TEST REPLACEMENT FOR DETECTION OF LATENT INFECTION**

<table>
<thead>
<tr>
<th></th>
<th>High income</th>
<th>Low-middle-income countries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAM</strong></td>
<td>40.96</td>
<td>8.65</td>
</tr>
<tr>
<td><strong>TAM 2020</strong></td>
<td>21.28</td>
<td>61.81</td>
</tr>
<tr>
<td><strong>PAM 2020</strong></td>
<td>13.95</td>
<td>17.75</td>
</tr>
</tbody>
</table>
| **PAM 2020 no utility in presence of HIV** | 12.55 | 12.88

*Due to the presence of HIV, the hypothetical test would not be useful in high-income countries.*
PPD skin test replacement with predictive capacity

The primary intended use for this test is detection of latent *M. tuberculosis* infection. The hypothetical test has much greater specificity than PPD skin testing. That is, the percentage of test-positive individuals who would progress to active TB within 2 years unless given preventive therapy would be 30%, instead of 5–10% as seen with PPD skin testing. The test requires more advanced laboratory infrastructure than the current benchmark. Though such a test could greatly facilitate TB control, effective implementation of testing and subsequent drug treatment would require tremendous expansion in health system services and laboratory infrastructure. Relative to current standard practice for detection of latent infection (PPD skin test), the hypothetical test fitness assessment is “Good”. In all seven country surveys of physician preferences, the characteristics of the hypothetical latent infection replacement test with predictive capacity ranked moderate.

<table>
<thead>
<tr>
<th></th>
<th>High income</th>
<th>High burden Asia</th>
<th>High-burden Russian Fed. and Brazil</th>
<th>High-burden Africa</th>
<th>Rest of world</th>
<th>Global total</th>
<th>High-burden total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAM</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>TAM 2020</td>
<td>21.3</td>
<td>495.5</td>
<td>46.2</td>
<td>65.7</td>
<td>137.9</td>
<td>766.7</td>
<td>607.4</td>
</tr>
<tr>
<td>PAM 2020</td>
<td>9.6</td>
<td>143.4</td>
<td>4.6</td>
<td>14.1</td>
<td>32.9</td>
<td>204.6</td>
<td>162.1</td>
</tr>
<tr>
<td>PAM 2020 with rural exclusion</td>
<td>9.6</td>
<td>30.6</td>
<td>2.8</td>
<td>4.0</td>
<td>9.6</td>
<td>56.5</td>
<td>37.4</td>
</tr>
<tr>
<td>PAM 2020 no utility in presence of HIV</td>
<td>8.6</td>
<td>129.1</td>
<td>4.2</td>
<td>6.5</td>
<td>24.2</td>
<td>172.6</td>
<td>139.7</td>
</tr>
</tbody>
</table>
Conclusions

Based on the best estimates of global TB epidemiologic trends and population growth, the total available markets for TB diagnostic testing will remain strong. A range of tests are needed to diagnose tuberculosis in its various forms. Worldwide, we estimate that the largest market for a new TB diagnostic would be for a test that detects latent infection and predicts progression to active disease (767 million patient evaluations/year). Such a test, if widely implemented and accompanied by successful treatment, would revolutionize TB control.

The infrastructure to achieve this globally is not available. Capturing 25% of the total available market by 2020 would result in some 200 million patient evaluations/year. The next largest total available market is for a point-of-care screening test (193 million patient evaluations/year), of which 70% (137 million patient evaluations/year) is concentrated in the 22 HBCs. We estimate that 40% of this TAM (57 million patient evaluations/year) could be captured by 2020.

These two tests represent totally new and potentially high-risk approaches, as their likelihood of market penetration is uncertain. However, substantial markets also exist for ‘replacement technologies’, for which there are already good candidates in the pipeline or for which testing platforms already exist. Specifically, the total available markets for a smear, culture, monitoring and DST replacement tests are 83 million, 57 million, 40 million, and 6 million patient evaluations, respectively. Compared to the 25–40% TAM capture for the new testing approaches described above, we estimate that replacement technologies could capture greater proportions of the market by 2020: smear 59% (49 million), culture 35% (20 million), monitoring 58% (23 million) and DST 45% (3 million). Without exception, between 70–90% of the potential available markets for these replacement technologies are in the 22 high-burden countries. The continued emphasis on improving market conditions will encourage market growth in the high-burden countries and increase the accessibility to new products.

More on methods...

1. Calculation of total available market (TAM)

The TAM for each of the seven hypothetical diagnostic products is based on the most optimistic sales scenario. The TAMs for the individual countries are built from the bottom-up. For each new hypothetical diagnostic product TAM calculations were developed and estimates generated using data readily available for almost every country covered by the WHO report 2005 on Global Tuberculosis Control: Surveillance, Planning, Financing (13, 15, 16). Global, regional and other aggregates are based on sums of individual countries.

The year 2005 serves as the base year for all subsequent TAM projections covering the period 2006–2020. Growth rates are applied to the relevant population targets for the set of hypothetical TB diagnostic products. The growth rates are combinations of one or more of the following:

- population growth rates in 2003 (14),
- estimates of the growth of future TB incidence (4).

The growth rates are planned with following the general formula:

$$\text{EndYearValue} = \text{BaseYearValue} \times (1+\text{GrowthRate})^{\text{EndYear}-\text{BaseYear}}$$

If more than one growth rate is applied then the following is applied:

$$\text{EndYearValue} = \text{BaseYearValue} \times (1+\text{GrowthRateA}) \times (1+\text{GrowthRate2})^{\text{EndYear}-\text{BaseYear}}$$
1.1 Point-of-care screening test

Assumptions
The hypothetical TB screening test is assumed to be appropriate for use in the following populations:

- All groups of TB suspects (adult/paediatric-pulmonary, extrapulmonary)
- High risk individuals including prisoners and immigrants
- People with symptoms suggesting TB
- Suspiciously sick people in high HIV prevalence settings.¹

Calculations
In countries where HIV prevalence (8) in the general population is less than 10%, TAM is the sum of:

- TAM for the smear replacement test
- Annual number of immigrants (9)
- Number of incarcerated people (12).

In countries where HIV prevalence in the general population (8) is 10% or greater, TAM is the sum of:

- Number of people aged 15 to 59 (10).²
- Paediatric TB cases* paediatric TB suspects per case detected.

Growth rate
Population growth rate (14).

1.2 Smear replacement test

Assumptions
The hypothetical smear replacement test is assumed to be a relevant test for diagnosing all forms of active TB³.

Therefore, it is assumed to be appropriate for use in the following populations:

- Pulmonary TB suspects
- Extrapulmonary TB suspects
- Paediatric TB suspects.

Calculations
The hypothetical smear replacement test would require only one test unit per TB suspect. Therefore, TAM is equal to the sum of:

- Served available market for diagnostic smear microscopy⁴/ number of smears per TB suspect⁵
- Extrapulmonary TB cases⁶ * extrapulmonary suspects per case detected⁷
- Paediatric cases⁸ * paediatric suspects per case detected (1,11,13)⁹.

¹ It is assumed that every adult becomes ill at some point over the course of a year.
² The adult population aged 15 to 59 includes all of the adult TB suspects, immigrants and prisoners, but it does not include pediatric suspects.
³ It does not differentiate between MDR and non-MDR-TB.
⁴ Smears performed for monitoring purposes excluded (equivalent to 25% of total microscopy SAM). See Chapter 3 for method of estimation.
⁵ Assumed to be 2 in low-income and middle-income countries, 3 in high-income countries and 4 in the Russian Federation and we assume no repeat testing. These assumptions were cross-checked with data from approximately 10 countries. These results consistently lie between 2 and 3 smears/suspect.
⁶ Extrapulmonary cases are estimated as the percent of currently treated cases that are extrapulmonary multiplied by the total number of cases as estimated by WHO (16). The percentage of cases that are extrapulmonary is based on an algorithm that takes into account the percentage of notified cases that are extrapulmonary and a weighted average of the probability that a given case of TB is extrapulmonary in an HIV-positive person with TB versus the probability in an HIV-negative person with TB (2).
⁷ This is assumed to be the greater of 10 or the suspects per detected case for pulmonary TB.
⁸ Number of paediatric TB cases is estimated as the ratio of paediatric TB cases to total cases multiplied by the total number of TB cases. In low-income countries the ratio is estimated as the percentage of TB cases that are 0-14 years multiplied by the percentage of cases among 0-14 years that are 0-5 year olds.
⁹ This is assumed to be 10, or the number of suspects per detected case for pulmonary TB, whichever is greater.
Growth rate
TB incidence growth rate(4) * population growth rate (14).

1.3 Culture replacement test
Assumptions
The hypothetical culture replacement test is assumed to be appropriate for use in the following populations:

1. In high-income countries and the Russian Federation, the TAM would be identical to the hypothetical smear replacement test TAM.

2. In middle- and low-income countries, the TAM would be limited to suspects who do not manifest pulmonary symptoms or in whom smear microscopy is negative. These include:
   - Extrapulmonary TB suspects
   - Paediatric TB suspects
   - Pulmonary TB suspects that are smear-negative or smear-unknown.

Calculations
1. In high-income countries and the Russian Federation, TAM is equal to the hypothetical smear replacement test TAM.

2. In middle- and low-income countries, TAM is the sum of:
   - Extrapulmonary TB cases * extrapulmonary TB suspects per case detected
   - Paediatric TB cases * paediatric TB suspects per case detected
   - SAM for diagnostic smear microscopy number of smears per suspect * Percentage of TB suspects that are smear-negative or smear-unknown (16).

Growth rate
TB incidence growth rate(4) * population growth rate (14).

1.4 Monitoring response to treatment test
Assumptions
The hypothetical monitoring tool would be used twice for all cases of TB.

Calculations
The TAM for the monitoring test is equal to: all estimated TB cases * 2.

Growth rate
TB incidence growth rate (4) * population growth rate (14).

1.5 Drug-susceptibility test
Assumptions
The hypothetical drug-susceptibility test is assumed to be appropriate for use in the following populations:

1. In high-income countries this test would be used in TB cases.

2. In countries where multidrug-resistant (MDR) TB constitutes more than 5% of all TB cases, the test would be used in all TB cases twice.
3. In middle- and low-income countries, where MDR-TB constitutes less than 5% of all TB cases, the diagnostic would be used for all diagnosed TB cases that do not respond to treatment.

Calculations

1. In high-income countries TAM is equal to the number of all cases of TB.

2. In countries where MDR-TB is greater than 5%, TAM is equal to twice the number of all cases of TB.

3. In low- and middle-income countries with MDR-TB less than 5%, TAM is equal to all TB cases * the percentage of cases requiring re-treatment (16).

Growth rate
TB incidence growth rate (4) * population growth rate (14).

1.6 Latent infection replacement test
Assumptions
The latent infection replacement test is assumed to be appropriate for use in the following populations:

1. In low-TB-incidence settings, all people at high risk of being in contact with active TB cases. This would include prisoners, immigrants, health workers and military personnel; close contacts of smear-positive pulmonary TB cases; and people known to be infected with HIV.

2. In high-TB-incidence settings, close contacts of smear-positive pulmonary TB cases and people known to be infected with HIV.

Calculations

1. In countries with TB incidence less than 50/100,000, TAM is the sum of the following population groups:
   - Immigrants (9)
   - Prisoners (12)
   - Soldiers (7)
   - Health workers (17)
   - 8 * number of smear positive pulmonary TB cases (16)
   - People living with HIV who know their status (5)

2. In countries with TB incidence greater than 50/100,000, TAM is the sum of:
   - 8 * number of smear positive pulmonary TB cases (16).
   - People living with HIV who know their status (5).

Growth rate
Population growth rate (14).

1.7 Latent infection with predictive ability test
Assumptions
The hypothetical latent infection with predictive ability test is assumed to be appropriate for use in the following populations:

\[^{1}\text{Several studies have been conducted to assess the percent of people who know their HIV status. The Statcompiler at www.measure DHS.com has compiled these studies. This analysis used existing data for some countries for other countries extrapolations were made based on regional averages.}\]
1. In low-TB-incidence countries the market would be the same as for the hypothetical latent infection replacement test (see above).

2. In high-TB-incidence countries, where the majority of the population has been exposed to TB, the test would be applied to all persons aged 15–59 years and any person aged 15 or less living in a household with an active pulmonary TB case.

Calculations

1. In countries where TB prevalence is less than 50/100,000 TAM is equivalent to the results presented for the hypothetical latent infection replacement test.

2. In countries where TB prevalence is greater than 50/100,000, TAM is the sum of the following population groups:
   - Population aged 15 – 59 (10)
   - Population aged 0 – 15 \( \times 4 \) (in Africa)
   - Population aged 0 – 15 \( \times 2 \) (everywhere except Africa)

Growth rate
Population growth rate \( (10) \).

2. Calculation of the potential available market (PAM)
The PAM consists of two parts: a part that can be captured from the served available market (SAM) and a portion that can be gained from the total available market (TAM) that is not currently served. In this report the latter portion is referred to as the growth market.

2.1 Estimating the capture of the served available market
Although a new diagnostic test may be superior in certain respects to the existing diagnostic test, a new technology/technique is not guaranteed to totally replace the old one. Furthermore, if replacement of the old with the new technology does occur, it will take place over a period of several years.

We estimate the replacement process based on two related sets of information. First, the characteristics of the hypothetical diagnostic test and the current diagnostic test are compared across several test characteristics (type of specimen needed, sensitivity, specificity, speed, equipment needs, training needs, price and whether it performs in HIV-infected patient samples) and assigned a score \( (+1,0,-1) \). For each of seven test characteristics, a score \( (-1,0,+1) \) was generated to indicate the relative attractiveness of the new product to replace the current test. For a given diagnostic test, the overall score will be the same for every country. Table 9 presents the scores for all seven of the hypothetical diagnostic tests, presented in Chapter 4.

---

1 United Nations 2001b
Diagnostics for tuberculosis: global demand and market potential

CHAPTER

250 public and private physicians in 7 high-TB-burden countries (Brazil, China, India, Russian Federation, Indonesia, Uganda, and South Africa) were interviewed as part of a conjoint analysis to determine their preferences for new diagnostic tools that detected active disease, latent infection and multidrug-resistance. Physicians were asked to rank, from highest to lowest preference, a series of 10–13 tests (per test indication) with varying performance and operational characteristics. Using these product cards as illustrated below (Figure 8), a conjoint analysis was performed to determine the relative weight of different product performance characteristics in driving local diagnostic decision-making. These preferences were then used to generate a physician preferences score. Tables 10, 11 and 12 present the results of this analysis for tests that detect active TB, multidrug-resistant TB tests and latent TB, respectively.

---

**TABLE 2. COMPARISON OF HYPOTHETICAL DIAGNOSTIC TEST WITH CURRENT DIAGNOSTIC TEST**

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>Smear microscopy replacement</th>
<th>Culture replacement</th>
<th>Monitoring</th>
<th>DST</th>
<th>Latent infection replacement</th>
<th>Latent infection with predictive ability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of specimen</strong></td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Speed</strong></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Equipment</strong></td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>-1</td>
</tr>
<tr>
<td><strong>Training</strong></td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td><strong>Price</strong></td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Overall fitness assessment</strong></td>
<td>Good</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Very Good</td>
<td>Excellent</td>
<td>Very Good</td>
<td>Good</td>
</tr>
</tbody>
</table>

---

*There are no current diagnostic tests applied for TB screening or detection of latent infection and risk of progression to active TB. In clinical practice, screening for TB is comprised of clinical history of cough for >2-3 weeks, and the hypothetical screening test was compared against this current practice. In the case of a test for latent infection that is predictive of future active disease, the characteristics were compared with the current test for latent infection (PPD skin test).*  

*Total fitness assessment score: 1-2 = Good 3 = Very Good 4-7 = Excellent*  

---

1 The method of analysis was a regression applied to rankings of the physicians (conjoint analysis).
TABLE 3. PHYSICIAN PREFERENCES FOR HYPOTHETICAL DIAGNOSTIC TESTS THAT DETECT ACTIVE TB

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Price</th>
<th>Speed</th>
<th>Works in HIV+ samples</th>
<th>Directs treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>VI</td>
<td>LI</td>
<td>LI</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>China</td>
<td>VI</td>
<td>LI</td>
<td>I</td>
<td>LI</td>
<td>VI</td>
</tr>
<tr>
<td>India</td>
<td>VI</td>
<td>I</td>
<td>LI</td>
<td>LI</td>
<td>VI</td>
</tr>
<tr>
<td>Indonesia</td>
<td>VI</td>
<td>LI</td>
<td>LI</td>
<td>LI</td>
<td>LI</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>VI</td>
<td>I</td>
<td>LI</td>
<td>LI</td>
<td>I</td>
</tr>
<tr>
<td>South Africa</td>
<td>VI</td>
<td>LI</td>
<td>LI</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Uganda</td>
<td>VI</td>
<td>LI</td>
<td>LI</td>
<td>I</td>
<td>VI</td>
</tr>
</tbody>
</table>

VI - very important
I - important
LI - little importance

TABLE 4. PHYSICIAN PREFERENCES FOR HYPOTHETICAL DIAGNOSTIC TESTS THAT DETECT MULTIDRUG-RESISTANT TB

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Price</th>
<th>Speed</th>
<th>Works in HIV+ samples</th>
<th>Directs treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>VI</td>
<td>LI</td>
<td>LI</td>
<td>I</td>
<td>VI</td>
</tr>
<tr>
<td>China</td>
<td>I</td>
<td>LI</td>
<td>VI</td>
<td>LI</td>
<td>VI</td>
</tr>
<tr>
<td>India</td>
<td>VI</td>
<td>LI</td>
<td>VI</td>
<td>LI</td>
<td>LI</td>
</tr>
<tr>
<td>Indonesia</td>
<td>VI</td>
<td>I</td>
<td>I</td>
<td>LI</td>
<td>VI</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>VI</td>
<td>LI</td>
<td>I</td>
<td>LI</td>
<td>VI</td>
</tr>
<tr>
<td>South Africa</td>
<td>VI</td>
<td>LI</td>
<td>LI</td>
<td>LI</td>
<td>VI</td>
</tr>
<tr>
<td>Uganda</td>
<td>VI</td>
<td>LI</td>
<td>LI</td>
<td>VI</td>
<td>VI</td>
</tr>
</tbody>
</table>

VI - very important
I - important
LI - little importance
Next, we compared physician preferences as defined by the results of the conjoint analysis with the characteristics of the hypothetical diagnostic test. If the diagnostic had the features desired by the physicians, then that diagnostic ranked high; if not, it was ranked low (Table 13).

### Table 5. Physician Preferences for Hypothetical Diagnostic Tests That Detect Latent TB

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Price</th>
<th>Speed</th>
<th>Works in HIV+ samples</th>
<th>Directs treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>China</td>
<td>VI</td>
<td>VI</td>
<td>LI</td>
<td>VI</td>
<td>VI</td>
</tr>
<tr>
<td>India</td>
<td>VI</td>
<td>VI</td>
<td>LI</td>
<td>VI</td>
<td>VI</td>
</tr>
<tr>
<td>Indonesia</td>
<td>LI</td>
<td>VI</td>
<td>VI</td>
<td>LI</td>
<td>VI</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>VI</td>
<td>I</td>
<td>VI</td>
<td>LI</td>
<td>I</td>
</tr>
<tr>
<td>South Africa</td>
<td>LI</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Uganda</td>
<td>LI</td>
<td>I</td>
<td>VI</td>
<td>I</td>
<td>I</td>
</tr>
</tbody>
</table>

Vi - very important
I - important
LI - little importance

### Table 6. Degree to Which Hypothetical Diagnostic Test Reflects Physician Preferences

<table>
<thead>
<tr>
<th>Screening</th>
<th>Replace-ment smear</th>
<th>Replace-ment culture</th>
<th>Replace-ment monitoring</th>
<th>Replace-ment DST</th>
<th>Latent replacement</th>
<th>Latent predictive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>Mod</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Mod</td>
<td>Mod</td>
</tr>
<tr>
<td>China</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Mod</td>
<td>Mod</td>
<td>Mod</td>
</tr>
<tr>
<td>India</td>
<td>Mod</td>
<td>Low</td>
<td>High</td>
<td>Mod</td>
<td>Low</td>
<td>Mod</td>
</tr>
<tr>
<td>Indonesia</td>
<td>Mod</td>
<td>Low</td>
<td>High</td>
<td>Mod</td>
<td>Mod</td>
<td>Mod</td>
</tr>
<tr>
<td>Russian Fed.</td>
<td>Mod</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>South Africa</td>
<td>Mod</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Uganda</td>
<td>Mod</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Mod</td>
<td>Mod</td>
</tr>
</tbody>
</table>

High - hypothetical diagnostic test matches physician preferences very well
Moderate - hypothetical diagnostic test matches physician preferences moderately well
Low - hypothetical diagnostic test matches physician preferences only partially

Ratings/rankings were extrapolated to the rest of the world based on responses from physicians in the seven countries. Table 14 illustrates the grouping of high-TB-burden countries of the world.

### Table 7. Reference Table for Extrapolation of Physician Preferences to High-Burden Countries Outside Survey Areas

<table>
<thead>
<tr>
<th>Country where physicians were surveyed</th>
<th>High-burden countries to which results were extrapolated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>Brazil</td>
</tr>
<tr>
<td>China</td>
<td>China, Viet Nam, Thailand</td>
</tr>
<tr>
<td>India</td>
<td>India, Bangladesh, Pakistan, Philippines, Afghanistan</td>
</tr>
<tr>
<td>Indonesia</td>
<td>Indonesia, Myanmar, Cambodia,</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>Russian Federation</td>
</tr>
<tr>
<td>South Africa</td>
<td>South Africa</td>
</tr>
<tr>
<td>Uganda</td>
<td>Uganda, Nigeria, Kenya, DR Congo, UR Tanzania, Uganda, Ethiopia, Mozambique, Zimbabwe</td>
</tr>
</tbody>
</table>
2.1.1 Product replacement analysis

Based on the approaches outlined above, Table 15 demonstrates the portion of the SAM that could be captured by the new diagnostic after a 14-year period (2006–2020) using the assumptions for product performance and physician preferences discussed above. For example, if the product performance characteristics were excellent relative to the current test and physician preferences were highly favourable, it was assumed that 90% of the SAM could be captured. For a smear replacement test, China is an example of such a country. The characteristics of the hypothetical smear replacement test are excellent relative to the current test and physicians in China expressed strong preferences for a diagnostic with the characteristics of this hypothetical test. On the other hand, where physician preferences were moderately favourable and the product characteristics only good relative to the current test, it was estimated that only 40% of the SAM could be captured. The market for a latent TB replacement diagnostic in Indonesia is such a case. The hypothetical new diagnostic improves on the standard in just a few areas and the preferences of physicians in Indonesia do not coincide with those improvements.

Table 16 presents a grid of Table 15 applied to Tables 9 and 13. Interpreting Tables 15 and 16 together, if the product characteristics are excellent relative to the current diagnostic test and physician preferences are highly favourable, we believe that 90% of the served available market could be captured.

### TABLE 8. PERCENTAGE OF SERVED AVAILABLE MARKET POTENTIALLY CAPTURED BY A HYPOTHETICAL NEW DIAGNOSTIC TEST AFTER 14 YEARS

<table>
<thead>
<tr>
<th>New product characteristics relative to current test</th>
<th>Overlap of product features with physician preferences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Excellent</td>
<td>90%</td>
</tr>
<tr>
<td>Very Good</td>
<td>75%</td>
</tr>
<tr>
<td>Good</td>
<td>50%</td>
</tr>
</tbody>
</table>

Table 16 presents a grid of Table 15 applied to Tables 9 and 13. Interpreting Tables 15 and 16 together, if the product characteristics are excellent relative to the current diagnostic test and physician preferences are highly favourable, we believe that 90% of the served available market could be captured.

### TABLE 9. FRACTION OF SERVED AVAILABLE MARKET POTENTIALLY CAPTURED BY A HYPOTHETICAL NEW DIAGNOSTIC AFTER 14 YEARS, APPLIED TO HYPOTHETICAL DIAGNOSTIC TESTS IN SURVEY COUNTRIES

<table>
<thead>
<tr>
<th>Screening</th>
<th>Smear replacement</th>
<th>Culture replacement</th>
<th>Monitoring</th>
<th>DST</th>
<th>Latent replacement</th>
<th>Latent predictive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>0.5</td>
<td>0.8</td>
<td>0.5</td>
<td>0.75</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>China</td>
<td>0.5</td>
<td>0.9</td>
<td>0.8</td>
<td>0.75</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>India</td>
<td>0.5</td>
<td>0.8</td>
<td>0.5</td>
<td>0.75</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Indonesia</td>
<td>0.5</td>
<td>0.8</td>
<td>0.5</td>
<td>0.75</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Russia</td>
<td>0.5</td>
<td>0.8</td>
<td>0.5</td>
<td>0.75</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>South Africa</td>
<td>0.5</td>
<td>0.8</td>
<td>0.5</td>
<td>0.75</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Uganda</td>
<td>0.5</td>
<td>0.8</td>
<td>0.5</td>
<td>0.75</td>
<td>0.5</td>
<td>0.4</td>
</tr>
</tbody>
</table>

2.2 Estimating the capture of the growth market

Growth market capture for the hypothetical diagnostic test will depend on:
1. Governmental response to public health problems;
2. Political, geographic and economic private market indicators that predict successful product introduction.

Current DOTS coverage (16), expansion of DOTS coverage over the last 8 years and DPT immunization coverage are used as a proxy for governmental response to public health problems. DOTS coverage, historical DOTS expansion rates and DPT immunization were scored as high, medium or low.
The second factor is an index of economic, geographic and political features that make a given country a good candidate for wide implementation of a new diagnostic product as part of TB control expansion efforts. Each country was assigned a score of high, medium or low on this index depending on whether or not they exceed the following thresholds:

- Private health expenditures (14) (threshold: greater than 38% of total health expenditures are private)
- Trade openness (6) (threshold: exceeding 3 on Heritage Foundation’s Index of Economic Freedom)
- Concentration of people (14) (threshold: urban population exceeding 58% of total population)
- Per capita income (14) (threshold: middle or high income countries)
- Ability of health system to reach all people (threshold: more than 90% of children are immunized with DPT (14)).

A country receives a point for each threshold that is exceeded (maximum score 5). Countries with a total score of 0, 1 or 2-3; 4-5 are rated low, medium and high, respectively. Table 17 presents market growth potentials as predicted by the extent of DOTS and immunization implementation and the market environment of each country. In the best case scenario, where the characteristics of the country are excellent and the DOTS coverage is high, we estimated that 90% of the growth market could be captured after 14 years. The smear replacement market in Thailand is an example of such a case. The DOTS programme in Thailand reaches 90% of the population and the market environment is excellent – trade is open, the private sector for health is large, per capita incomes are relatively high and the public health system reaches nearly everyone. Where the conditions are poor and DOTS coverage is low, we estimated that only 20% would be captured. Afghanistan is an example of such a country. In Afghanistan, DOTS coverage is just 53% and the market environment is difficult – per capita incomes are very low, the private sector is weak, the country is mainly rural and the public health system reaches relatively few people.

### TABLE 10. PERCENTAGE OF GROWTH MARKET POTENTIALLY CAPTURED BY A NEW DIAGNOSTIC AFTER 14 YEARS

<table>
<thead>
<tr>
<th>Government public health response in absence of new diagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>Excellent</td>
</tr>
<tr>
<td>Good</td>
</tr>
<tr>
<td>Poor</td>
</tr>
</tbody>
</table>

#### 3 Global and regional estimates for served, potential and total available markets

Below we describe and graphically present the SAMs, TAMs and PAMs for each of the 7 hypothetical diagnostic products (Table 5, Chapter 4). For illustration, countries are aggregated as follows: – High-income Countries (as defined by the World Bank), countries with high burden of TB as defined by WHO (16), and the rest of the world. High-TB-burden countries are further disaggregated into three categories:

1. **High-burden Asia** – China, India, Indonesia, Bangladesh, Pakistan, Philippines, Viet Nam, Thailand, Myanmar, Afghanistan and Cambodia.
3. Brazil and Russian Federation.

In addition, the markets were segmented by HIV prevalence rates where appropriate in order to assess the impact of test performance in HIV-infected people on national adoption success.  

---

1 New diagnostic tests will facilitate expansion of national TB control programmes by reaching more people and more effectively diagnosing those that are reached.
TABLE 11. COMPARISON OF PAM 2020 WITH SAM AND TAM 2020 FOR HYPOTHETICAL PRODUCTS, BY REGION (IN MILLION OF PATIENTS EVALUATED)

<table>
<thead>
<tr>
<th>Test type</th>
<th>Served Available Market (SAM)</th>
<th>Total Available Market in 2020 (TAM)</th>
<th>Potential Available Market in 2020 (PAM)</th>
<th>PAM in 2020 (HIV exclusion)a</th>
<th>PAM in 2020 (rural exclusion)b</th>
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</thead>
<tbody>
<tr>
<td><strong>GLOBAL</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>POC screening</td>
<td>98.75</td>
<td>193.36</td>
<td>79.17</td>
<td>42.64</td>
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<tr>
<td>Smear replacement</td>
<td>29.46</td>
<td>83.02</td>
<td>48.98</td>
<td>36.55</td>
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<tr>
<td>Culture replacement</td>
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<td>57.71</td>
<td>20.29</td>
<td>16.34</td>
<td>9.81</td>
</tr>
<tr>
<td>Monitoring</td>
<td>21.12</td>
<td>40.35</td>
<td>23.45</td>
<td>16.50</td>
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</tr>
<tr>
<td>DST replacement</td>
<td>0.56</td>
<td>5.94</td>
<td>2.72</td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>PPD replacement</td>
<td>49.61</td>
<td>83.09</td>
<td>31.70</td>
<td>25.43</td>
<td></td>
</tr>
<tr>
<td>Predictive PPD replacement</td>
<td>0.00</td>
<td>766.70</td>
<td>204.60</td>
<td>172.60</td>
<td>56.50</td>
</tr>
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<td><strong>22 HIGH BURDEN</strong></td>
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<td></td>
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<tr>
<td>POC screening</td>
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<td>136.76</td>
<td>56.62</td>
<td>27.00</td>
<td></td>
</tr>
<tr>
<td>Smear replacement</td>
<td>21.39</td>
<td>63.90</td>
<td>36.62</td>
<td>27.79</td>
<td></td>
</tr>
<tr>
<td>Culture replacement</td>
<td>3.71</td>
<td>43.89</td>
<td>13.73</td>
<td>11.01</td>
<td>4.47</td>
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<tr>
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<td>31.56</td>
<td>17.97</td>
<td>12.82</td>
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<tr>
<td>DST replacement</td>
<td>0.31</td>
<td>5.17</td>
<td>2.35</td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>PPD replacement</td>
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<td>607.40</td>
<td>162.10</td>
<td>139.70</td>
<td>37.40</td>
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<td><strong>HIGH INCOME</strong></td>
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<tr>
<td>POC screening</td>
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<td>3.56</td>
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<tr>
<td>Smear replacement</td>
<td>1.23</td>
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<td>2.70</td>
<td>2.43</td>
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<tr>
<td>Culture replacement</td>
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<td>3.00</td>
<td>2.70</td>
<td>3.00</td>
</tr>
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<td>0.11</td>
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<td>21.28</td>
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<td>12.55</td>
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<td>21.28</td>
<td>9.58</td>
<td>8.62</td>
<td>9.58</td>
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<td><strong>REST OF WORLD</strong></td>
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<td>POC screening</td>
<td>24.25</td>
<td>49.03</td>
<td>19.00</td>
<td>12.43</td>
<td></td>
</tr>
<tr>
<td>Smear replacement</td>
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<td>15.92</td>
<td>9.66</td>
<td>6.33</td>
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</tr>
<tr>
<td>Culture replacement</td>
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<td>10.07</td>
<td>3.56</td>
<td>2.62</td>
<td>2.34</td>
</tr>
<tr>
<td>Monitoring</td>
<td>4.92</td>
<td>8.29</td>
<td>5.09</td>
<td>3.33</td>
<td></td>
</tr>
<tr>
<td>DST replacement</td>
<td>0.18</td>
<td>0.62</td>
<td>0.26</td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>PPD replacement</td>
<td>8.65</td>
<td>61.81</td>
<td>17.75</td>
<td>12.88</td>
<td></td>
</tr>
<tr>
<td>Predictive PPD replacement</td>
<td>0.00</td>
<td>137.90</td>
<td>32.90</td>
<td>24.20</td>
<td>9.60</td>
</tr>
</tbody>
</table>

a Calculations assume no utility in settings where the overall HIV infection rate was >5% in the adult population.
b Calculations assume no utility in rural settings.
The socioeconomic burden of TB

Summary

The reach of tuberculosis (TB) is global, and the disease imposes an economic burden on societies and communities and on individuals of all ages, and in all social and economic classes. The capacity of TB to exact this economic toll is in part due to its ability to cause latent infection early in life and active disease later, during an individual’s prime wage-earning years (15–45 years). When individuals are lost to society through disability or death, their families, communities and, ultimately, society, pay the price through lost income, assets and productivity.

In this chapter, we describe the magnitude of the economic burden that TB places on individuals, communities and society in both high-income and low-income countries. We further describe how inadequate diagnostic tools perpetuate financial and opportunity losses through delays in diagnosis, the need for repeat testing and misdiagnosis. We conclude that new TB diagnostic tools could reduce the overall economic and medical burdens that cases of TB impose on patients’ families and on various higher levels of the health sector.

Defining economic costs

Ill-health has the potential to impose both direct and indirect financial costs. For most people in most countries, including the middle classes, health-seeking behaviour is affected by economic considerations and social costs. If the person who is ill decides to seek treatment, he or she will incur direct financial costs in the form of increased personal and/or household expenditure, most notably through out-of-pocket costs for medicines, diagnoses, the services of a health care provider and travel. Sickness can also result in various indirect financial costs, i.e. the associated financial and non-financial losses due to the lack of current income. Indirect costs are incurred both by the patient and the caretaker, and other people in the household may be required to work more or to devote time to the care of the ill household member (1). Indirect costs thus refer to the value of the resources lost, including reduced levels of work output and loss of productivity resulting from the inability to work or from a change of employment. The cost of care provided by relatives and friends may be direct, if it is reimbursed, or indirect in the form of time spent by household members on care rather than at work. These “time costs” may represent a significant fraction of the total cost of illness (2, 3). Information on these costs, however, is subject to various errors. Estimates of loss of productivity and income are inevitably approximate, especially for occupations such as housework, where the product cannot easily be measured. In retrospective household surveys, recall biases may influence the quality of information, including that relating to cost estimates, for example, for drugs and consultations, laboratory examinations and hospital expenses.

Socioeconomic burden on individuals and households

In many countries, to become ill can impose a tremendous economic burden upon those who are forced to support the inefficiencies of the health care system. In Sierra Leone, treatment costs for all types of disease conditions accounted for 26% of yearly household income in the lowest income groups and 3.7% in the highest income groups (4).
In a study in Tamil Nadu, India, 75% of urban TB patients’ households and 67% of rural TB patients’ households were in debt after TB diagnosis and treatment. The average amount borrowed was US$ 59 (5).

The economic impact of TB on an individual and on his or her household is particularly impressive. Patients’ direct costs can be between 10% and 20% of their annual income. Data on these costs, across a range of geographic settings, are available in the published literature, see Figures 1 and 2 (6–12). As these costs represent significant fractions of the total annual income of individuals and households, they can also be significant when compared to the total operational costs of the TB programme itself, (see Figure 3) (13).

In many countries, TB is highly stigmatizing. Thus, people, particularly women, may be ineligible for marriage, and face rejection by their spouse and families. In much of sub-Saharan Africa, TB is often linked in people’s minds with HIV coinfection, which may compound a person’s fear of isolation and rejection. If the major financial supporter is a male who dies from TB, the economic costs of illness may fall upon young widows, who often have dependent children, and who may have no work or educational experience.

Widows are generally compelled to seek employment at the expense of their child-rearing responsibilities (14, 15). Children are severely affected by

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**Figure 1**

**DIRECT COSTS** OF TUBERCULOSIS BORNE BY INDIVIDUALS AND HOUSEHOLDS AROUND THE WORLD BASED ON SELECTED REPORTS (US$)

<table>
<thead>
<tr>
<th>Country</th>
<th>Direct Cost</th>
<th>Individual Annual Income</th>
<th>Household Annual Income</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOUTH AFRICA</td>
<td>45.2 US$ (pre diagnosis)</td>
<td>22-957 US$</td>
<td>0.8-6.6%</td>
</tr>
<tr>
<td>PERU</td>
<td>3.3 US$ (post diagnosis)</td>
<td>10 US$</td>
<td>14%</td>
</tr>
<tr>
<td>THAILAND</td>
<td>99 US$</td>
<td>128 US$</td>
<td>15.8%</td>
</tr>
<tr>
<td>MALAWI</td>
<td>12-131 US$</td>
<td>130 US$</td>
<td>31%</td>
</tr>
<tr>
<td>INDIA</td>
<td>14%</td>
<td>12-121 US$</td>
<td>4.40%</td>
</tr>
<tr>
<td>NEPAL</td>
<td>15.8%</td>
<td>130 US$</td>
<td>31%</td>
</tr>
<tr>
<td>BANGLADESH</td>
<td>0.8-6.6%</td>
<td>22-957 US$</td>
<td>0.8-6.6%</td>
</tr>
</tbody>
</table>

*a* In US$ and as a percentage of household or individual income.

*b* Definitions and methods are not standardized; refer to the sources for more information.
having one or more parents with TB. Such disruptions may mean that children do not continue their education or that they move to an urban area to find a job, or both (4, 14, 15). Girls, in particular, are often taken out of school in order to help at home, care for sick relatives or find paid work outside the home.

In these circumstances, children may never return to school and will be permanently disadvantaged for the rest of their lives.

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Figure 2

INDIRECT COSTS* OF TUBERCULOSIS BORNE BY INDIVIDUALS AND HOUSEHOLDS AROUND THE WORLD BASED ON SELECTED REPORTS (US$)**

<table>
<thead>
<tr>
<th>Country</th>
<th>Direct Cost</th>
<th>Individual Type of Annual Income</th>
<th>Household Type of Annual Income</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>468 US$ (mean)</td>
<td>272 US$</td>
<td>4.6 US$</td>
</tr>
<tr>
<td>Peru</td>
<td>48 US$ (mean)</td>
<td>272 US$</td>
<td>4.6 US$</td>
</tr>
<tr>
<td>Malawi</td>
<td>46 US$ (mean)</td>
<td>272 US$</td>
<td>4.6 US$</td>
</tr>
<tr>
<td>India</td>
<td>115 US$ (pre diagnosis)</td>
<td>272 US$</td>
<td>51%</td>
</tr>
<tr>
<td>Nepal</td>
<td>115 US$ (pre diagnosis)</td>
<td>51-58 US$</td>
<td>31-39%</td>
</tr>
<tr>
<td>Thailand</td>
<td>115 US$ (pre diagnosis)</td>
<td>272 US$</td>
<td>31-39%</td>
</tr>
</tbody>
</table>

* In US$ and as a percentage of household or individual income that includes lost time from work.
** Definitions and methods are not standardized; refer to the sources for more information.

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Figure 3

DIRECT AND INDIRECT COSTS OF AMBULATORY TB TREATMENT BORNE BY PATIENTS IN DAR ES SALAAM, TANZANIA, 1996 (US$)

- Inability to work: 154–1384 US$
- Transport: 13–20 US$
- Consultation and drugs: 17–50 US$
- Examination and lab costs: 2 US$

[Source: reference 13]
Socioeconomic burden on specific communities and larger groups

Certain groups of individuals in a community are at increased risk of TB. Miners, the elderly, prisoners and immunocompromised, i.e. HIV-positive, individuals are among them. The last two groups have been associated with outbreaks of multidrug-resistant tuberculosis (MDR-TB), which has serious medical as well as economic consequences. In the United States, MDR-TB treatment costs US$ 250,000 per case.

Socioeconomic effect on women

Bushra’s story

she was rejected by her husband and his family

Bushra died of TB aged 26. She weighed barely 28 kg by then, having steadily lost weight for a couple of years. “Her coffin weighed no more than a sparrow’s”, said her grieving mother, Hameeda. Visitors to her parents’ two-roomed house in Lahore, where she had lain listlessly since being brought back from the hospital in July, barely recognized the vivacious bride of just two and a half years earlier, when she was wedded to her first cousin in Sargodha town, six hours drive from Lahore. Hameeda believes that her daughter died due to neglect and psychological abuse stemming from her TB disease. In the 11 months she was with her family, her treatment cost them US$ 4000, which they scraped together by borrowing, selling her mother’s jewellery, and using up their entire savings. “She came to visit us one year after her marriage and we were shocked at her appearance. We took her to see a doctor who took X-rays and various tests. She tested negative for TB but the doctor warned that she was very weak and would be susceptible to TB. He prescribed a three-month treatment to prevent this. We got the medicines he prescribed but the very next day her in-laws came and took her back. We protested, but they didn’t listen.”

Bushra’s in-laws are a family of “hakeems”, traditional healers. They said they did not believe in allopathic medicine (though when their son, Bushra’s husband, had been ill with meningitis, he had been treated by allopathic doctors). Her health steadily deteriorated and her mother was finally allowed to take her back home to Lahore. They had to shoulder the expense. Bushra saw more than one doctor and was prescribed different regimens of drugs.

Source: reference 16.

Socioeconomic effect on children

Shehab Ali never went to school, so he was determined that his sons and daughter should receive an education. Shehab was a rickshaw puller and struggled to earn enough so that his children could go to school, but when he discovered he had TB and became too ill to work, his 15-year old son was forced to leave school and take up his father’s trade. “But he is new and does not know many places,” explained his concerned father. “He cannot get many passengers.” Shehab has also taken his ten-year old daughter out of school and she is working in a factory. Shehab and his family are hungry; they are having to subsist on half the rice they need every day, so his two other sons will also leave school and go out to work.
Miners: TB as an “occupational disease”

Exposure to silica dust is recognized as one of the risk factors for occupation-related tuberculosis. The extent to which current tuberculosis is related to occupational risk is not known. Risk attributable to occupational causes may be being missed, particularly against the background of the increasing incidence of tuberculosis disease due to HIV and overcrowded housing (17).

Tuberculosis has long been recognized as an occupational disease associated with the mining industry, e.g., in South Africa, where TB has now overtaken (mining) accidents as the leading cause of mortality in the gold-mining industry (18). More than 2% of the workforce in the gold-mining sector is likely to become infected with tuberculosis each year. By 1996, the mortality rate had become about 0.15% (18). Research in the gold-mining industry has shown that the incidence of tuberculosis (new cases per year) has more than doubled since 1990. It is likely that much of the increase is a result of the HIV epidemic since, in the same period, the prevalence of HIV has increased almost threefold. For each unskilled worker with TB working in certain regions in South Africa, AngloGold Limited of South Africa estimates that US$ 410 in work shifts are lost (19). At some point, the burden of TB may reduce business profits by cutting the supply of labour and skills (which results in the need for worker retraining, and thus additional expense), undermining income and restricting demand, increasing business costs (increased sick pay and death benefits), disrupting production and reducing productivity, and, ultimately, by reducing the size of the potential market for the business’s products.

Prison populations

Where data are available, much higher levels of active TB disease, as well as MDR-TB, are reported among prison populations than among civilian populations. Prisons promote the transmission of TB infection through prolonged and repeated exposure to Mucobacterium tuberculosis, a result of late case detection and the high turnover of prisoners. Since prisoner turnover is so high, the concentration of risk factors can ignite TB epidemics that are not restricted to the confines of the prison. The transmission of M. tuberculosis in correctional facilities presents a health problem for both inmates and the communities into which they are released (20).

Treating MDR-TB is more than 100 times more expensive than treating drug-susceptible TB (about US$ 250,000 compared to about US$ 2,000 in the United States). In patients with MDR-TB, DOTS is useless because the two best drugs, isoniazid and rifampicin, are ineffective.

Rapid and sensitive methods for drug-susceptibility testing are critical. In the special case of a TB referral prison in central Siberia, drug-susceptibility testing for 164 new DOTS patients showed an initial resistance rate of 66% for isoniazid.
and an initial MDR rate (isoniazid and rifampicin) of 22.6% (21). It is essential that accurate testing for drug susceptibility be carried out at an early stage to enable these patients to be treated appropriately and to prevent transmission of MDR strains in the community, particularly after the release of patients from prison, since expensive second-line anti-TB drugs are required to treat MDR-TB.

Immunocompromised individuals

In an optimistic, but ultimately misguided belief that TB would soon be eliminated in North America, health officials in New York City dismantled the entire TB public health infrastructure of hospitals, sanatoria and diagnosis centres in the 1970s. Only a decade later, New York City was forced to rebuild that system, at a cost of US$1 billion, in order to contain a TB outbreak that included deadly drug-resistant strains in predominantly HIV-infected persons. Missed, and, therefore, delayed diagnosis of TB in immunocompromised patients can have significant economic consequences, since TB patients coinfected with HIV are more likely to suffer a recurrence or relapse of TB. These individuals are more likely to die from their TB or relapse after treatment (24).

The elderly

Post-industrial countries have large and growing elderly populations. In 1989, only 11.6% of the Japanese population was aged 65 years and older; however, it is projected that 25.6% will be over 65 years of age by 2030. The shift will make Japan one of the world’s most elderly societies, and the change will have taken place in a shorter span of time than in any other country. Among the elderly, the incidence of TB is disproportionately high (25).

The diagnosis of TB is often poor in elderly patients because of low clinical suspicion, unusual presentation and the presence of associated illnesses. Evidence suggests that, compared with their community-dwelling counterparts, the institutionalized elderly are at a greater risk for reactivation of latent TB and for acquisition of new TB infection (26). Failure to diagnose TB in this age group can have important public health and economic consequences. See, for example, Ijaz and others, who documented molecular and traditional epidemiological studies and revealed an outbreak of TB that began in a nursing home and spread to a second nursing home, a local hospital and then the community (29).

**TB burden at the societal level**

Surprisingly few analyses of the socioeconomic burden of TB have been carried out in the higher levels of the health sector. Notable studies have been performed in India (30) and Peru (6) (Figures 4 and 5).

![Figure 4: TOTAL ECONOMIC IMPACT OF TB IN PERU, 2001 (US$)](source: reference 6)
Socioeconomic consequences of current TB diagnostics

Figure 6 is a schematic diagram of the timescale of a patient’s encounters with both the TB bacillus and the health care system. For a variety of reasons, the patient’s journey from the first appearance of symptoms to the point at which the patient is offered treatment rarely follows a straight line. The main reasons are:

1. The patient begins at a lower level in the health care system where TB diagnostic tests may not be available.
2. Physicians and other health care workers do not suspect TB and do not order the appropriate tests.
3. The operational demands of the test are too great, leading to non-compliance with the test protocols.
4. The technical performance of the test is suboptimal.

One or more of these factors contribute to missed or delayed TB diagnosis, which can have important economic and medical consequences. A critical economic burden imposed by misdiagnosis is that substantial resources of the patients and the health care system can be used up before a definitive diagnosis is obtained. There are three main consequences of existing barriers to the rapid and accurate diagnosis of TB. Firstly, people who have TB can be missed, and, for various reasons, they do not bother to find out the results, but return to the community to spread the infection. Secondly, people who do not have TB are misdiagnosed, because of a lack of faith in negative smear microscopy results.

Thus, scarce health system resources are “wasted”. Thirdly, some patients who are already cured will be treated again since there is no reliable way to track the progress of the infection.

![Threshold for visibility of AFB by smear microscopy](image)

*AFB* = acid-fast bacilli = smear+*
Effect of misdiagnosis
Many health care providers rely solely on chest radiographs for TB diagnosis. For instance, a survey in India found that only half of the 518 physicians studied used sputum-smear microscopy; the rest relied solely on chest X-ray for diagnosis (29); an earlier study had shown that over 75% of all patients in private clinics in western India had not been subjected to sputum examination at all by the private physicians. Because of low specificity, chest X-ray alone frequently results in over-diagnosis and over-treatment, which further burdens patients and health systems. Physicians often favour radiography because of its point-of-care use in many settings (or at least independence of laboratories), visual results and the fact that radiographs obviate the need to collect and handle offensive, possibly infectious, clinical specimens such as sputum. Patients may prefer it because they can plainly see the results (e.g. the “spots”), and thus are directly involved in their own diagnosis.

Effect of the need for repeat testing and diagnostic uncertainty
The need for repeat testing threatens case holding as patients often lose faith in the tests and/or exhaust their savings by delivering multiple samples and/or by returning to collect the results. A study in a Malawi hospital that followed up AFB-positive patients showed that nearly 60% did not start actual treatment because they failed to collect their results (32). Diagnostic uncertainty leads to waste of resources. For example, in a New York City hospital, nearly 90% of the hospital resources allocated to TB were used during the diagnostic period before a definitive culture result was obtained (33). In patients with discordant diagnoses (i.e. culture-negative but smear-positive, and vice versa), the ratio between correct and incorrect diagnoses and treatment recorded at the time of the patients’ discharge was no better than 50:50 (34). The response of many clinicians to a smear-positive diagnosis is “TB until proven otherwise”, even if the culture is negative. The declining incidence of TB in the United

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>REFERENCE</th>
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<tr>
<td>Fear of diagnosis</td>
<td>Calder et al., 2000 (38)</td>
</tr>
<tr>
<td>Desire to self-treat</td>
<td>Calder et al., 2000 (38)</td>
</tr>
<tr>
<td>Perception that TB is incurable</td>
<td>Khan et al., 2000 (40)</td>
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<tr>
<td>Poor knowledge about TB</td>
<td>Ngamwithayaspong et al., 2001 (41)</td>
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<tr>
<td></td>
<td>Godfrey-Faussett et al., 2002 (42)</td>
</tr>
<tr>
<td>Poor perception of quality of health service</td>
<td>Asch et al., 1998 (43)</td>
</tr>
<tr>
<td>Concern about long waiting times</td>
<td>Asch et al., 1998 (43)</td>
</tr>
<tr>
<td>Lack of finances to cover all costs involved</td>
<td>Asch et al., 1998 (43)</td>
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<tr>
<td>Distance to health services</td>
<td>Asch et al., 1998 (43)</td>
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<td>Muula, 2001 (44)</td>
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<td></td>
<td>Khan et al., 2000 (40)</td>
</tr>
<tr>
<td>Language differences between patient and doctor</td>
<td>Greenaway et al., 2002 (39)</td>
</tr>
<tr>
<td>Ageb</td>
<td>Lienhardt et al., 2001 (45)</td>
</tr>
<tr>
<td></td>
<td>Leung et al., 2002 (46)</td>
</tr>
</tbody>
</table>

---

* Some evidence of a longer delay among women.
* Some evidence of a longer delay among the elderly.
States is being accompanied by an increasing false-positive smear rate, and, as the rarity of TB increases, the greater may be the proportion of resources consumed by persons who, in fact, do not have TB at all.

Delayed diagnosis

The economic impact of current regimes for TB diagnosis is compounded by delays on the part of the patient, following the onset of symptoms, in seeking care (patient delay) and on the part of health providers in requesting appropriate diagnostic tests and laboratories in delivering quality results promptly to the patient (health system delay). The relative importance of these delay periods varies from country to country and from region to region. The factors contributing to delays in patients seeking care and in health systems offering diagnostic and treatment services to TB patients are presented in Tables 1 and 2, respectively.

Delay in patients seeking medical care (patient delay)

Delays in diagnosis can be associated with increased costs to patients in the form of out-of-pocket payments for medications, special foods, tests, and lost work time. It is not uncommon for a patient with TB to have multiple encounters with the health system prior to diagnosis. When people delay seeking care, they remain sick, and they therefore work at a less efficient and profitable pace or are unable to work at all (see Figure 2). As a result of diagnostic delays, people with TB remain infectious and transmit the infection to their families or to other people in the community.

Table 1 suggests that the delay in patients seeking care usually occurs because people cannot afford any extra expense – the costs of travel to a clinic, as well as the time off work while making the journey, can be considerable. People with low incomes, especially those in rural areas, frequently have to travel further or longer than those who are better off (36, 43, 48, 49). In many developing countries, there are different providers, for example, herbalists and traditional healers. People with symptoms will first seek advice and treatment from a private practitioner or, depending on the context, a traditional healer. Significantly, patients seeking a diagnosis often shop around among private practitioners, which adds to the direct costs. A study conducted in Zambia found that the average TB patient had nearly seven encounters with a health care provider before being diagnosed (42). Any requirement for multiple visits to the hospital limits the number of cases of smear-positive tuberculosis that are both diagnosed and treated.

Delay in health system offering diagnostic and treatment services (provider, laboratory and treatment delays)

Delays in the offer of diagnostic tests and treatment by health care providers are primarily due to the failure of the health care professional to enquire about TB in the family, the inability to recognize symptoms, the lack of tuberculin testing, poor diagnostic capability, and administrative inefficiency (Table 2). These failures are common in areas of high TB burden. Studies conducted in Delhi, Karnataka and Tamil Nadu, India, showed that, even after multiple visits, less than one third of patients underwent sputum-smear examination, despite incurring costs representing 1–6 months’ income (Figures 1 and 2) (9, 50).

### TABLE 2. HEALTH SYSTEM FACTORS CONTRIBUTING TO TB DIAGNOSTIC DELAY

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of diagnostic facilities in general practitioners’ clinics</td>
<td>Teo, 2002 47</td>
</tr>
<tr>
<td>Lack of trained personnel for performing smear tests</td>
<td>Teo, 2002 47</td>
</tr>
<tr>
<td>Initial consultation with private practitioner</td>
<td>Rajeswari et al., 2002 5</td>
</tr>
<tr>
<td>Initial consultation at private pharmacy or public hospital</td>
<td>Lonnroth et al., 1999 34</td>
</tr>
<tr>
<td>Consultation with multiple doctors</td>
<td>Calder et al., 2000 38</td>
</tr>
<tr>
<td>Pre-existing lung condition in patient</td>
<td>Calder et al., 2000 38</td>
</tr>
<tr>
<td>No requirement for chest X-ray</td>
<td>Calder et al., 2000 38</td>
</tr>
<tr>
<td>Hospital with low rate of admission for TB*</td>
<td>Greenaway et al., 2002 39</td>
</tr>
</tbody>
</table>

* Canadian study.
A lack of education on the part of the physician or a preference for more "modern" methods such as chest X-rays may explain poor diagnostic capability. In many countries, a surprisingly high proportion of physicians do not follow recommended diagnostic and sputum-monitoring procedures (51–53). The results of a study in the United States in 1996 were disturbingly similar to the findings of the above studies. Only 22% of 840 community paediatricians and family physicians surveyed in four mid-Atlantic states and the District of Columbia adhered to the recommendations published by the American Academy of Pediatrics (54). Standardized culture and drug-susceptibility testing methods for diagnosing TB are inherently time-consuming. Evidence suggests that delays in the actual reporting of laboratory results occur because of faulty equipment, shortages of staff and supplies, and patient drop-out (i.e. people failing to return to deliver multiple specimens); anecdotal evidence supports these findings.

Implications for the test developer or investor

From the information presented, several important conclusions for test developers and their investors can be drawn about the behaviour of the health care purchaser in most countries, which can be summarized as follows:

> Patients in all socioeconomic groups find ways to mobilize the funds necessary to cover the expenses incurred by the use of health services for the diagnosis and treatment of TB. While this health-seeking behaviour does not necessarily equate with a willingness to pay for a new diagnostic technique or diminish the importance of finding affordable tests, it clearly indicates an ability to pay for diagnosis. Almost everyone, even those in the poorest socioeconomic groups, eventually pays for curative treatments, and people on low incomes will spend a higher proportion of their earnings on health care than those in higher income brackets.

> Awareness of patients' health-seeking behaviour is an important aspect of market appraisal because the extent to which tests are patient-friendly will undoubtedly influence uptake.

> Case holding is a challenge when test accuracy is suboptimal and the operational demands are high. A diagnostic test with increased sensitivity, i.e. one that would be capable of detecting smaller mycobacterial loads, would allow treatment to be started earlier, even before a patient was diagnosed as positive for AFB and before the need for culture (55).

> Both cost savings and health benefits would result from reducing the number of new cases and accelerating the recovery of existing cases. These savings could very well justify increased prices for new TB diagnostic tools.

> Any new test must be attractive to physicians as well as to patients. The perceived advantages of chest X-rays over sputum smears – i.e. control by the physician over testing and interpretation; reduced reliance on overworked laboratory staff; and the use of a technique that is simple, visual and not "messy" – might be just those criteria that we should look for in an ideal diagnostic assay for TB. The increasing prevalence of TB in some countries and in some populations (children, the elderly, prisoners and the immunocompromised) will almost inevitably lead to increased laboratory workloads. Given the present and predicted future course of HIV/AIDS, the availability of trained laboratory personnel will become increasingly limited. Business managers should be aware that reducing or eliminating delay in the accurate diagnosis of TB might provide sufficient incentive on its own to justify increased prices for new TB diagnostics.
Diagnostics for tuberculosis: global demand and market potential
Summary

The presence of tuberculosis (TB) in both established market economies and developing nations, coupled with the inadequacy of current diagnostic methods, provides a unique opportunity for the introduction of a range of improved diagnostics that can gain wide acceptance in both the private and public markets across the world. Although a number of companies have successfully introduced new diagnostic products for tuberculosis over the last few years, the performance or use characteristics of these tests have not been ideal, and penetration in large TB markets has been limited, especially in developing countries. Physicians, patients, governments and global health agencies are looking for new ways to quickly and accurately identify active tuberculosis, detect individuals who have latent TB infection, and determine the antibiotic sensitivity patterns of clinical isolates of Mycobacterium tuberculosis (MTB). The TB diagnostics marketplace is characterized by some unique features which are important for the diagnostic industry to understand in order to be commercially successful over the long term. The following discussion will provide some background information on opportunities and challenges in the TB diagnostic market and gives an overview of anticipated changes in this environment.

Public awareness

Despite its global position as one of the leading infectious killers of man, most people in industrialized countries, including corporate strategists, consider tuberculosis to be a resolved public health problem that is only of historic relevance. This is largely attributable to the great success in TB treatment and control in the industrialized world following the introduction of effective TB treatment in the 1950s, and the defeat of a brief resurgence of TB in the United States in the early 1990s. The close association of TB with poverty, malnutrition and ‘social outcast’ status in developed countries further compounds the lack of public interest and awareness. Today it is practically unheard of that any person of public notoriety in industrialized societies becomes ill or dies from TB. This situation is vastly different from other diseases of public concern, such as AIDS or even the hepatitis viruses which have killed movie stars, songwriters and other high-profile individuals. Low public interest, combined with the lack of reliable data on the size and, more importantly, the dynamics of the TB diagnostic market (see below), have created an favourable environment for considering investment in TB diagnostics.

However, this situation has recently changed to a significant extent, in part due to growing awareness of the inextricable link between HIV and TB. In many countries hard hit by the HIV pandemic, TB incidence has risen markedly to become the leading cause of death in 15–44 year olds. This relationship was highlighted in Nelson Mandela’s declaration, at the XV International AIDS Conference in Bangkok, Thailand (2004), that “we can not win the battle against AIDS if we do not also fight TB”. Such messages have helped to put TB on the agenda of powerful HIV/AIDS advocacy groups and significant funding is now being directed towards the diagnosis and treatment of TB in HIV/AIDS suspects and patients. Ironically, the tragedy of HIV is serving to end public ignorance of tuberculosis as an omnipresent health problem in developing countries, and as a resurging threat in the developed world.
Market data

Market data for selected technologies (like NAAT testing) and regions (mostly industrialized countries) have been reported sporadically, but reliable data on a global scale, covering all currently utilized methods and demonstrating the true market potential of improved products, have not been available. This document closes several information gaps and provides a more complete view on the TB diagnostic market situation. An analysis of this depth is required for several reasons:

- Conventionally employed methods have significant shortcomings, resulting in important over or underestimates of the TB diagnostics market size even for industrialized countries;
- New dynamics in the marketplace (e.g. TB-HIV coinfection, emerging multidrug-resistance in Eastern Europe, and the increase in labour migration) necessitate a change from the status quo of reliance on conventional diagnostics, and will lead to qualitative changes in the approach to TB testing in the future;
- In most developing countries there is a significant private sector where testing for tuberculosis exceeds testing performed in industrialized countries by several fold. These markets can provide a healthy return on investment for diagnostic companies willing to invest in tools which overcome the weaknesses of currently employed procedures;
- Increased funding has become available, notably through the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), for countries previously unable to purchase TB diagnostics using their own financial resources. This will allow test developers to tap into a market of growing potential, including vast numbers of people thus far unserved by any TB diagnostic procedures.

The availability of relevant and reliable market data promotes a fresh look at the TB diagnostic market as an opportunity, without requiring compromise of sound business analysis and common standards for investments.

Pricing

The most widely used method for detection of active TB, sputum microscopy, is characterized by very low reagent costs but a significant burden of labour. In industrialized countries, commercial laboratories are accustomed to diagnostic procedure assessments based on the "cost per reportable result"; not exclusively reagent costs. Determining cost per reportable result requires consideration of many factors beyond mere reagent cost, including labour, depreciation (or rent) for instrument(s), calibration and quality controls, repeat measurements for results outside pre-established limits, waste of reagents for priming, other consumables and laboratory overheads. When fully considered, the cost per reportable microscopy result is not trivial. While it is conventional to use this more sophisticated costing approach for analysis in the private sector of developed and developing nations, the public health sector of developing countries often applies a different logic in which laboratory personnel is largely considered a fixed expense and the focus on reagent costs prevails. On the other hand, public health officials are increasingly sensitive to the fact that the limited sensitivity of smear microscopy in many settings results in many secondary costs, as undetected TB patients continue to spread disease in the community, and as additional diagnostic testing, like culture or chest X-ray, is performed on smear-negative patients.

A further important aspect to determine the value (and the potential price) of a more accurate, rapid and convenient diagnostic tool is whether or not repeat patient visits can be minimized or avoided altogether. Tests like smear microscopy require the analysis of multiple samples (often 2 or 3 samples taken on different days), which places a burden on patients as well as laboratories. Again, it will be easier to have this value appreciated in the private setting, where all costs (the diagnostic procedure as well as the costs for transport, loss of salary, etc.) are commonly borne by the patient as opposed to in the public health sector, where the cost of the diagnostic procedure may be partially or wholly covered by the national health system. In tenders for the public health
system it is common practice, justified by lower marketing and distribution costs, to offer products at a significantly lower price than in the private markets. In this context it must be kept in mind that some countries accept only a certain maximum difference between the price for the private market and the public (tender) market.

**Cost of product development**

Every investor will carefully weigh their engagement in a given market opportunity in terms of upfront investment required, the degree of risk, and the anticipated overall return on investment. For TB diagnostics, expensive discovery research on a biohazardous, slow-growing organism, and significant upfront product development costs have frequently deterred companies, particularly smaller ones, from leveraging existing in-house platforms towards the development of improved TB diagnostics. Fortunately, there is significant public sector funding for basic research and target discovery available through a variety of organizations, some of which are highlighted in Chapter 1. For diagnostics development specifically, FIND (Foundation for Innovative New Diagnostics), with funding from the Bill and Melinda Gates Foundation, was established in 2003 to financially and logistically support promising new product development for TB diagnostics once proof of principle has been demonstrated.

**Global TB organizations**

TB is one of the few diseases in which medical research and the development of public health policy have been quite well organized through a limited number of international organizations, all working toward coordinated activity through the Stop TB Partnership hosted by the World Health Organization. This has resulted in effective global action, such as the development and the implementation of the DOTS strategy, with its emphasis on high rates of cure, control of transmission, and limiting the emergence of drug resistance in TB-endemic countries. However, until recently, there has been comparatively less attention on fostering new developments in diagnostics that can better address the needs in specific market segments. The establishment of the Working Group on New Diagnostics within the Stop TB Partnership is one example of a new gateway for innovative diagnostic solutions into routine practice of tuberculosis management.

**Regulatory aspects**

ISO certification (preferably according to ISO 13485:2003) not only eases the regulatory process in many places, but more importantly, is becoming a prerequisite for participation in public tenders in a number of countries, including those that do not yet have a fully developed regulatory system in place.

**Distribution**

Because smear microscopy largely uses generic reagents, is in widespread use, and has changed little in the past 100 years, the infrastructure necessary to promote new TB diagnostic products, to ensure their safe delivery, and to train people in their use, does not yet exist universally. In general, the distribution of TB diagnostics will have to follow the established rules for diagnostics in the target markets via manufacturer subsidiaries and local distributors, in accordance with local rules for product importation and registration.

In the public sector, a new avenue
for moving approved diagnostic products into developing countries is evolving via the Global Drug Facility (GDF) a component of the Stop TB Partnership (see Chapter 1). Established in 2001 to ensure the smooth delivery of high-quality drugs to developing countries, at the time of printing, the GDF has delivered anti-tuberculous drugs to over 5 million patients in 58 countries and implemented pilot projects delivering diagnostic kits for smear microscopy in 3 countries (Congo, Nigeria and Tajikistan). If the pilot programme is successful, the GDF will move to acquire diagnostics from prequalified vendors through a central procurement process, allowing vendors to avoid the burden of importation procedures and local distribution. The regulatory hurdle may also be eased, as the GDF stipulates that the receiving country actively support the product registration process, where required.

Another innovative solution to reduce distribution costs is to piggyback on the infrastructure of the related pharmaceutical industry. For instance, in India, some pharmaceutical manufacturers of generic products are examining the idea of offering TB diagnostics through their channels for drug delivery. The extensive sales and logistic infrastructures of these companies could thus become a channel through which innovation in TB diagnostics is brought to a key decision-maker, the physician.

**Conclusion**

The worldwide market for TB diagnostics is on the verge of change. Diagnostic needs are still poorly addressed with the present procedures but, for the first time, public awareness is increasing and new funding is becoming available for countries that had previously not been able to afford innovative diagnostic solutions. Other barriers to entry can be lowered by making good use of external funding for product development, or utilizing the Global Drug Facility of the Stop TB Partnership as a cost-efficient inroad into the high-burdened and developing countries. The data compiled in this report (including the update on regulatory requirements) provide an essential prerequisite for sound business decisions. An increasingly organized marketplace, reliable information about the size and character of that market, clarity about the global diagnostic needs, and novel avenues for public sector assistance with research, development and even distribution, have intersected to elevate the status of TB diagnostics as an investment opportunity worth serious consideration. This should encourage investors in the diagnostic industry to take a fresh look at a market that is still growing – in the developed and developing world–including the financially rewarding private sector of emerging markets, where better diagnostics can help to defeat a disease which today is treatable and curable, if only diagnosed properly and at the right time.
Health system capacity and expenditures (4)

- % GDP spent on health care: 9.5
- Per capita total health expenditure (US$): 1,995
- No. of hospital beds/1000 population: 4.1
- No. of doctors/1000 population: 2.5

Total health expenditures

Government: 67.9%
Private: 32.1%

Private prepaid plans as % of private expenditure on health: 22.7

Accreditation bodies

TB epidemiology (7)

Total estimated new TB cases: 1,128
Notified new “other” cases:
- DOTS and: 813 (> 100%)
- Non-DOTS: 813 (> 100%)

Notified new “other” TB cases:
- DOTS: 341 (55%)
- Non-DOTS: 485 (79%)
- Not notified new “other” TB cases: 0 (0%)

Total estimated new “other” TB cases: 622

TB laboratory network (8)

National Reference Lab(s): Queensland Diagnostic and Reference Laboratory for Mycobacterial Diseases, Brisbane.

Smear laboratories
- Total: 132
- Per million: 7

Culture laboratories
- Total: 39
- Per million: 2

DST laboratories
- Total: 10
- Per million: 0.5

Health care system delivery (5)

Public
- The Federal Government funds universal benefits schemes for medical services (Medicare) and for pharmaceuticals, while states and territories have the major responsibility for the financing and public provision of health services, including public and psychiatric hospitals. Local governments mainly focus on environmental health and the provision of community-based and home-care services.
- The government plays a very dominant role, as funder, purchaser, provider and regulator, particularly at the federal level.

Private
- One of the largest private sectors outside the US.
- Private insurance is purchased by individuals (not employers) and is supported through government subsidies and regulation. It offers the services covered under Medicare plus expanded hospital care, products and a greater choice of hospitals and doctors, and earlier access to elective services.

Laboratory infrastructure (6)

Estimated total no. of labs: 2,600

Notified new “other” TB cases
- DOTS: 341 (55%)
- Non-DOTS: 485 (79%)
- Not notified new “other” TB cases: 0 (0%)

Total estimated new “other” TB cases: 622

Notified new Sm + cases
- DOTS: 48 (9%)
- Non-DOTS: 65 (13%)
- Not notified new Sm + cases: 392 (78%)

Total estimated new Sm + TB cases: 505

% Multidrug-resistance in new cases: 1.6

Estimated % adult TB cases that are HIV co-infected (15-49 years): 8.1
**Estimated in vitro diagnostics market** *(9)*

- **US$ 210-240 million**
- Annual Growth 3-5%

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**Major markets** *(10)*

- Major cities: Brisbane, Sydney, Perth, Melbourne, and Adelaide. Many companies use Australia as a stepping stone or as a base from which to market to other countries of Asia-Pacific.

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**National regulatory policies for in vitro diagnostics** *(11)*

**Regulatory body/regulatory legislation**
- Before any medical device can be supplied in Australia, details must be included in the Australian Register of Therapeutic Goods (ARTG), which is regulated by the Australian Therapeutic Goods Administration (www.tga.gov.au, TGA). If United States-manufactured products do not have a CE mark/EC certificate, application must be made to the TGA for a conformity assessment of the product.

**Who registers the product?**
- Whoever imports, manufactures, exports or modifies the product for supply is considered the Sponsor for that product in Australia and is responsible for its entry in the ARTG before it may be legally supplied. The sponsor must be an Australian entity.

**Classification of in vitro diagnostics**

**Is local testing required to license the product?**
- No

**Are quality management systems/factory audits a required component of post-market entry?**
- The TGA carries out a range of assessment and monitoring activities to ensure that therapeutic goods meet an acceptable standard. Overall control of the supply of therapeutic goods is exercised through pre-market assessment, licensing of manufacturers, and post-market vigilance.

**Movement towards regulatory harmonization**
- Member of the Global Harmonization Task Force.

**Regulatory requirements for manufacturers/importers of TB-IVDs** *(12)*

- Requirements will depend on the "public health risk" rating of tuberculosis. See the Annex.

**Import tariffs and other taxes** *(12)*

- The customs duty rates for medical products range from 0 to 5%, with medical consumables taxed at the higher rate end and medical equipment generally entering free of duty.

- Exporters should contact the Australian Customs Service (www.customs.gov.au) for exact rates for their products. The federal government introduced a goods and services tax (GST) on 1 July, 2000. While prescription or pharmacist-only medicines and medical/surgical goods are exempt from the tax, all other medical products are subject to a 10% GST.

**Cost of registration** *(13)*

- Fees for devices classified as "registerable" vary according to the level of evaluation required. For "listable" goods each application for listing costs US$ 220, and a further US$ 220 is payable once the product is placed on the ARTG.

**Duration of registration process** *(14)*

- For listable goods, the process currently takes around four weeks.

**Local manufacturing capacity** *(15)*

- There are an estimated 670 domestic medical device manufacturers. Most are small operations that produce for localized or niche markets and serve mainly domestic markets.

**Local distribution** *(16)*

- Distribution channels are quite lean. The importer, whether the local subsidiary of a multinational or a locally owned distributor, generally sells directly to end-users, without any intervening layer of wholesalers or sub-dealers.

- The most common and effective method for new companies to market medical products and services is through the appointment of a distributor. It is advisable to have representation, for both distribution and support, in each state for comprehensive coverage. Australian companies are extremely receptive to joint-venture arrangements, particularly in cases where high costs or specialized technology/services are involved. These are solely regulated by the terms of the joint-venture agreement between the individual parties.

**Procurement** *(17)*

- Purchase of any infectious diseases diagnostic test is managed at the state level and most organizations buy individually - by tender for large equipment and by personal contact for smaller purchases.

- The tendering process is variable; some tenders are sent out to local companies, some are only advertised in the local press.
Public hospital procurement can vary greatly in different states.

- In New South Wales and Queensland, purchases tend to be made centrally, while in other states, hospitals are afforded greater autonomy over procurement within a designated budget.
- In Victoria, the majority of equipment and supplies are acquired through the private Victorian Hospitals Association. For major items, sales to hospitals are made by tender. The hospitals may publish the tender or directly seek out a known and approved supplier.
- Australia has not signed the World Trade Organization (WTO) Agreement on Government Procurement and, as such, is not bound by tender conditions that prohibit the specification of locally made products. Government buyers are, in fact, obliged to consider local content when making purchasing decisions.

**Intellectual property rights issues (18)**

| Year in which country joined World Trade Organization (WTO) and is therefore under the TRIPS agreement | 1995 |
| Year in which the country must be in accordance with TRIPS | 1996 |

**Industry associations**

- Medical Industry Association of Australia, Inc. (MIAA)
  PO Box 299
  St Leonards NSW 1590
  Tel: (02) 9437 1151
  Fax: (02) 9437 3177
  www.miaa.org.au

MIAA represents the interests of manufacturers, importers and distributors of medical devices and diagnostic reagents. Members distribute over 85% of the non-pharmaceutical products used in the diagnosis or treatment of disease.

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a “Other” includes smear-negative pulmonary TB and smear-unknown.
b Includes patients previously treated for tuberculosis and relapses.
c May include microbiological TB-IVD/IVD for detection of TB-antigen and TB-antibodies; nucleic acid based TB-IVDs.
References:


   d. Personal communication.


    c. Medical Industry Association of Australia Inc.

    b. Personal communication


14. *Diagnostics for tuberculosis: global demand and market potential*
BRAZIL

Population (1) 178,470,000 * GNI (2) US$ 479.5 billion * GNI/capita (3) US$ 2720
Federative republic * 26 states * 1 federal district

Health system capacity and expenditures (4)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% GDP spent on health care</td>
<td>7.9</td>
</tr>
<tr>
<td>Per capita total health expenditure (US$)</td>
<td>206</td>
</tr>
<tr>
<td>No. of hospital beds/1000 population</td>
<td>3.6</td>
</tr>
<tr>
<td>No. of doctors/1000 population</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Total health expenditures</strong></td>
<td></td>
</tr>
<tr>
<td>Government</td>
<td>45.9%</td>
</tr>
<tr>
<td>Private</td>
<td>54.1%</td>
</tr>
<tr>
<td>Private prepaid plans as % of private expenditure on health</td>
<td>35.8</td>
</tr>
</tbody>
</table>

Laboratory infrastructure (6)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated total no. of labs</td>
<td>9,100</td>
</tr>
<tr>
<td>Percentage of automated and semi-automated laboratories</td>
<td></td>
</tr>
<tr>
<td>1100 automated</td>
<td></td>
</tr>
<tr>
<td>1500 semi-automated</td>
<td></td>
</tr>
<tr>
<td>Accreditation bodies</td>
<td></td>
</tr>
<tr>
<td>Inmetro: <a href="http://www.inmetro.gov.br/">http://www.inmetro.gov.br/</a></td>
<td></td>
</tr>
<tr>
<td>Sociedade Brasileira de Análises Clinicas</td>
<td></td>
</tr>
<tr>
<td><a href="http://www.sbac.org.br/">http://www.sbac.org.br/</a></td>
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TB epidemiology (7)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total estimated new TB cases</td>
<td>1,103,19</td>
</tr>
<tr>
<td>Total notified new TB cases</td>
<td>74,044</td>
</tr>
<tr>
<td>DOTS</td>
<td>15,359 (21%)</td>
</tr>
<tr>
<td>Non-DOTS</td>
<td>58,685 (79%)</td>
</tr>
<tr>
<td>Total gap between estimated and notified new TB cases</td>
<td>36,275</td>
</tr>
</tbody>
</table>
| Notified new 
  "other" TB cases DOTS                   | 6,298 (10%) |
| Notified new 
  "other" TB cases non DOTS                 | 27,808 (46%) |
| Total estimated new "other" TB cases                | 30,106 |
| Notified new 
  Sm + cases DOTS                        | 9,061 (18%) |
| Notified new 
  Sm + cases non DOTS                    | 30,877 (63%) |
| Total estimated new Sm + TB cases                  | 39,387 |
| Not notified 
  Sm + cases DOTS                          | 9,449 (19%) |
| Not notified 
  Sm + cases non DOTS                      | 20,825 (44%) |
| Total estimated new Sm + TB cases                 | 30,323 |
| Estimated % adult TB cases that are HIV co-infected (15-49y) | 3.8 |
| Estimated % adult TB cases that are HIV co-infected (15-49y) | 0.7 |

Health care system delivery (5)

Public

- Sistema Unico de Saude (SUS) provides services as well as purchases services from privately owned facilities for the entire population. It finances 95% of primary care, 70% of secondary care and 90% of tertiary care for the whole population. However, an estimated 11 million have no real access.
- Hospital care dominates health care expenditure. There are over 6,300 inpatient facilities under the umbrella of SUS (30% public; 70% private) and 54,000 primary care facilities (79% public; 21% private).
- Reimbursement rates are fixed and are in need of updating.

Private

- The private sector has grown rapidly over the past two decades and is well funded.
- Several hundred firms offer four principal types of medical plans: private health insurance, prepaid group practice, medical cooperatives, and company health plans. Some private hospitals depend on SUS financing; others have their own insurance plans.
- Coverage is usually limited to low-cost procedures and transfers the burden of care for high-risk individuals to the publicly funded health system.
- Overall, 30% of the population utilize comprehensive services through private insurers, as opposed to SUS.
National TB policy

- DOTS population coverage 2003: 34%
- Percentage of government health spending on TB control: 0.30%
- Total TB control costs 2005 (based on budget US$): 46 million
- Government share of total TB control costs, including loans: 94%
- National TB programme (NTP) budget (based on budget US$): 21 million

NTP budget by source of funding, 2005

Major markets

- The state of São Paulo concentrates over 70% of all medical facilities in the country; the city of São Paulo alone is one of the largest markets in South America for the health sector.

TB laboratory network

- There are also 14 major public health laboratories (Laboratorio Central de Vigilancia Epidemiologica) that conduct approximately 95% of TB testing.

Smear laboratories
- Total: 3124
- Per million: 18

Culture laboratories
- Total: 815
- Per million: 4.6

DST laboratories
- Total: 76
- Per million: 0.4

Estimated in vitro diagnostics market

- US$ 340-350 million

National regulatory policies for in vitro diagnostics

- Agencia Nacional de Vigilancia Sanitaria (ANVISA) http://www.anvisa.gov.br/
- Registration of IVDs is mandatory.
- Hiring of specialized consultants to prepare and submit the registration papers is generally required.
- Yes, depending on IVD classification.
- Yes, depending on class (A, B, C or D) through Instituto Nacional de Controle de Qualidade em Saúde - INCQS (www.incqs.fiocruz.br).
- Yes, depending on class (A, B, C or D) through INCQS.
- Yes, depending on class (A, B, C or D) through INCQS.
- The Global Harmonization Task Force of the Pan American Health Organization is developing a post-market surveillance programme for medical devices. No formal timeline has been established.
- Some of the larger and private labs are ISO-certified and post-market activities such as traceability of the reagents consumed by the lab are part of the ISO system.
- ANVISA demands certified ISO 13 485: 2003 at least for TB-diagnostics, and most probably for class D. Very few distributors have the resources to have a post-market surveillance program. Most manufacturers have a product tracing system that tracks sales to distributors and from distributors to end-user.
- Member of MERCOSUR (Brazil, Argentina, Uruguay, Paraguay, Chile, Bolivia) which is developing common GMPs and a harmonized device registration system. Quality standards, known as Buenas Prácticas de Fabricación (BPFs), are based on ISO 9001 and FDA GMPs. The goal is a CE mark-like system.
High level of requirements: TB diagnostics are regarded as “high risk IVD”- Group C-IVD:

i) Free Sales Certificate
ii) package inserts with performance and stability claims
iii) production procedures
iv) detailed “product dossier” to support claims
v) certified ISO 13 485 Quality Management System from foreign manufacturer which replaces former certified EN 46001 or ISO 9000-series.

Import tariffs and other taxes (13)

There are no import or value added taxes on 42 medical device products, including IVDs.

Both imported and locally manufactured medical equipment products are subject to Excise Tax (IPI) and the State Sales Tax (ICMS).

ICMS varies between 12% and 18%, depending upon the State, while IPI averages 10%. Public and philanthropic hospitals are exempt from IPI and ICMS.

Cost of registration (14)

US$ 2500, valid for 5 years.

Duration of registration process (15)

Often > 1 year; however, distribution can begin 3 months after application for registration on the condition that the company assumes full product liability claims if the device proves to be unsafe.

Local manufacturing capacity (16)

Brazilian manufacturers are capable of producing and exporting over 11 000 basic medical products. There are 515 manufacturers in the medical sector in Brazil, which are estimated to supply 70% of the sector needs for equipment and devices. Approximately 20% are multinationals or have foreign participation in their capital structure.

About 90% of the local production of medical equipment and devices is for the internal market. The remaining is exported, mainly to other South American countries.

Local labour is highly trainable, particularly in the most developed parts of the country (south/southeast regions). On price and quality parity, government policies continue to favour domestic production.

Local distribution (17)

Medical devices can only be sold in Brazil if the foreign company establishes a local Brazilian manufacturing unit or local office, or appoints a Brazilian distributor who is authorized by Brazilian authorities to import and distribute medical products. Products are registered in the distributor’s name.

Large distributors with fully developed networks, and the capacity to provide service and technical assistance, are available.

Public hospitals are responsible for the purchase of approximately 60% of medical supplies in Brazil. All hospitals under federal, state and municipal administration have to issue a public bid for every purchase of more sophisticated items, such as equipment, diagnostic devices and blood derivatives. Public and non-profit hospitals are not subject to import duties or value-added taxes. In order to take advantage of this tax-free status, hospitals generally import directly or do so with the assistance of an import agent. In such circumstances, the import agents usually receive their commission directly from the foreign supplier.

Public health labs can buy directly through their own tenders. Public tenders for national distribution among the public labs take place at the beginning of the year in Brasilia. All bids and tenders are published on the internet for federal, state and municipal acquisitions of products (www.comprasnet.gov.br). There is also a new purchase mode in place called PREGO, which is a mode similar to a public auction, where companies and dealers make their best offers on pricing (first call) on a public PREGO in a hospital or public lab. In the case of products being financed with international funds from organizations such as the World Bank and the Inter-American Development Bank (IDB), the hospitals buy after issuing an international bid. The Government publishes the bid in the Official Gazette (“Diário Oficial”).

The private sector buys in a free market system, with tenders for larger purchases and smaller procurements via company representatives. Private hospitals purchase their supplies directly from local distributors and/or importers, and often also import directly from foreign suppliers. Price and after-sales servicing are the key factors for buyers, as well as payment terms and alternatives forms of finance.

Intellectual property rights issues (19)

Year in which country joined World Trade Organization (WTO) and is therefore under the TRIPS agreement 1995

Year in which the country must be in accordance with TRIPS 2000

Foreign manufacturers are also strongly advised to register their brand names and any patented technology with INPI - Instituto Nacional da Propriedade Industrial, or the National Industry Property Institute (www.inpi.gov.br).
Diagnostics for tuberculosis: global demand and market potential

References:
12. a. US Department of Commerce, Medical Device Regulatory Requirements for Brazil, 03/21/02.
b. September 2002, Brazil’s Health care Market Overview, Canadian Export Services InfoExport Website: http://www.infoexport.gc.ca
13. a. US Department of Commerce, Medical Device Regulatory Requirements for Brazil, 03/21/02.
b. September 2002, Brazil’s Health care Market Overview, Canadian Export Services InfoExport Website: http://www.infoexport.gc.ca
14. a. US Department of Commerce, Medical Device Regulatory Requirements for Brazil, 03/21/02.
b. September 2002, Brazil’s Health care Market Overview, Canadian Export Services InfoExport Website: http://www.infoexport.gc.ca
15. a. US Department of Commerce, Medical Device Regulatory Requirements for Brazil, 03/21/02.
b. September 2002, Brazil’s Health care Market Overview, Canadian Export Services InfoExport Website: http://www.infoexport.gc.ca
17. a. US Department of Commerce, Medical Device Regulatory Requirements for Brazil, 03/21/02.
b. Industry Canada Website: http://strategis.gc.ca/csr_mkt/bindcd contingencies/1313811.html
c. STAT-USA, US Department of Commerce.
d. September 2002, Brazil’s Health care Market Overview, Canadian Export Services InfoExport Website: http://www.infoexport.gc.ca
b. http://www.wto.org/english/tratop_e/trips_e/trips_e.htm#WTO
d. http://www.wto.org/english/tratop_e/trips_e/trips_e.htm#WTO

Industry associations

- **ABIMED**
  Assoc. Bras. dos Importadores Equip. Prod. Médicos, Alameda dos Tupiniquins 203 Moema São Paulo - SP, Brazil 04077-000 Tel: (55-11) 5052-2664 Fax: (55-11) 5052-7074 abimed@uol.com.br
  http://www.abimed.org.br

- **ABIMO**
  Assoc. Bras. Ind. Equip. Médicos e Odontológicos Av. Paulista 1313 - 8o andar – sala 806 São Paulo - SP, Brazil 01311-923 Tel: (55-11) 3285-0155 Fax: (55-11) 3285-0118 abimo@abimo.org.br
  http://www.abimo.org.br

ABIMO is the Brazilian association of manufacturers of hospital, dental, medical and laboratory equipment and supplies.

- **“Other”** includes smear-negative pulmonary TB and smear-unknown.
- **Includes patients previously treated for tuberculosis and relapses.**
- **May include microbiological TB-IVD; IVD for detection of TB-antigen and TB-antibodies; nucleic acid based TB-IVDs.**

Brazil
### Health System Capacity and Expenditures (4)

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% GDP spent on health care</td>
<td>9.6</td>
</tr>
<tr>
<td>Per capita total health expenditure (US$)</td>
<td>2,222</td>
</tr>
<tr>
<td>No. of hospital beds/1000 population</td>
<td>3.3</td>
</tr>
<tr>
<td>No. of doctors/1000 population</td>
<td>1.89</td>
</tr>
</tbody>
</table>

#### Total Health Expenditures

- **Government:** 69.1%
- **Private:** 30.1%

Private prepaid plans as % of private expenditure on health: 42.1%

### Laboratory Infrastructure (6)

- Estimated total no. of labs: >1000 medical laboratories

#### Accreditation Bodies
- Standards Council of Canada, Program for the Accreditation of Laboratories [http://www.scc.ca/](http://www.scc.ca/)

### TB Epidemiology (7)

#### Total Estimated New TB Cases
- Total estimated new TB cases: 1,745
- Total notified new TB cases: 1,384
  - DOTS: 1,384 (100%)
  - Non-DOTS: 0 (0%)
- Total gap between estimated and notified new TB cases: 361

#### TB Laboratory Network
- National Reference Lab(s): Laboratory Centre for Disease Control, Ottawa.

#### Additional Data
- Total notified re-treatment cases: 67
- % Multidrug-resistance in new cases: 0.7%
- % Multidrug-resistance in re-treatment cases: 3.4%
- Estimated % adult TB cases that are HIV co-infected (15-49 years): 15
## Estimated in vitro diagnostics market

- **US$ 380 million**

## Major markets

- Approximately 40% of Canada’s population lives in Ontario and Quebec. Most major distributors and manufacturers are established in these provinces, as are the major medical schools and hospital research programmes.

## National regulatory policies for in vitro diagnostics

### Regulatory body/regulatory legislation


### Product registration process

- Product registration process is made up of two main layers:
  - **Layer 1**: Establishment licences are required for establishments that import or distribute any medical device.
  - **Layer 2**: A medical licence fee is required for each product.

- The following are exempt:
  - Class I medical devices
  - Custom-made medical devices
  - Medical devices for special access
  - Medical devices for investigational testing involving human subjects.

### Classification of in vitro diagnostics

- Annex: Scheme 3.

### Is local testing required to license the product?

- No

### Are quality management systems/factory audits a required component of post-market entry?

- Yes, for all tests.

### Movement towards regulatory harmonization

- Member of the Global Harmonization Task Force.

### Regulatory requirements for manufacturers/importers of TB-IVDs

- Requirements vary depending on nature of TB-IVD. See Annex.

### Import tariffs and other taxes


## Cost of registration

- **Establishment Licences**: approximately US$ 2 000 is charged for the initial licence (there is a sliding scale based on the revenue base of the company). Subsequent annual licences and the reinstatement of a licence is approximately US$ 140. The fees are applied equally to foreign and domestic establishments.

- **Medical Licences**: initial product licensing fee is approximately US$ 1 440 (class II are less expensive, class IV and V the most expensive) and an annual renewal fee of US$ 80 per product licence.

## Duration of registration process

- Most product licenses are reviewed in 75 to 100 days.

## Local manufacturing capacity

- There are more than 60 manufacturers of diagnostic reagents, instruments, point-of-care devices, lab automation and lab supplies in Canada.

## Local distribution

- Distribution channels are fairly lean. The importer (local subsidiary of a multinational or locally owned distributor) generally sells directly to end-users (80% sales to hospitals and private laboratory chains).

- Under regulatory obligations, importers and distributors must obtain an establishment license and are prohibited from selling devices that are not licensed by the manufacturer.

## Procurement

- Each hospital laboratory manages its own purchases - tender for large equipment purchases and at the discretion of the lab manager for smaller purchases. Each hospital lab has a global budget, there is no fee for service. In Quebec, the Ministry of Health and Social Services office in every major city has a list of preferred vendors, but labs have the option to buy outside the list.

- Public health laboratories buy strictly on tender issued to selected companies. Each lab manages its own procurement and tender procedure.

## Intellectual property rights issues

- Year in which country joined World Trade Organization (WTO) and is therefore under the TRIPS agreement: **1995**

- Year in which the country must be in accordance with TRIPS: **1996**
Industry associations

The primary organizations are:

- Medical Devices Canada (MEDEC)
  www.medec.org

- Canadian Association For Clinical Microbiology and Infectious Diseases (CACMID)
  www.cacmid.ca

---

a "Other" includes smear-negative pulmonary TB and smear-unknown.
b Includes patients previously treated for tuberculosis and relapses.
c May include microbiological TB-IVDs for detection of TB-antigen and TB-antibodies; nucleic acid based TB-IVDs.
References:

c. Personal communication.
e. Contact Canada: www.contactcanada.com
d. Global Harmonization Task Force Website: http://www.ghtf.org/
e. Policy Division, Bureau of Policy and Coordination Therapeutic Products Programme, Health Canada.
11. a. Espicom Business Intelligence.
b. Industry Canada Website.
13. Policy Division, Bureau of Policy and Coordination Therapeutic Products Programme, Health Canada.
b. www.advanced.org/public/ide/diagchabanc1.ppt
c. Espicom Business Intelligence – and Industry Canada Website.
16. Personal communication.
b. http://www.wto.org/english/tratop_e/trips_e/trip04_e.htm/whosisigned
http://www.wto.org/english/tratop_e/trips_e/trip04_e.htm/whosisigned
c. http://www.wto.org/english/tratop_e/trips_e/trip04_e.htm/whosisigned

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CHINA

Population (1) 1,311,709,000 * GNI (2) US$ 1.4 trillion * GNI/capita (3) US$ 1,100
Communist state * 23 provinces * 5 autonomous regions * 4 municipalities

Health system capacity and expenditures (4)

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
<th>Per Capita Total Health Expenditure (US$)</th>
<th>No. Hospital Beds/1000 Population</th>
<th>No. Doctors/1000 Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Government</td>
<td>33.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>66.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total health expenditures

- Government: 33.7%
- Private: 66.3%
- Private prepaid plans as % of private expenditure on health: 0.4%

Health care system delivery (5)

Public
- **Government Insurance Scheme**: insurance programme for government employees, retirees, disabled veterans, and university teachers and students (covers 2.5% of the population).
- **Labor Insurance Scheme**: Insurance programme for state enterprise employees, retirees and their dependents (covers 11.7% of the population).
- **Cooperative Medical System**: Once insured 90% of the rural population, now insures less than 10%.
- Outside of these insurance schemes, health care is essentially self-pay.
- The vast majority of hospitals (63,000) are publicly owned and managed at the provincial, county and city levels. Below county level, hospitals are often understaffed and underfunded. The MOH is rolling out a plan to divide hospitals into non-profit and profit-making institutions. The former will benefit from government subsidies and price guidance, while the latter will be relatively free to compete for business.
- Health care in urban centres is largely run out of hospitals, and most laboratories are located in hospitals. Commercial laboratories are rare.
- Since the 1980s, there have been a series of health insurance system reforms culminating in the Government's policy decision in December, 1998 to establish a social insurance programme for urban workers.

Private
- Private medical insurance, first introduced in 1982 (Shanghai Insurance Company), covered workers in rural collective industries in the suburbs of Shanghai, including Children Immunization Insurance (CII), Mother-Infant Medical Insurance (MIMI) and Medical Operation Insurance (MOI). An estimated >50% of children aged 0-7 are covered by CII.
- Commercial insurance market and privately owned and joint venture hospitals are expected to grow substantially.

Laboratory infrastructure (6)

- Estimated total no. of labs: 45,000
  - Concentrated in public hospitals
- Percentage of automated and semi-automated laboratories:
  - 6.6%
  - These labs handle two thirds of national laboratory workload.

Accreditation bodies

TB epidemiology (7)

- Total estimated new TB cases: 1,334,066
- Total notified new TB cases: 546,987
  - DOTS: 491,584 (90%)
  - Non-DOTS: 55,403 (10%)
- Total gap between estimated and notified new TB cases: 787,079

Notified new 
"other" TB cases DOTS
- 234,297 (32%)
- 45,276 (6%)
- 454,734 (62%)

Total 
estimated  new "other" TB cases
- 734,307

Total 
estimated  new Sm +
TB cases
- 599,758

Notified new 
Sm + cases DOTS
- 352,344 (55%)
- 257,287 (43%)
- 10,127 (2%)

Total estimated new Sm +
TB cases
- 599,758

Total notified re-treatment cases
- 136,590

Diagnostics for tuberculosis: global demand and market potential
% Multidrug-resistance in new cases

<table>
<thead>
<tr>
<th>Region</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henan</td>
<td>7.8%</td>
</tr>
<tr>
<td>Hupeib</td>
<td>2.1%</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>0.8%</td>
</tr>
<tr>
<td>Liaoning</td>
<td>10.4%</td>
</tr>
</tbody>
</table>

% Multidrug-resistance in re-treatment cases

<table>
<thead>
<tr>
<th>Region</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henan</td>
<td>36.6%</td>
</tr>
<tr>
<td>Hupeib</td>
<td>21.8%</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>11.2%</td>
</tr>
<tr>
<td>Liaoning</td>
<td>24.4%</td>
</tr>
</tbody>
</table>

Estimated % adult TB cases that are HIV co-infected (15-49 years) 0.7

National TB policy (8)

DOTS population coverage 2003 91%
Percentage of government health spending on TB control 0.5%
Total TB control costs 2005 (based on budget US$) 158 million
Government share of total TB control costs, including loans 74%
National TB programme (NTP) budget (based on budget US$) 158 million

NTP budget by source of funding, 2005

- Government: 98 million US$
- Loans: 14 million
- Grants: 4 million
- GFATM: 21 million
- Funding gap: 21 million

Culture laboratories

- Total: 578
- Per million: 0.45

DST laboratories

- Total: 52
- Per million: 0.04

Estimated in vitro diagnostics market (10)

- US$ 600-700 million
- Growth in 2003-18%; Projected annual growth of 10% over next 5-10 years and over half of market will be controlled by international companies.

Major markets (11)

- Commercial activity is concentrated along the eastern seaboard, particularly in Shenyang, Beijing, Tianjin, Shanghai and Guangzhou. Urban centres inland have generally less developed infrastructure, particularly the further west one travels. Distributors and agents cover larger regions in the east, and few cover the entire country, thus, sometimes several distribution arrangements are required. However, many of the larger distributors are establishing their own network of country-wide agents.
- Advertising of medical products and technology in China is strictly controlled by the state. As a result, product manufacturers are more likely to take advantage of local trade shows to promote their products and services.

National regulatory policies for in vitro diagnostics (12)

Regulatory body/regulatory legislation
- China’s State Drug Administration (SDA)
  Department of Medical Devices
  38 A, Beilishilu, Xicheng District, Beijing 100810
  (SFDA has offices in each province)
  www.sda.gov.cn/eng

Who registers the product?
- Product approval and registration are complex and foreign companies are recommended to authorize a locally based representative distributor or specialized agent to manage product registration and approval.

Is a detailed product dossier for performance required?
- If the product is to be registered as a DRUG, SDA

TB laboratory network (9)

- National Reference Lab(s): Beijing Tuberculosis and Thoracic Tumor Research Institute, Henan Anti-tuberculosis Institute, and Yung Fung Shee Memorial Centre.

Smear laboratories

- Total: 3500
- Per million: 3

Diagnostics for tuberculosis: global demand and market potential
requires data that corresponds to the content of a "product dossier". For registration as Medical Devices (MD) significantly fewer detailed data are required.

**Classification of in vitro diagnostics**

- Annex: Scheme 4: IVDs are classified as either Drugs or Medical Devices (MD). IVD’s classified as medical devices are Class II.

<table>
<thead>
<tr>
<th>Reagents regulated as Drug</th>
<th>Reagents regulated as Medical Device (MD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Blood type, tissue match reagents;</td>
<td>1. Basic clinical examination reagents;</td>
</tr>
<tr>
<td>2. Antigen, antibody of microbiology and nucleic acid test reagents;</td>
<td>2. Clinical chemical examination reagents;</td>
</tr>
<tr>
<td>3. Tumor marker reagents;</td>
<td>3. Blood gas and electrolyte analysis reagents;</td>
</tr>
<tr>
<td>4. Immunological histochemistry and human tissue cell reagents;</td>
<td>4. Vitamin determination reagents;</td>
</tr>
<tr>
<td>5. Human gene examination reagents</td>
<td>5. Chemical stain reagent for cell and tissue;</td>
</tr>
</tbody>
</table>

**Is local testing required to license the product?**

- Yes, depending on IVD classification. However, oversight is not rigorous. Since 2005, China demands all exporting manufacturers of MD (including IVDs) to be ISO 13485:2003 certified.

**Movement towards regulatory harmonization**

- Member of the Asian Harmonization Working Party Member of the Global Harmonization Task Force.

**Regulatory requirements for manufacturers/ importers of TB-IVDs**

- Very high level of requirements:
  1. Free Sales Certificate
  2. package inserts with performance claims
  3. detailed "product dossier" to support claims
  4. test kit samples for Government controlled validation trials

**Import tariffs and other taxes**

- In accordance with WTO provisions, tariffs on medical equipment (including reagents and analytical laboratory instruments) must be reduced to 3.9% as of January 2005.

**Cost of registration**

- The cost of registration is US$ 8,000 to US$ 15,000 per product. In addition to product registration, foreign companies have to finance Chinese technicians to inspect the products on site.

**Duration of registration process**

- > 1 year (medical device)
- > 2 years for pharmaceuticals.

**Local manufacturing capacity**

- China has a large domestic production sector, split between locally owned manufacturing and joint venture projects with overseas companies. There are around 2,900 medical device manufacturers in China, most of which are state-owned, medium to small companies, with less than 400 employees.

**Local distribution**

- China’s entry into the WTO means that foreign companies will no longer be restricted from importing and selling goods directly to the Chinese market. Historically, due to these restrictions, it is common practice for them to have a distribution partner(s) sell to a variety of end-users. Distribution channels are multilayered, small and regionally based. Much of the value in the distribution chain for diagnostics accrues in hospitals. Local health and price bureaus set the test price. Each hospital is independently responsible for its own medical and health care product purchases. Products are procured through provincial and municipal health bureaus. Only purchase of large capital equipment is put to tender.

- In 2002, 25-30% of IVD spending was on imported products (mainly automated lab instruments).

**Procurement**

- Each province and municipality in China manages its own foreign trade system managed by a local Foreign Trade Bureau or equivalent organization. A selection of these can be found on the web page of the Ministry of Commerce of the People’s Republic of China (http://english.mofcom.gov.cn/difang.shtml).

- Hospitals must procure goods through their local government agencies; however, they are afforded a high degree of autonomy over purchasing supplies and laboratory products. Hospital managers are usually responsible for making procurement decisions and are, therefore, appropriate targets for promotional material and direct marketing activities.
For large capital purchases, the Ministry of Health has been working to standardize bidding and tendering, which should be more fair to suppliers and more efficient for purchasers.

Intellectual property rights issues (19)

Year in which country joined World Trade Organization (WTO) and is therefore under the TRIPS agreement 2001

Year in which the country must be in accordance with TRIPS 2001

Industry associations

China Association for Medical Device Industry
SPAC Building
14th Floor, 38A Beilishi Road
Beijing 100810, China
Tel: (861) 831-3344, ext. 1610
Fax: (861) 831-5675

Chinese Association for Medical Biotechnology
Zhang QuanYi, Ph.D.
Sectraire General, 422 Datunli
Chaoyang District
Beijing 100 101, China
Tel: (861) 432-1117
Fax: (861) 432-2851

Chinese Medical Association
www.chinamed.com.cn

a. "Other" includes smear-negative pulmonary TB and smear-unknown.
b. Includes patients previously treated for tuberculosis and relapses.
c. May include microbiological TB, IVD/VD for detection of TB-antigen and TB-antibodies; nucleic acid based TB-IVDs.

References:

CHINA

Diagnostics for tuberculosis: global demand and market potential

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FRANCE

Population (1) 60 144 000 • GNI (2) US$ 1.5 trillion • GNI/capita (3) US$ 24 730
Republic • 22 regions, with dependent areas

Government 76% • Private 24%

FRANCE

Health system capacity and expenditures (4)

<table>
<thead>
<tr>
<th>% GDP spent on health care</th>
<th>9.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per capita total health expenditure (US$)</td>
<td>2348</td>
</tr>
<tr>
<td>No. of hospital beds/1000 population</td>
<td>8.3</td>
</tr>
<tr>
<td>No. of doctors/1000 population</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Total health expenditures

Government 76% • Private 24%

Private prepaid plans as % of private expenditure on health 54.9

Health care system delivery (5)

Public
• In 2001, the World Health Organization (WHO) ranked France’s health-care system as the best in the world. Assurance Maladies universally covers the population and is financed through salary-related social contributions which cover the partial cost of all care. Exceptions exist for certain patient groups, diseases, and treatments. Parliament determines the level of spending annually.
• The public sector dominates hospital care and owns 75% of beds.
• Patients are free to choose providers.

Private
• Mutuelles provide private insurance which supplements to varying degrees the charges not covered under Assurances Maladies. 87% of the population own complementary insurance.
• Ambulatory care professionals and facilities dominate the private sector.
• Out-of-pocket financing varies according to the service or product.

Laboratory infrastructure (6)

Accreditation bodies

• Le Comité français d’accréditation: http://www.cofrac.fr/

TB epidemiology (7)

Total estimated new TB cases 7 257
Total notified new TB cases 5 740
• DOTS 0 (0%)
• Non-DOTS 5 740 (100%)
Total gap between estimated and notified new TB cases 1 517

TB laboratory network (8)

• National Reference Lab(s); National Reference Centre for the Surveillance of TB, Paris.

Smear laboratories
Total 350
Per million 6
Culture laboratories
Total 350
Per million 5.8

DST laboratories
Total 130
Per million 2.2

Estimated in vitro diagnostics market (9)
- US$ 1.4 billion
- Growth 10-15% annually

Major markets (10)
- Urban centres such as Paris, Marseille and Lyon.
  Generally, agents and distributors have the capacity
  and jurisdiction to market products across the
  country. Many also re-export products to French-
  speaking countries in Africa.

National regulatory policies for in vitro diagnostics (11)
Regulatory body/regulatory legislation
- European Union (EU) IVD directive.
- All medical devices imported into and sold in France
  must conform to EU medical devices directives and
  display the Conformité Européene (CE) mark. The CE
  mark process for each class of IVD products can be
  found at www.us.tuv.com/product_testing/
  medical_devices/index.html
- The Agence Française de Sécurité Sanitaire des
  Produits de Santé is the designated competent
  authority responsible for implementing the direc-
  tives.
  http://agmed.sante.gouv.fr/
- The conformity of medical devices must be verified
  by the only appointed notified body, G-Med
  (Groupement pour l’Evaluation des Dispositifs
  Médicaux). A voluntary product certification system
  has recently been introduced in France for Class I
  devices, managed by G-Med.

Who registers the product?
- The manufacturer - when located inside the
  European Community (EC) - or his “authorized repre-
  sentative” if the manufacturer is located
  outside the EC.

Is a detailed product dossier for performance
required?
- Yes, for all risk classes (EU IVD Directive Annex IIa, IIb,

Classification of in vitro diagnostics
- Annex: Scheme 1.

Is local testing required to license the product?
- Yes, depending on IVD classification.

Are quality management systems/factory audits
a required component of post-market entry?
- Yes, all 4 IVD classes need a quality management
  system - from 31 July 2006 onwards exclusively ISO
  13 485: 2003-11 - ; however, IVDs in class Annex III
  (“other IVD”) are exempted from certification by
  “Notified Body”. Diagnostics companies must imple-
  ment a vigilance system capable of reacting to any
  user incident report, of analysing any potential problem
  or risk, of assessing problems and finding solutions
  acceptable to the client. The system requires that
  companies report incidents concerning devices.
- Agence Française de Sécurité Sanitaire des Produits
  de Santé (AFSSAPS) regularly evaluates products and
  can decide to remove from the market those that do
  not meet defined criteria.

Movement towards regulatory harmonization
- Member of the Global Harmonization Task Force
  (through the EU).

Regulatory requirements for manufacturers/
importers of TB-IVDs (12)
- Low level of requirements for TB-IVDs that belong to
  Class “Annex III-other IVD”. Attachment of the CE-mark
  to the IVD is the manufacturers’ responsibility
  following self-declaration of conformity with the EC
  IVD Directive to the respective “competent authority”.
  They must prepare for an “intervention”- inspection
  through health authorities including:
  i) evidence of an adequate quality management sys-
  tem - preferably ISO 13 485 - AND
  ii) Technical documentation as proof for performance
  claims.
- Intervention inspections only occur in case of severe
  IVD failures on the market.

Import tariffs and other taxes (12)
- Imports: Official trade barriers, such as quotas, do not
  exist. Both diagnostic and diagnostic reagents are
  tariff-free. Customs duty ranges from 4.9 to 6.2% of
  the value of medical devices including freight and
  insurance. The average rate is 5.3%.
- Value-Added Tax (VAT) is due at each point
  of transaction with the current rate at 20.6%.

Cost of registration (13)
- US$ 5 000 to US$ 25 000 depending on the level of
  inspection required and the entire process.

* Diagnostics for tuberculosis: global demand and market potential *
France

Duration of registration process (14)
- Following application submission, the process requires on average 6-8 weeks.

Local manufacturing capacity (15)
- Approximately 20 major manufacturers of IVD products - the largest are ABX, a subsidiary of Horiba, Japan, and bioMérieux. All the major IVD companies are represented in France.

Local distribution (16)
- Before marketing a diagnostic product in the EU, the IVD directive orders that all foreign (non EU) diagnostic products manufacturers appoint an authorized representative in an EU nation. Foreign companies seeking to directly approach an EU market that do not have an EU subsidiary will have to choose between:
  (i) cooperation with a local EU pharmaceutical manufacturer by licensing the foreign product/production know-how OR:
  (ii) acquisition of an EU company.
- Once CE marking is obtained, the IVD can be sold throughout the 25 member countries. Exporting through a distributor or agent is the most common practice. An agent’s commission for scientific lab equipment is usually 15-20%. Distributors add 30% -50% mark up.

Procurement (17)
- For patients to be reimbursed by the Social Security, medical devices used by private clinics must be listed on the Tarif Interministériel de Prestations Sanitaires (TIPS), which consists of a list of product descriptions (no brand names) and the respective prices.
- TIPS applications from medical devices suppliers are evaluated, and reimbursement prices are set according to the medical and economic benefits of each device. When possible, the price is determined in comparison to already available equipment. Public purchasers will use the TIPS price as a reference. For medical products/equipment to be listed under the TIPS, they must first be presented to the Ministry of Health in order to be tested and approved by hospitals, laboratories or clinics recognized by the Ministry. This process may take up to six months.
- Public hospitals are free to make medical equipment purchase decisions within the confines of their overall budget. However, they must abide by EU directives concerning public-sector purchasing. These directives were established to ensure that the procurement process in the public system in any EU member country is fair, transparent and competitive. As stipulated by EU directives, any contract for goods or services with a value exceeding certain thresholds must be put to public tender. See http://europa.eu.int/business/en/topics/publicproc/index.html for more information on thresholds for public procurement under EU directives.
- Announcements of public tenders are advertised in the Official Journal of the European Union (S Series), which is available on CD-ROM and at the Tenders Electronic Daily (TED) Internet site http://tenders.publications.eu.int/CD/application/plf/resources/shtml/common/home/home.html.

Intellectual property rights issues (18)
- Year in which country joined World Trade Organization (WTO) and is therefore under the TRIPS agreement: 1995
- Year in which the country must be in accordance with TRIPS: 1996

Industry associations
- EDMA (European Diagnostic Manufacturers Association)
  www.edma-ivd.be
- SNITEM (Syndicat National de l’Industrie des Technologies Médicales)
  39-41, rue Louis Blanc
  92400 Courbevoie
  Postal Address:
  Cedex 72
  2038 Paris, La Defense
  Tel: (33) 1 47 17 63 88
  Fax: (33) 1 47 17 63 89
- AFSSaPS (Agence Française de Sécurité Sanitaire des Produits de Santé – health products safety agency)
  143 avenue Anatole
  93285 Saint Denis Cedex
  Tel: (33) 01 55 87 30 11
  Fax: (33) 01 55 87 30 12
  www.afssaps.sante.fr
- SFRL (Syndicat de l’Industrie du Réactif de Laboratoire - in vitro diagnostic trade association)
  6, rue de la Trémoille
  75008 Paris
  Tel: (33) 01 40 70 00 12
  Fax: (33) 01 40 70 00 13
  accueil@sfrl.fr
  www.sfrl.fr/index.html

Diagnostics for tuberculosis: global demand and market potential
a. "Other" includes smear-negative pulmonary TB and smear-unknown.
b. Includes patients previously treated for tuberculosis and relapses.
c. May include microbiological TB-IVD; IVD for detection of TB-antigen and TB-antibodies; nucleic acid based TB-IVDs.

References:
e. European Diagnostic Manufacturers Association, www.edma-ivd.be
b. Global Harmonization Task Force Website: http://www.ghtf.org/
12. a. Espicom Business Intelligence – and Industry Canada Website.
b. www.advamed.org/public/docs/deutschebanc1.ppt
c. Espicom Business Intelligence – and Industry Canada Website.
GERMANY

Population (1) 82 476 000 • GNI (2) US$ 2.1 trillion • GNI/capita (3) US$ 25 270
Federal Republic • 16 states

Health system capacity and expenditures (4)

- % GDP spent on health care 10.9
- Per capita total health expenditure (US$) 2 631
- No. of hospital beds/1000 population 9.6
- No. of doctors/1000 population 3.6

Total health expenditures

Government 78.5%
Private 21.5%

Private prepaid plans as % of private expenditure on health 39.9

0.1% of Germans remain uninsured by either public or private plans.

Laboratory infrastructure (6)

Accreditation bodies
- German Accreditation Council
  http://www.dar.bam.de/darhomee.html

TB epidemiology (7)

- Total estimated new TB cases 6 749
- Total notified new TB cases 6 339
  - DOTS 6 339 (100%)
  - Non-DOTS 0 (0%)
- Total gap between estimated and notified new TB cases 410

- Total notified re-treatment cases 346
- % Multidrug-resistance in new cases 0.8
- % Multidrug-resistance in re-treatment cases 7.4
- Estimated % adult TB cases that are HIV co-infected (15-49 years) 5.5
**Germany**

**TB laboratory network** *(8)*

- National Reference Lab(s): National Reference Centre for Mycobacteria, Borstel.

**Smear laboratories**
- Total: 300
- Per million: 4

**Culture laboratories**
- Total: 250
- Per million: 3

**DST laboratories**
- Total: 100
- Per million: 1.2

**Estimated in vitro diagnostics market** *(9)*

- US$ 2.2 billion
- Annual growth: 1-2%

**Major markets** *(10)*


**National regulatory policies for in vitro diagnostics** *(11)*

**Regulatory body/regulatory legislation**

- European Union (EU) IVD directive

- All medical devices imported into and sold in Germany must conform to EU medical devices directives and display the Conformité Européenne (CE) mark. The CE mark process for each class of IVD products can be found at [www.us.tuv.com/product_testing/medical_devices/index.html](http://www.us.tuv.com/product_testing/medical_devices/index.html).

- Federal Institute for Drugs and Medical Devices responsible for Group C and D products. Paul-Ehrlich Institute (Federal Institute of Sera and Vaccines) is responsible for Group A and B products.

**Who registers the product?**

- The manufacturer - when located inside the EC - or his "authorized representative" if the manufacturer is located outside the EC.

**Is a detailed product dossier for performance required?**

- Yes, for all risk classes (EU IVD Directive Annex IIa, IIb, Annex III-other IVD and Annex II-selfmonitoring test).

**Classification of in vitro diagnostics**

- Annex: Scheme 1.

**Is local testing required to license the product?**

- Yes, depending on IVD classification.

**Are quality management systems/factory audits a required component of post-market entry?**

- Yes, all 4 IVD classes need a quality management system - from 31 July 2006 onwards exclusively ISO 13 485: 2003-11 -; however, IVDs in class Annex III ("other IVD") are exempted from certification by "notified body".


- BfArM is responsible for ensuring compliance with the IVDD for Annex III products. Oversight for Annex IIa and IIb products is carried out by Paul-Ehrlich Institute, the Federal Institute of Sera and Vaccines ([www.pei.de/english/eninfo.htm](http://www.pei.de/english/eninfo.htm)).

**Movement towards regulatory harmonization**

- Member of the Global Harmonization Task Force (through the EU).

**Regulatory requirements for manufacturers/importers of TB-IVDs**

- Low level of requirements for TB-IVDs that belongs to Class "Annex III-other IVD". Attachment of the CE-mark to the IVD is the manufacturers’ responsibility following self-declaration of conformity with the EC IVD Directive to the respective “competent authority". They must prepare for an “intervention”-inspection through health authorities including:
  1. evidence of an adequate quality management system - preferably ISO 13 485 - AND:
  2. Technical documentation as proof for performance claims.

- Intervention inspections only occur in case of severe IVD failures on the market.

**Import tariffs and other taxes** *(12)*

- Official trade barriers, such as quotas, do not exist. Both diagnostic and diagnostic reagents are duty-free. However, a 16% import-turnover tax (Einfuhrumsatzsteuer) must be paid at the border, and is later transferred to the end-user in the form of the value-added tax (VAT or “Mehrwertsteuer” - MWST).

**Cost of registration** *(13)*

- US$ 5 000 to US$ 25 000 depending on the level of inspection required and the entire process.

**Duration of registration process** *(14)*

- Following application submission, the process requires on average 6-8 weeks.

- The reimbursement listing process can take between three and six months.
Local manufacturing capacity (15)
- Germany has a well-developed medical manufacturing industry. It is the world’s second largest exporter of medical equipment and supplies.

Local distribution (16)
- Before marketing a diagnostic product in the EU, the IVD directive orders that all foreign (non-EU) diagnostic products manufacturers appoint an authorized representative in an EU nation. Foreign companies seeking to directly approach an EU market that do not have an EU subsidiary will have to choose between:
  (i) cooperation with a local EU pharmaceutical manufacturer by licensing the foreign product/production know-how OR:
  (ii) acquisition of an EU company.
- Once CE marking is obtained, the IVD can be sold throughout the 25 member countries.
- Medical device companies most commonly market their products in Germany through a local distributor. Germany has a vast number of wholesalers and distributors of medical devices, most of which operate on a regional basis. Direct sales to hospital groups, particularly those in the private sector are not uncommon.

Procurement (17)
- Primary end-users of diagnostic reagents and instruments are hospitals, accounting for 50% of sales; general laboratories account for 25%, and specialty labs also account for 25% of sales. Medical equipment procurement is decentralized, with central government having little executive responsibility for the provision of health care.
- Most purchasing is conducted by individual hospitals or independent doctors. The larger municipal and university teaching hospitals are obliged to purchase equipment through public tender.
- Market access is highly dependent on reimbursement. Reimbursable medical devices are listed in a catalogue which is compiled by the Statutory Health Insurance System (Gesetzliche Krankenkassen - GKV) and which contains 34 product groups, as well as many subgroups. In order to obtain reimbursable status for a product, a manufacturer must submit an application to the GKV.

Intellectual property rights issues (18)
- Year in which country joined World Trade Organization (WTO) and is therefore under the TRIPS agreement: 1995
- Year in which the country must be in accordance with TRIPS: 1996

Industry associations
- Bundesverband Medizintechnologie e.V. - BVMed (Association of the Medical Device Industry)
  Hasengartenstraße 14c
  65189 Wiesbaden, Germany
  Tel.: (49-611) 976-750
  Fax: (49-611) 719-769
  info@bvmed.de
  http://www.bvmed.de
- Zentralvereinigung medizinisch-technischer Fachhändler, Hersteller, Dienstleister und Berater e.V. – ZMT (Association of Medical Device Companies)
  Saliering 44
  50677 Cologne, Germany
  Tel.: (49-221) 240-7845
  Fax: (49-221) 240-8670
  info@zmt.de
  http://www.zmt.de
- Verband der Diagnostica-Industrie e.V. (Association of the Diagnostics Industry)
  Muenchener Straße 49
  D-60329 Frankfurt Main, Germany
  Tel.: (49-69) 23-02-67
  Fax: (49-69) 23-66-50
  vdgh@vdgh.de
  http://www.vdgh.de

a “Other” includes smear-negative pulmonary TB and smear-unknown.
b Includes patients previously treated for tuberculosis and relapses.
c May include microbiological TB- IVD, IVD for detection of TB-antigen and TB-antibodies; nucleic acid based TB-IVDs.
India

Population (1) 1,085,462,000 * GNI (2) US$ 570.8 billion * GNI/capita (3) US$ 540
Federal republic * 28 states * 7 union territories

**Health system capacity and expenditures (4)**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% GDP spent on health care</td>
<td>6.1</td>
</tr>
<tr>
<td>Per capita total health expenditure (US$)</td>
<td>30</td>
</tr>
<tr>
<td>No. of hospital beds/1000 population</td>
<td>0.78</td>
</tr>
<tr>
<td>No. of doctors/1000 population</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Total health expenditures</strong></td>
<td></td>
</tr>
<tr>
<td>Government</td>
<td>21.3%</td>
</tr>
<tr>
<td>Private</td>
<td>78.7%</td>
</tr>
</tbody>
</table>

Private prepaid plans as % of private expenditure on health

0.7

**Health care system delivery (5)**

**Public**

- The government sponsors two major programmes:
  - ii) Central Government Health Scheme: insurance for members/retirees of the central government and their dependents (covers 4 million lives).
  - Several state-owned enterprise delivery systems, such as Indian Railways, which covers 10 million lives.
  - Federal and state governments together support an extensive system of hospitals, primary health centers, and clinics. Population health and quality of services varies from state to state.

**Private**

- Voluntary health insurance covers limited hospital services with numerous exclusions (covers fewer than 2 million lives).
- Individual out-of-pocket expenditures account for the majority of health financing and the sector is growing rapidly. Recent estimates indicate that India has over 67,000 private hospitals, accounting for 93% of all hospitals and 64% of hospital beds.

**Laboratory infrastructure (6)**

Estimated total no. of labs

21,000

**Percentage of automated and semi-automated laboratories**

- 20% workload supported by 200-300 automated labs; 40% workload supported by 3,000-4,000 semi-automated labs; 40% workload performed by 17,000 manual labs.
- Automated labs are concentrated in private hospitals and commercial establishments.

**Accreditation bodies**

- Diagnostic laboratory facilities are being upgraded to meet ISO standards and this is expected to increase demand for automatic diagnostic instruments.

**TB epidemiology (7)**

Total estimated new TB Cases

1,788,043

Total notified new TB Cases

1,024,948

- DOTS
  - 790,073 (77%)
- Non-DOTS
  - 234,875 (23%)

Total gap between estimated and notified new TB Cases

763,095

Total notified re-treatment cases

163,906
% Multidrug-resistance in new cases

Regional surveys

<table>
<thead>
<tr>
<th>Region</th>
<th>Multidrug-resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnataka</td>
<td>2.5%</td>
</tr>
<tr>
<td>Tamil Nadu</td>
<td>2.8%</td>
</tr>
<tr>
<td>Maharashtra</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Estimated % adult TB cases that are HIV co-infected (15-49 years) 5.2

National TB policy (8)

DOTS population coverage 2003 67%

Percentage of government health spending on TB control 2%

Total TB control costs 2005 (based on budget US$) 89 million

Government share of total TB control costs, including loans 86%

National TB programme (NTP) budget (based on budget US$) 46 million

NTP budget by source of funding, 2005

<table>
<thead>
<tr>
<th>Source</th>
<th>Amount (in millions US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Government</td>
<td>5</td>
</tr>
<tr>
<td>Loans</td>
<td>11</td>
</tr>
<tr>
<td>Grants</td>
<td>4</td>
</tr>
<tr>
<td>GFATM</td>
<td>8</td>
</tr>
<tr>
<td>Funding gap</td>
<td>15</td>
</tr>
</tbody>
</table>

Estimated in vitro diagnostics market (10)

* US$ 125-150 million
* Growth rate 25-30%; Projected market in 2005 is US$ 350 million

Major markets (11)

* Majority of hospitals are located in: New Delhi, Madras, Bombay, Calcutta, Hyderabad and Bangalore. Private hospitals outnumber state facilities by two to one and purchase 40-50% of imported devices.

National regulatory policies for in vitro diagnostics (12)

Regulatory body/regulatory legislation
* Drugs Controller under the Directorate-General of Health Services
  Nirman Bhawan – Maulana Azad Road, New Delhi, 110011, India
  www.cdsco.nic.in

Who registers the product?
* Manufacturers must appoint a distributor or agent or have an affiliate to file a registration application.

Is a detailed product dossier for performance required?
* Yes

Classification of in vitro diagnostics
* Annex: Scheme 2.

Is local testing required to license the product?
* All ‘critical’ kits must be evaluated by the National Institute of Biologicals (NIB).

Are quality management systems/factory audits a required component of post-market entry?
* There is no comprehensive system of post-market surveillance of drugs or IVD products. Some companies do track products and customer complaints.

Movement towards regulatory harmonization
* Observer of the Asian Harmonization Working Party.

Regulatory requirements for manufacturers/importers of TB-IVDs
* Low level of requirements:
  i) Free Sales Certificate (FSC)
  ii) package inserts with performance claims
  iii) labels.
* For "dubious foreign manufacturers" the Health Authorities may also request a certified GMP and ISO-Quality Management System.

TB laboratory network (9)

* National Reference Lab(s): TB Research Centre (TRC), Indian Council of Medical Research and New Delhi TB Centre.

Smear laboratories
Total 8000
Per million 8

Culture laboratories
Total 90
Per million 0.09

DST laboratories
Total 67
Per million 0.06

Major markets (11)

Karnataka Tamil Nadu Maharastra

0.5% 2.8% 2.5%

Regional surveys

Who registers the product?

Is a detailed product dossier for performance required?

Classification of in vitro diagnostics

Is local testing required to license the product?

Are quality management systems/factory audits a required component of post-market entry?

Movement towards regulatory harmonization

Regulatory requirements for manufacturers/importers of TB-IVDs

Diagnostics for tuberculosis: global demand and market potential
Import tariffs and other taxes (13)
* Import duty on laboratory, scientific, and analytical instruments range from 20% to 40%. However, government, and government-approved research laboratories are exempt from duty on laboratory instruments used for research and development purposes.

Cost of registration (14)
* Non-critical: US$ 21

Duration of registration process (15)
* Non-critical: 3 months
  Critical: 9-12 months and registration is valid for 3 years.

Local manufacturing capacity (16)
* Manufacturers of low-tech supplies and routine lab reagents are in abundance and supply local markets. Several manufacturers have developed into major suppliers for the continent and these represent most of the large IVD manufacturers. Examples include: Transasia Bio-Medicals Ltd; Tulip Group; Accurex Biomedical Pvt. Ltd and Span Diagnostics Ltd.

Local distribution (17)
* Distribution channels are multilayered. Most foreign companies choose from an abundance of skilled small and midsized local distributors who are eager to sell imported products. The challenge is finding one with a wide territory and that is not offering competing product lines.
* Medical laboratories and government and private hospitals are the major end-users of laboratory instruments, reagents, and supplies. Private specialty hospitals are located in metropolitan areas. Government medium-sized hospitals and small clinics have limited if any diagnostic laboratory services. Large commercial stand-alone clinical laboratories import the latest medical instruments and offer a range of specialty diagnostic services at competitive prices.

Procurement (18)
* There is no standard approach to public laboratory IVD product procurement. Each state establishes its own buying system. However, in general, expensive items are always tendered and reagents and consumables may be purchased without tender. Private hospitals and laboratories source IVD products through agents and/or distributors.

Intellectual property rights issues (19)
Year in which country joined World Trade Organization (WTO) and is therefore under the TRIPS agreement 1995
Year in which the country must be in accordance with TRIPS 2000

Industry associations
* All India Manufacturers’ Organization
  Jeevan Sahakar, Sir P.M. Rd
  Mumbai 400 001, India
  Tel: (91-22) 266-1016/1272
* All India Association of Industries
  98 Mittal Chambers, Nariman Point
  Mumbai 400 021, India
  Tel: (91-22) 202-3390
  Contact: Mr Vijay G. Kalantri, President
  aiai@gems.vsnl.net.in
  aiai@giabm01.vsnl.net.in
  www.sourceindia.com/aiai/
* Confederation of Indian Industry
  23 Institutional Area Lodi Rd
  New Delhi 110 003, India
  Tel: (91-11) 462-9994/6164
  Fax: (91-11) 462-6149/463-3168
  www.indianindustry.com

a “Other” includes smear-negative pulmonary TB and smear-unknown.
b Includes patients previously treated for tuberculosis and relapses.
c May include microbiological TB-IVD; IVD for detection of TB-antigen and TB-antibodies; nucleic acid based TB-IVDs.
References:

    c. Interviews with private sector representatives.
    c. Interviews with private sector representatives.
    b. Personal communications.
INDONESIA

Population (1) 219,833,000 * GNI (2) US$ 173.5 billion * GNI/capita (3) US$ 810
Republic * 27 provinces * 2 special regions * 1 special capital city district

Health system capacity and expenditures (4)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% GDP spent on health care</td>
<td>3.2</td>
</tr>
<tr>
<td>Per capita total health expenditure (US$)</td>
<td>26</td>
</tr>
<tr>
<td>No. Hospital beds/1000 population</td>
<td>0.6</td>
</tr>
<tr>
<td>No. Doctors/1000 population</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Total health expenditures

- Government: 36%
- Private: 64%

Private prepaid plans as % of private expenditure on health 5.2

Health care system delivery (5)

Public
- The economic crisis of 1997 had an immediate and enduring affect on a heavily government-subsidized health system. The vast majority of people (85%) have no health insurance. Out-of-pocket co-payments are required for most services. Community financing (Dana sehat) covers 13.5% of the population; Civil Service Health Insurance (Askes) covers 8.5%.
- Health Cards for the Poor (Kartu sehat) cover 2.5% and social security for workers covers 0.8%

Private
- Private health insurance (Swasta) covers 0.3% of the population.

Laboratory infrastructure (6)

Estimated total no. labs Approximately 3000

Percentage of automated and semi-automated laboratories
- 200-250 automated; many semi-automated.

Accreditation Bodies
- Governmental National Standardization Agency: http://www.bsn.or.id/BSNSite2/inggris.shtml

Accredited laboratories
- 203

TB epidemiology (7)

Total estimated new TB cases 627,047
Total notified new TB cases 174,174
- DOTS 174,174 (100%)
- Non-DOTS 0 (0%)

Total gap between estimated and notified new TB cases 452,873

Total notified re-treatment cases 4,086
Estimated % adult TB cases that are HIV co-infected (15-49 years) 0.5

National TB policy (8)

DOTS population coverage 2003 98%
Percentage of government health spending on TB control 5%
Total TB control costs 2005 (based on budget US$) 50 million
Government share of total TB control costs, including loans 63%
National TB programme (NTP) budget 43 million (based on budget US$)

NTP budget by source of funding, 2005

<table>
<thead>
<tr>
<th>Source</th>
<th>Amount (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Government</td>
<td>24</td>
</tr>
<tr>
<td>Loans</td>
<td>4</td>
</tr>
<tr>
<td>Grants</td>
<td>15</td>
</tr>
<tr>
<td>GFATM</td>
<td>0</td>
</tr>
<tr>
<td>Funding gap</td>
<td>0</td>
</tr>
</tbody>
</table>
**TB laboratory network** *(9)*

- National reference lab(s): none established

<table>
<thead>
<tr>
<th>Laboratories</th>
<th>Total</th>
<th>Per million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear laboratories</td>
<td>3300</td>
<td>15</td>
</tr>
<tr>
<td>Culture laboratories</td>
<td>60</td>
<td>0.28</td>
</tr>
<tr>
<td>DST laboratories</td>
<td>60</td>
<td>0.28</td>
</tr>
</tbody>
</table>

**Estimated in vitro diagnostics market** *(10)*

- **US$ 32 million**
- Modest growth of 3-5% per year

**Major markets** *(11)*

- Most large agents and distributors are located in Jakarta and have a national distribution network. Jakarta is the government and economic centre of Indonesia. Surabaya is the leading industrial centre and port.

**National regulatory policies for in vitro diagnostics** *(12)*

- **Regulatory body/Regulatory legislation**
  - Indonesian Directorate General of Pharmaceutical, Medical Equipment and Diagnostics Services Directorate for Drug and Medical Devices Control

- **Who registers the product?**
  - Registration is conducted by an authorized local distributor. First the distributorship and product brand must be registered with the Ministry of Trade then official registration from the Department of Health must be obtained. Registration process is modelled after the US FDA system.

- **Is a detailed product dossier for performance required?**
  - The following documents are required:
    1. materials used in the formula
    2. components
    3. product specifications
    4. production methods (for reagent or in vitro diagnostic products)
    5. finished product specifications
    6. stability (for in vitro diagnostic medical devices)
    7. functions & methods
    8. Free Sales Certificate
    9. GMP-certificate, if registered as a drug.

**Classification of in vitro diagnostics**


- **Is local testing required to license the product?**
  - Yes, for Class III IVD's.

- **Are quality management systems/factory audits a required component of post-market entry?**
  - No

**Movement towards regulatory harmonization**

- Member of the Asian Harmonization Working Party.

**Regulatory requirements for manufacturers/importers of TB-IVDs**

- Low level of requirements:
  1. Free Sales Certificate
  2. package inserts that include performance and stability claims
  3. production procedures
  4. labels

- For "dubious foreign manufacturers" health authorities may also request a certified GMP and (ISO)-Quality Management System.

**Import tariffs and other taxes** *(13)*

- Laboratory and scientific equipment is subject to a 5% import duty.
- All products and services are subject to a 10% value added tax.

**Cost of registration** *(14)*

- Estimated US$ 55 not including Department of Health fee that will be imposed in the near future.

**Duration of registration process** *(15)*

- 3 months and must be renewed bi-annually.

**Local manufacturing capacity** *(16)*

- Very few local IVD producers; most reagents and virtually all instrumentation are imported.

**Local distribution** *(17)*

- There are restrictions on foreign companies that wish to establish marketing and distribution networks unless the product is manufactured locally. However, there is an abundance of competent local distributors and much of the market is easily accessible from Jakarta. Government sales must involve Indonesian agents.

**Procurement** *(18)*

- For small purchases, end-users obtain equipment direct from the free market. Bulk purchases of laboratories financed by international lending institutions are through international competitive bidding procedures, and both local and foreign bidders are accepted. Projects receiving donor country financing procure equipment from that donor country.
**INDONESIA**

**Intellectual property rights issues (19)**

Year in which country joined World Trade Organization (WTO) and is therefore under the TRIPS agreement  **1995**

Year in which the country must be in accordance with TRIPS  **2000**

**Industry associations**

* Gakeslab (Indonesian Laboratory and Health Care Equipment Association)
  
  Jl. Raya Kebayoran Lama No.9
  
  Jakarta 12240, Indonesia
  
  Tel: (62) 21 7204878
  
  Fax: (62) 21 7260729
  
  www.gakeslab.or.id/masuk.htm (Indonesian only)

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a  "Other" includes smear-negative pulmonary TB and smear-unknown.

b  Includes patients previously treated for tuberculosis and relapses.

c  May include microbiological TB-IVD; IVD for detection of TB-antigen and TB-antibodies; nucleic acid based TB-IVDs.
INDONESIA

References:

c. BCG Report for WHO, SAI Health care.
12. a. US Department of Commerce, Office of Microelectronics, Medical Equipment and Instrumentation.
c. Addresses obtained online – individual country regulatory websites
g. mediSTAT Country Profiles, Indonesia, 2003.
c. Industry Canada Website: http://strategy.gc.ca/scr/mkt/shardec/engdoc/121.html
15. d. STAT-USA, US Department of Commerce
b. STAT-USA, US Department of Commerce
c. Interviews with private sector and comments from WHO expert reviewers
d. International Market Insight, www.buyusa.com; Indonesia’s Ministry of Health Aims to Improve Quality of Manpower in Health care Services, by: Sharon Chandra, 02/26/2004
Health system capacity and expenditures (4)

- % GDP spent on health care: 7.9
- Per capita total health expenditure (US$): 2,476
- No. of hospital beds/1000 population: 14.8 (includes beds for geriatric care)
- No. of doctors/1000 population: 2

Total health expenditures

- Government: 81.7%
- Private: 18.3%

Private prepaid plans as % of private expenditure on health: 1.5

Health care system delivery (5)

Public
- Health insurance schemes are segmented by occupation/age and each provides comprehensive care coverage.
- Seiken, Kenpo, and Kyosai are insurance schemes for employees and their dependents.
- National health insurance, or Kokuho is provided for the self-employed, retirees, and their dependents.
- Roken system covers those >70 and >65, if bedridden. Cost of care for the elderly is financed by pooling contributions from all insurance schemes.

Private
- Hospitals are predominantly privately owned, including 70% of hospital beds.
- All private hospitals are not-for-profit, meaning that distribution of profits is restricted to inside the hospital. Ultimately, these hospitals operate as entrepreneurial businesses like their for-profit counterparts.

Accreditation bodies
- The Japan Accreditation Board for Conformity Assessment: http://www.jab.or.jp/index_e.html

TB epidemiology (7)

- Total estimated new TB cases: 39,927
- Total notified new TB cases: 30,624
  - DOTS: 20,465 (67%)
  - Non-DOTS: 10,159 (33%)
- Total gap between estimated and notified new TB cases: 9,303

TB laboratory network (8)
- National Reference Lab(s): Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Tokyo.

Laboratory infrastructure (6)

Estimated total no. of labs: 800-900 commercial labs, 9,000 hospital based laboratories

Estimated in vitro diagnostics market (9)
- US$ 3 billion
- Annual growth 3%
Major markets (10)

- Most Japanese agents and sales representatives of health-industries products are located and concentrate their marketing efforts in Tokyo, Osaka and Nagoya, although there are agents representing most regions.

National regulatory policies for in vitro diagnostics (11)

Regulatory body/regulatory legislation


- Registration requirements for in vitro diagnostics (IVDs) in Japan are very complex. The major difficulty arises from the classification of IVDs in Japan as pharmaceuticals rather than as a separate category. Japan is in the process of revising its classification and regulation of diagnostic products to include a risk-based system.

- Products classified as High Risk will require ministry approval, products classified as Low Risk will require third-party certification, products classified as Low Risk Standard Substances will require only self-declaration.

- A medical device manufacturer (whether domestic or foreign) must first obtain two types of consent from the MHLW: kyoka (“licence”) and shonin (“approval”). Kyoka essentially grants the medical device manufacturer (or distributor) permission to market its products in Japan.

- Kyoka is required for each manufacturing plant and representative office in Japan. Kyoka must be renewed every five years.

- Shonin is granted once the MHLW is satisfied with the safety and effectiveness of the medical device. If a manufacturer wishes a product to be reimbursable under the National Health Insurance system, this must be indicated on the device’s application for product approval.

Who registers the product?

- A foreign company can register its products directly through the foreign manufacturer’s office in Japan, through a Japanese distributor, or by means of an in-country caretaker (ICC).

Is a detailed product dossier for performance required?

- Yes

Classification of in vitro diagnostics

  http://www.asiahwp.org/Paper_3TC_Jpn.pdf

Is local testing required to license the product?

- Yes, clinical trials in Japan may be required for unique products that have or have not already undergone testing in the U.S. or Europe. Kosheisho will make case-by-case decisions in determining need for local testing. This applies in particular for “specially controlled devices” in the revised PAL - see Scheme 4.

Are quality management systems/factory audits a required component of post-market entry?

- The new PAL requires a certified ISO 13 485:2003-quality management system. A complete outline of post-market required activities is found at www.jpma.or.jp/12english/publications/pub023.pdf or the website of the Japan Pharmaceutical Manufacturers Association, www.jpma.or.jp

Movement towards regulatory harmonization

- Member of the Global Harmonization Task Force.

Regulatory requirements for manufacturers/ importers of TB-IVDs

- Highest level of requirements based on revised Pharmaceutical Affairs Law (PAL):
  i) Free Sales Certificate
  ii) package inserts including performance and stability claims
  iii) production procedures
  iv) detailed “product dossier” to support claims
  v) certified ISO 13 485 quality management system
  vi) Government-controlled clinical evaluation.

Import tariffs and other taxes (12)

- There is no duty on the import of medical equipment into Japan.

Cost of registration (13)

- Initial registration fees using an ICC for common or not-novel devices average between US$ 10 000 and US$ 30 000 per product, while new medical devices that may or may not require clinical studies can cost between US$ 50 000 and US$ 250 000 per product, including clinical trial costs. In addition, after registration, an ICC is required to perform ongoing duties that can cost about US$ 15 000 per year for non-novel products and approximately twice that per year for unique products that have required clinical studies in Japan.

Duration of registration process (14)

- Estimated 1 year for new medical equipment and 4 months for other medical equipment. New technologies often have to wait two years before gaining reimbursable status.

Local manufacturing capacity

- Japan is the fourth largest exporter of medical devices in the world, behind the United States, Germany and the Netherlands. Domestic production of medical devices in Japan is expected to decline over the next four years due to several Japanese companies moving production facilities to other
Asian countries, which is expected to make export more cost-effective.

Local distribution (15)

* Foreign sales approval requires the appointment of a Japanese representative that holds a licence to sell medical devices. Both foreign manufacturers and the local representative are jointly responsible for regulatory compliance (import practices, GMP, post-marketing surveillance). Nearly all manufacturers sell through wholesalers, which cuts profit margins but ultimately controls access to the end-users.

* Direct sales to government procurement agencies (i.e. http://www.mti.go.jp/; http://www.mpt.go.jp/; http://www.jetro.go.jp/) by responding to public tenders is an alternative; however, since most tender documentation is written in Japanese, and because Japanese buyers demand comprehensive after-sales service in their national language, foreign suppliers are advised to seek representation by Japanese agents and distributors.

* There are many medical devices distributors in Japan, most of which are based in Tokyo and Osaka. While agents solicit business and enter into agreements on behalf of the exporter they are representing, they do not take ownership over the products they sell.

* As with distributors, agents tend to specialize by product category. Agents frequently act as intermediaries between suppliers and distributors.

* Japan’s universal health care system covers all medical services provided by physicians, including medical devices. With few exceptions, medical institutions must use approved medical devices, covered by national medical insurance. An importer or manufacturer must apply separately (from product registration) for insurance coverage.

Procurement (16)


* National government procurement is conducted on a basis where contracts are tendered by individual ministries or government entities in a decentralized manner. In the case of medical devices, tenders are issued by the MHLW.

* Hospitals run by public organizations purchase equipment and devices through invitations to tender, based on an approved list system. Considering there are close to 1500 public organizations and associations operating hospitals in the country, it would be difficult to register with every one of them. Companies are, therefore, encouraged to use the services of Japanese agents already registered with these bodies.

* Japan’s National Health Insurance (NHI) system covers all medical services provided by physicians, including medical devices. With few exceptions, medical institutions must use approved medical devices, covered by national medical insurance.

* An importer or manufacturer must also apply for reimbursement coverage. The MHLW conducts end-user surveys to find out what prices are actually being charged for products throughout the country.

* The official reimbursement price is derived by taking the average market price and then adding an extra margin to allow for a reasonable level of discount. In December 2001, the Japanese Government passed a new pricing policy for medical products.

* The first phase of this new system was introduced in April 2002. It is based on foreign reference prices; the MHLW will determine the foreign price of a product, presumably by looking at a device’s price in various markets around the world. The Japanese reimbursement price will then be set so as not to exceed 1.5 times this foreign price.

Intellectual property rights issues (17)

Year in which country joined World Trade Organization (WTO) and is therefore under the TRIPS agreement 1995

Year in which the country must be in accordance with TRIPS 1996

Industry associations

* Japan Analytical Instruments Manufacturers Association
  Taimei Building, 3-22 Ogawamachi, Kanda, Chiyoda-ku
  Tokyo 101
  Tel: (03) 3 3292 0642
  Fax: (03) 3 3292 7157

* Japan Association of Clinical Reagents Industries
  Yu Building, 1-5-7 Nihonbashl Horidomecho, Chuo-ku
  Tokyo 103
  Tel: (03) 3 3669 9101
  Fax: (03) 3 3567 6247


**Japan Association of Medical Device and Material Industries**
Kujaku Building, 1-4-6 Ginza, Chuo-ku
Tokyo 104
Tel: (081) 3 3567 6246
Fax: (081) 3 3567 6247

**Japan Federation of Medical Devices Associations**
Ikakiki Kaikan 3F, 3-39-15 Hongo, Bunkyo-ku
Tokyo 113
Tel: (081) 3 3818 2310
Fax: (081) 3 3818 2448

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a. "Other" includes smear-negative pulmonary TB and smear-unknown.
b. Includes patients previously treated for tuberculosis and relapses.
c. May include microbiological TB-IVD; IVD for detection of TB-antigen and TB-antibodies; nucleic acid based TB-IVDs.

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**References:**

g. WHO/TDR Global Tuberculosis Laboratory Services Survey 2002.

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**Worldwide IVD Market,**

a. Kalorama Information, 2002,


c. Merrill Lynch Research Report, in vitro Diagnostics,

d. Global Harmonization Task Force Website: http://www.ghtf.org/
e. European Business Council in Japan, Trade Issues Report, 2002,

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**Medical Devices Market in Japan,**

a. Halasey, S and Park, R.
d. c. EU Priority Proposals for Regulatory Reform in Japan, October 17, 2002.
e. Global Harmonization Task Force Website: http://www.ghtf.org/

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**Japan**

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**Diagnoses for tuberculosis: global demand and market potential**

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**JAPAN**
RUSSIAN FEDERATION

Population (1) 143 246 000  *  GNI (2) US$ 374.8 billion  *  GNI/capita (3) US$ 2 610
Federation  *  49 oblasts  *  21 republics  *  10 autonomous okrugs  *  6 krays
2 federal cities  *  1 autonomous oblast

Health system capacity and expenditures (4)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
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<tr>
<td>% GDP spent on health care</td>
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<tr>
<td>Per capita total health expenditure (US$)</td>
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<tr>
<td>No. of hospital beds/1000 population</td>
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<tr>
<td>No. of doctors/1000 population</td>
<td>4.7</td>
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<tr>
<td>Total health expenditures</td>
<td></td>
</tr>
<tr>
<td>Government</td>
<td>55.8%</td>
</tr>
<tr>
<td>Private</td>
<td>44.2%</td>
</tr>
<tr>
<td>Private prepaid plans as % of private</td>
<td>14.7</td>
</tr>
<tr>
<td>expenditure on health</td>
<td></td>
</tr>
</tbody>
</table>

Health care system delivery (5)

Public
- Virtually all health facilities are owned by the State and universal access (Semashko) to necessary health services is provided. Employers contribute 3.6% of their payroll to federal and regional state insurance funds. Regional funds are distributed to independent, though highly regulated insurance companies on a per capita basis. Insurers pay for hospitalization through a DRG-based payment system and outpatient facilities are paid on a per capita basis.

Private
- Private ventures are few, small, generally highly specialized and charge higher than average prices.
- Few people hold private insurance, which covers high-end health products.
- Religious organizations own a number of private ventures.

Laboratory infrastructure (6)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated total no. of labs</td>
<td></td>
</tr>
<tr>
<td>clinical laboratories</td>
<td>26 150</td>
</tr>
</tbody>
</table>

Accreditation bodies
- Various federal authorities carry out accreditation

and a unified system based on European standards EN 45000 is being planned.

TB epidemiology (7)

Total estimated new TB cases 160 688
Total notified new TB cases 118 564
- DOTS 20 118 (17%)
- Non-DOTS 98 446 (83%)

Total gap between estimated and notified new TB cases 42 124

Total notified re-treatment cases 27 989

% Multidrug-resistance in new cases
- Regional surveys
  - Tomsk Oblast 13.7%
  - Orel Oblast 2.6%
- Various federal authorities carry out accreditation

% Multidrug-resistance in re-treatment cases
- Regional surveys
  - Tomsk Oblast 43.6%
  - Orel Oblast 42.4%

Estimated % adult TB cases that are HIV co-infected (15-49 years) 6.2
RUSSIAN FEDERATION

National TB policy (8)

DOTS population coverage 2003 25%
Percentage of government health spending on TB control 4%
Total TB control costs 2005 (based on budget US$) 399 million
Government share of total TB control costs, including loans 87%
National TB programme (NTP) budget (based on budget US$) 316 million

NTP budget by source of funding, 2005

National regulatory policies for in vitro diagnostics (12)

Regulatory body/regulatory legislation
* Two documents are required for importing medical devices, including diagnostics, into Russia: a registration certificate issued by the Ministry of Health Department of State Control over Quality, Efficiency, and Safety of Drugs and Medical Equipment, and a certificate of conformity issued by the State Committee for Standardization, Metrology, and Certification (Gosstandart - GOST R certificate). The role of the Ministry is to ensure clinical safety and efficacy.

Gosstandart works to ensure product conformity with established technical and safety standards.
* The Ministry of Health and Social Development has launched a new website devoted to regulatory issues: www.regmed.ru

Who registers the product?
* Foreign companies are recommended to complete procedures through an accredited representative’s office in Russia or through a hired Russian agent or distributor.

Is a detailed product dossier for performance required?
* Yes

Classification of in vitro diagnostics

Is local testing required to license the product?
* Yes, through MOH and Gosstandart systems.
* GOST R-equivalent certificates obtained from foreign certification organisations accredited by Gosstandart are accepted.

Are quality management systems/factory audits a required component of post-market entry?
* No

Movement towards regulatory harmonization
* Gosstandart is incorporating ISO and IEC standards.

Regulatory requirements for manufacturers/importers of TB-IVDs
* Very high level of requirements:
  (i) Free Sales Certificate
  (ii) Package inserts including performance and stability claims
  (iii) Production procedures
  (iv) Detailed “product dossier” claims
  (v) Government-controlled clinical evaluation which are avoidable only in rare cases.

Import tariffs and other taxes (13)
* Customs duties for medical devices are generally 5%. Products included on the Government’s “Approved Important and Vitally Essential Medical Equipment” list receive 0% duty rates.

TB laboratory network (9)

* Central Tuberculosis Research Institute, Moscow.

Smear laboratories
Total 12,000
Per million 83

Culture laboratories
Total 730
Per million 5.1

DST laboratories
Total 300
Per million 2.1

Estimated in vitro diagnostics market (10)

* US$ 300 million
* Annual growth: 10

Major markets (11)

* Moscow, St. Petersburg and the areas in between. This constitutes where 75% of the population live.
RUSSIAN FEDERATION

including in vitro diagnostics and laboratory equipment are value-added tax (VAT) exempt. A limited number of reagents are also VAT exempt, and otherwise subject to 10% VAT.

Cost of registration (14)
* For disposable systems and smaller devices i.e. test kits, fees range between US$ 200 and US$ 2 500. Certification is valid for 5 years.

Duration of registration process (15)
* Often > 3-6 months.

Local manufacturing capacity (16)
* The level of local production of laboratory diagnostic equipment, supplies, and reagents is extremely inadequate to meet the demand of health care facilities and laboratories in Russia.
* In the early 1990s, production started to develop at small and medium-sized private firms and former defence plants. Locally made medical equipment and devices are three to five times less expensive than similar Western-made equipment.
* Russia has legislated a gradual upgrade of the medical industry to Good Manufacturing Practice (GMP) standards by 2005.

Local distribution (17)
* The majority of diagnostic equipment and supplies are purchased by laboratories either directly from manufacturers or through distributors, sub-distributors and dealers. About 300 distributors of clinical diagnostic products operate in Russia.
* Major distributors are located in Moscow and work in the regions either through local independent distributors or through their own regional representatives. Owing to lack of financing, the centralized purchasing system has almost broken down.

Procurement (18)
* Local government finances support 97% of the purchases of medical supplies, including reagents for clinical laboratories, while the federal government finances 3%. Local health care authorities arrange a number of tenders to buy medical equipment and supplies for their territorial hospitals and clinics.
* The list of tenders is published in a special magazine called Competitive Bids (www.bob.ru). Foreign companies are allowed to take part only in some of the tenders either directly or through their local distributors.

Intellectual property rights issues (19)

Year in which country joined World Trade Organization (WTO) and is therefore under the TRIPS agreement
Not signed; an observer government of the WTO

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\[\text{a} \quad \text{“Other” includes smear-negative pulmonary TB and smear-unknown.}\]

\[\text{b} \quad \text{Includes patients previously treated for tuberculosis and relapses.}\]

\[\text{c} \quad \text{May include microbiological TB-IVD; IVD for detection of TB-antigen and TB-antibodies; nucleic acid based TB-IVDs.}\]
References:
b. US Department of Commerce, Office of Microelectronics, Medical Equipment and Instrumentation: Medical Device Regulatory Requirements for Russia Updated 10/24/00.
*e. Global Harmonization Task Force Website http://www.ghtf.org/
b. Espicom Business Intelligence.
c. Industry Canada Website: http://strategies.gc.ca/sc_mktvibnddc/ eigndoc/111.html
d. Interviews with private sector and comments from WHO expert reviewers.
e. Espicom Business Intelligence.
b. Industry Canada Website: http://strategies.gc.ca/sc_mktvibnddc/ eigndoc/111.html
SOUTH AFRICA

Population (1) 45 026 000 * GNI (2) US$ 126 billion * GNI/capita (3) US$ 2750
Republic * 9 provinces

Health system capacity and expenditures (4)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% GDP spent on health care</td>
<td>8.7%</td>
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<tr>
<td>Per capita total health expenditure (US$)</td>
<td>206</td>
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<tr>
<td>No. of hospital beds/1000 population</td>
<td>5.1</td>
</tr>
<tr>
<td>No. of doctors/1000 population</td>
<td>0.6</td>
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</table>

Total health expenditures

<table>
<thead>
<tr>
<th>Sector</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Government</td>
<td>45.9%</td>
</tr>
<tr>
<td>Private</td>
<td>52.1%</td>
</tr>
</tbody>
</table>

Private prepaid plans as % of private expenditure on health 77.7

Health care system delivery (5)

Public

- A national district-based health system offers South African nationals health care at more than 684 hospitals and almost 3 000 clinics and community health centres. Hospitals are classified into four categories:
  - District (Level 1) hospitals receive referrals from, and provide generalist support to, community health clinics.
  - Regional (Level 2) hospitals normally receive referrals from, and provide specialist support to, a number of district hospitals.
  - Central (Level 3) hospitals receive from, and provide sub-specialist support to, a number of regional hospitals.
  - Specialized hospitals include chronic psychiatric and TB hospitals, as well as specialized spinal injury and acute infectious disease hospitals.
- Services offered by primary health care clinics and community health centres are free. Allocation of resources and standard of health care vary from province to province. Coverage extends to > 80% of the population.
- The Global Fund to Fight AIDS, Tuberculosis and Malaria has approved budgets of US$ 167.4 millions (over 5 years) for programmes in South Africa.

Private

- The private sector offers specialized, high-tech services and is fast growing. Facilities are either large corporate for-profit hospitals or not-for-profit workplace health services or charities.
- Approximately 18% of the population access comprehensive health care through private medical scheme coverage.
- These schemes spend more than four times as much as the state per head of covered population.
- Non-medical scheme members spend considerable amounts on care in the private sector.

Laboratory infrastructure (6)

Estimated total no. of labs approximately 120

Accreditation bodies


TB epidemiology (7)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total estimated new TB cases</td>
<td>241 537</td>
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<tr>
<td>Total notified new TB cases</td>
<td>210 590</td>
</tr>
<tr>
<td>- DOTS</td>
<td>210 548 (100%)</td>
</tr>
<tr>
<td>- Non-DOTS</td>
<td>42 (0%)</td>
</tr>
<tr>
<td>Total gap between estimated and notified new TB cases</td>
<td>30 947</td>
</tr>
<tr>
<td>Notified new &quot;other&quot; TB cases</td>
<td>94 217 (66%)</td>
</tr>
<tr>
<td>Not notified new &quot;other&quot; TB cases</td>
<td>49 103 (34%)</td>
</tr>
<tr>
<td>Total estimated new &quot;other&quot; TB cases</td>
<td>143 329</td>
</tr>
<tr>
<td>Total estimated new Sm + TB cases</td>
<td>98 228</td>
</tr>
<tr>
<td>Notified new Sm + Cases (DOTS)</td>
<td>116 331 (118%)</td>
</tr>
<tr>
<td>Not notified new Sm + cases (DOTS)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total notified re-treatment casesb</td>
<td>44 832</td>
</tr>
</tbody>
</table>

* Diagnostics for tuberculosis: global demand and market potential *
SOUTH AFRICA

% Multidrug-resistance in new cases

Regional surveys¹

<table>
<thead>
<tr>
<th>Region</th>
<th>Kw</th>
<th>Ec</th>
<th>Mp</th>
<th>Ga</th>
<th>Fr</th>
<th>Wc</th>
<th>Li</th>
<th>Nw</th>
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<tr>
<td>Kw</td>
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<td>Li</td>
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<tr>
<td>Nw</td>
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% Multi-Drug Resistance in retreatment cases

Regional surveys¹

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<tr>
<td>Mp</td>
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</tr>
</tbody>
</table>

Estimated % adult TB cases that are HIV co-infected (15-49 years) 61

National TB policy (8)

DOTS population coverage 2003 99.5%

Percentage of government health spending on TB control 7%

Total TB control costs 2005 (based on budget US$) 300 million

NTP budget by source of funding, 2005

Grants (US$) 8.3 million (over 5 years)

GFATM (US$) 8.4 million (over 2 years)

TB laboratory network (9)

National reference lab(s): National Tuberculosis Research Programme-MRC, Pretoria

Smear laboratories

Total 341

Per million 8

Culture laboratories

Total 14

Per million 0.3

DST laboratories

Total 13

Per million 0.3

¹ Kwazulu-Natal Province, Eastern Cape Province, Mpumalanga, Gauteng Province, Free State Province, Western Cape Province, Limpopo Province, North West Province.

Estimated in vitro diagnostics market (10)

* US$ 150–160 million

Major markets (11)

* Approximately 90% of South Africa’s population resides in or around Johannesburg, Cape Town, Durban, Pretoria and Port Elizabeth, which are the country’s major economic hubs and consumer markets. Distribution bases are also concentrated in these areas, although distributors and agents are generally well-positioned to market products throughout the country.

National regulatory policies for in vitro diagnostics (12)

Regulatory body/regulatory legislation

* No comprehensive system of medical device regulation (exception electromedical devices); however, new diagnostic products must be “approved” by the National Centre for Occupational Health (www.doh.gov.za/index.html) and the South African Institute for Medical Research (www.mrc.ac.za). More specifically, blood grouping tests and diagnostics for HIV, HCV HBsAg, malaria, TB and STDs must be evaluated by the National Laboratory. This evaluation is obligatory unless the test has been “approved” by a WHO test kit evaluation programme and results have been published in the corresponding report. http://www.who.int/diagnostics_laboratory/evaluations/en/

Who registers the product?

* There are no registration requirements for any diagnostic test for sale in the country.

Classification of in vitro diagnostics

* Annex: Scheme 7.

Are quality management systems/factory audits a required component of post-market entry?

* There is no official post-market surveillance, but more successful companies track product performance and problems. This is seen by buyers as a necessary service in light of the fact that there is no official procedure.

Movement towards regulatory harmonization

* If and when regulation is brought into effect, it is likely to be based on the European Union Directives, which include a risk-based classification system, third-party accrediting agencies, and clinical trials for new technologies.
### Regulatory requirements for manufacturers/ importers of TB-IVDs

- No specific requirements.

### Import tariffs and other taxes (13)

- Medical devices used solely for the purpose of a medical procedure are registered under the South African tariff code: 1980 9018 90 and are duty-free.

### Local manufacturing capacity (14)

- Local producers tend to be small or medium-sized businesses and often combine some distribution activity with manufacturing. Multinationals present in South Africa often operate in a joint venture capacity with local firms.

### Local distribution (15)

- The health care market is complex and fragmented, with extensive representation necessary in order to gain a foothold in the medical market. Foreign suppliers that do not have a local office cannot sell directly to public-sector customers. However, direct sales to the private sector (such as private hospitals, clinics, pharmacies and health-care product retail chains) are permitted. Foreign suppliers that are not participating in South Africa through a local office or partnership are precluded from bidding on public tenders. However, a local agent can act independently on the supplier’s behalf for this purpose.

- A local agent or distributor can also assist a foreign supplier who wishes to sell to the private sector. Most agents and distributors are based in major urban centers and have jurisdiction to market products across the nation.

- Companies are advised to contact their embassy in Johannesburg for a list of reliable agents or distributors involved in the health-care sector. For smaller medical device manufacturers and first-time exporters to South Africa, engaging in a joint venture with a locally established company may be preferable to using a distributor. The distribution of medical equipment in South Africa is from the manufacturer or import agent direct to the hospitals. There are no middlemen such as wholesalers.

### Procurement (16)

- The government sector is still the major purchaser of health care equipment and supplies. The public tendering system is governed by the State Tender Board Act of 1968 and is administered through the State Tender Board. The State Tender Board is empowered by the South African Government to procure supplies and services on behalf of individual government departments. Tender notices are published in the State Tender Bulletin. Government medical product tenders are also posted at: http://www.medisource.co.za/tenders/govt.shtml, while tenders issued by the South African Medical Device Industry Association (SAMED) are available from http://www.medauction.co.za/cgi-bin/tenders/recent.cgi.

- Provincial health departments have the authority to procure items independently of the Department of Health and often issue their own tenders. They are not published.

### Intellectual property rights issues (17)

| Year in which country joined World Trade Organization (WTO) and is therefore under the TRIPS agreement | 1995 |
| Year in which the country must be in accordance with TRIPS | 2000 |

### Industry associations

- **South African Medical Device Industry Association (SAMED)**
  - PO Box 933, Pretoria 0001
  - Gauteng, South Africa
  - Tel: (27) 12 327 1487
  - Fax: (27) 12 327 1501
  - www.samed.co.za
  - SAMED has 58 members, comprising local manufacturers, multinationals, wholesalers and distributors.

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* “Other” includes smear-negative pulmonary TB and smear-unknown.

* Includes patients previously treated for tuberculosis and relapses.

* May include microbiological TB-IVD; IVD for detection of TB-antigen and TB-antibodies; nucleic acid based TB-IVDs.
References:

A System in Transition.

b. US Department of Commerce, Office of Micronanoelectronics, Medical Equipment and instrumentation, Medical Device Regulatory Requirements for South Africa. Updated 03/07/2002.
b. US Department of Commerce, Office of Micronanoelectronics, Medical Equipment and instrumentation, Medical Device Regulatory Requirements for South Africa. Updated 03/07/2002.
b. US Department of Commerce, Office of Micronanoelectronics, Medical Equipment and instrumentation, Medical Device Regulatory Requirements for South Africa. Updated 03/07/2002.
b. US Department of Commerce, Office of Micronanoelectronics, Medical Equipment and instrumentation, Medical Device Regulatory Requirements for South Africa. Updated 03/07/2002.
d. Industry Canada Website: http://strategiq.gc.ca/.
b. US Department of Commerce, Office of Micronanoelectronics, Medical Equipment and instrumentation, Medical Device Regulatory Requirements for South Africa. Updated 03/07/2002.
UGANDA

Population (1) 26 827 000  •  GNI (2) US$ 6.2 billion  •  GNI/capita (3) US$ 250
Republic  •  56 districts

---

**Health system capacity and expenditures (4)**

- % GDP spent on health care: 7.4
- Per capita total health expenditure (US$): 18
- No. of hospital beds/1000 population: 0.9
- No. of doctors/1000 population: 0.05

**Total health expenditures**

- Government: 27.9%
- Private: 72.1%

Private prepaid plans as % of private expenditure on health: 0.2

---

**Health care system delivery (5)**

**Public**

- Uganda National Minimum Health Care Package attempts to ensure all Ugandan nationals free access to at least an essential package of health services.
- Roughly two thirds of all health facilities (approximately 1 100) are government-owned but many are lacking basic capacities for care. One fifth of citizens depend on these health care facilities. Access in rural areas, where the majority of the population lives, is a challenge due to poor infrastructure.
- The Government also has programmes to support NGO health units, and other privately run facilities.
- NGO’s or donors contribute about 43% of all health spending.
- The Global Fund to Fight AIDS, Tuberculosis and Malaria has approved budgets totaling 6 million US$ worth of projects in Uganda.

**Private**

- Almost half of the population visit traditional healers and one fifth utilize NGO-run health care facilities, which operate on a fee-for-service basis.
- Private micro-insurance schemes (similar to medical schemes in other African countries) provide a complementary strategy for improving equity of access to health care by offsetting substantial costs of care and drugs, under-the-table payments and the cost of travelling, especially from rural areas.

- Specialist care is often provided at NGO hospitals or other private hospitals on a fee-for-service basis.

---

**TB epidemiology (6)**

- Total estimated new TB cases: 106 201
- Total notified new TB cases: 40 181
  - DOTS: 40 181 (100%)
  - Non-DOTS: 0 (0%)
- Total gap between estimated and notified new TB cases: 66 020
- Notified new “other” TB cases DOTS: 19 861 (33%)
- Not notified new “other” TB cases non DOTS: 0 (0%)
- Notified new “other” TB cases non DOTS: 40 164 (67%)
- Total estimated new “other” TB cases: 60 025

**National TB policy (7)**

- DOTS population coverage 2003: 100%
- Percentage of government health spending on TB control: 2%
- Total TB control costs 2005 (based on budget US$): 6.9 million
- Government share of total TB control costs, including loans: 38%
- National TB programme (NTP) budget (based on budget US$): 6 million

---

* Diagnostics for tuberculosis: global demand and market potential *
UGANDA

NTP budget by source of funding, 2005

![Budget Chart]

- **TB laboratory network** (10)
  - National Reference Lab(s): Central Tuberculosis Laboratory, Kampala.
  - **Smear laboratories**
    - Total: 400
    - Per million: 16
  - **Culture laboratories**
    - Total: 2
    - Per million: 0.08
  - **DST laboratories**
    - Total: 2
    - Per million: 0.08

- **Major markets** (9)
  - Major markets in Uganda are related to the distribution of hospitals services.
  - National referral hospitals - Mulago and Butabika are teaching hospitals in the Kampala district.
  - Regional referral hospitals: Arua, Gulu, Hoima, Jinja, Kabale, Kabarole, Masaka, Mbane, Mbarara and Soroti. These are teaching hospitals and resource centers to the regions they are situated in.
  - Non-Government Hospitals include Nsambya, Rubaga, Mengo (Kampala district), Lacor (Gulu district), and Matany (Moroto district). Many of these provide specialized services.

- **National regulatory policies for in vitro diagnostics** (10)

  **Regulatory body/Regulatory legislation**
  - No comprehensive system of medical device regulation exists. However, to import an IVD product either a wholesaler or a health care program under the auspices of the Ministry of Health must apply to the National Drug Authority to have a Certificate of Verification. Once this certificate is given, the organization may enter into a Memorandum of Understanding with the National Medical Stores to distribute the test kit to authorized buyers. The National Advisory Committee on Medical Equipment may advise the importer on the suitability/compatibility of the device in question but has no authority to bar an importer from importing whatever device a company wishes to import.

  **Classification of in vitro diagnostics**
  - Annex: Scheme 7.

  - **Is local testing required to license the product?**
    - Local evaluation is done for selected diagnostics. However, it is not required if the test has been “approved” by a WHO test kit evaluation programme and results have been published in the corresponding report. http://www.who.int/diagnostics_laboratory/evaluations/en/
    - WHO-“approval” is a pre-requisite to export HIV-diagnostics to Uganda.

  **Regulatory requirements for manufacturers/importers of TB-IVDs**
  - No specific requirements.

  **Import tariffs and other taxes** (11)
  - Import certificates, which are non-good-specific, are required and valid for 6 months. The certificates replace import licenses.
  - Import duties on IVDs are 15% and excise surcharges have been unified at 10%. Reductions are planned during the next two years.

  **Cost of registration** (12)
  - The Certificate of Verification costs 0.8% the Free On Board (F.O.B.) value of the products.

  **Duration of registration process** (13)
  - Not available.

  **Local manufacturing capacity** (14)
  - Local manufacturing for diagnostic tests is sparse.
  - Contact the Uganda Manufacturers Association for more information.

  **Local distribution** (15)
  - Most foreign products are marketed through a local company with experience/expertise in the respective area. There are no restrictions on foreign investors forming joint ventures with local investors.

  **Procurement** (16)
  - Procurement of drugs and medical supplies by the Ministry of Health is done through National Medical Stores (NMS). In 2004, the NMS procurement is for drugs and pregnancy tests. For all other products the NMS may act as a storage and distribution centre at the request of an NGO or local health service, or National Health Program, or importer. In this case the NMS enters into a Memorandum of Understanding to act as procurement office. The National Medical Stores
UGANDA

charges 6-20% of the F.O.B value of the products for their services. All hospitals and laboratories can buy diagnostic products.

* A tender system is used for larger purchases, issued to known distributors and personal contact is used for smaller purchases. Open procurement is possible when a government institution or specific health programme is not involved in the use of a specific test or device.

* Since government purchases are normally made using loans/grants from donor countries, conditions are typically attached to the use of that money requiring that equipment be purchased from the donor country.

Intellectual property rights issues

Year in which country joined World Trade Organization (WTO) and is therefore under the TRIPS agreement 1995

Year in which the country must be in accordance with TRIPS January 2006

January 2016

*If IVDs are considered pharmaceuticals

Industry associations

* Uganda Manufacturers Association
  P.O. Box 6966, Kampala
  Tel: (256) 41-221-034
  www.uma.co.ug

* Uganda National Chamber of Commerce and Industry
  P.O. Box 3809, Kampala
  Tel: (256) 41-258-791
  Fax (256) 41-258-793

* Uganda Small Scale Industry Association
  P.O. Box 7725, Kampala
  Tel: (256) 41-221-785
  Fax: (256) 41-221-038

a “Other” includes smear-negative pulmonary TB and smear-unknown.

b Includes patients previously treated for tuberculosis and relapses.

c May include microbiological TB-IVD/IVD for detection of TB-antigen and TB-antibodies; nucleic acid based TB-IVDs.
References:
d. The World Bank Group Private and Public Initiatives: Working together in Health and Education.
c. US Department of Commerce STAT USA Market Research, Trade and Investment, Uganda.
b. Uganda Ministry of Health Website: http://www.health.go.ug/
c. US Department of Commerce STAT USA Market Research, Trade and Investment, Uganda.
11. US Department of Commerce STAT USA Market Research, Trade and Investment, Uganda.
12. US Department of Commerce STAT USA Market Research, Trade and Investment, Uganda.
b. Uganda Ministry of Health Website: http://www.health.go.ug/
14. d. STAT USA, US Department of Commerce.
e. National Medical Stores. www.natmedstores.org
14. Personal communication.
http://www.wto.org/english/thewto_e/whatis_e/tif_e/org6_e.htm
### Health system capacity and expenditures (4)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
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<td>% GDP spent on health care</td>
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<tr>
<td>Per capita total health expenditure (US$)</td>
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<tr>
<td>No. of hospital beds/1000 population</td>
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<td>No. of doctors/1000 population</td>
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<table>
<thead>
<tr>
<th>Total health expenditures</th>
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</thead>
<tbody>
<tr>
<td>Government</td>
<td>83.4%</td>
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<tr>
<td>Private</td>
<td>16.6%</td>
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Private prepaid plans as % of private expenditure on health: 18.6%

### TB epidemiology (7)

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<thead>
<tr>
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<tr>
<td>Total estimated new TB cases</td>
<td>7,056</td>
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<tr>
<td>Total notified new TB cases</td>
<td>6,400</td>
</tr>
<tr>
<td>DOTS</td>
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<tr>
<td>Non-DOTS</td>
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</table>

<table>
<thead>
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</thead>
<tbody>
<tr>
<td>Total gap between estimated and notified new TB cases</td>
<td>656</td>
</tr>
</tbody>
</table>

Notified new re-treatment cases\(^b\): 206

% Multidrug-resistance in new cases: 0.9

% Multidrug-resistance in re-treatment cases: 4.2

Estimated % adult TB cases that are HIV co-infected (15-49 years): 6.2

### TB laboratory network (8)

- National Reference Lab(s): PHLS Mycobacterium Reference Unit, London; Northern Ireland Reference Laboratory/MRV, Belfast; Scottish Mycobacteria Reference Laboratory, Edinburgh.

#### Smear laboratories

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<thead>
<tr>
<th>Category</th>
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<th>Per million</th>
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<tbody>
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| Culture laboratories

<table>
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<th>Category</th>
<th>Total</th>
<th>Per million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>273</td>
<td>4.6</td>
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</tbody>
</table>
| DST laboratories

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>Per million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5</td>
<td>0.08</td>
</tr>
</tbody>
</table>

### Health care system delivery (5)

**Public**

- National Health Service (NHS) provides free, universal comprehensive care. Financed by tax revenue, and managed by the Government's Department of Health, which in turn sets overall policy.
- Primary care groups (PCGs) purchase health care services for the population it serves.

**Private**

- Private insurance covers 12% of the population but applies to a limited range of treatments. It supplements NHS and it serves individuals who prefer to pay for certain elective services rather than to wait in the public system.
- There are approximately 300 private sector hospitals.

### Laboratory infrastructure (6)

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Estimated total no. of labs</td>
<td></td>
</tr>
<tr>
<td>Majority are affiliated with the NHS</td>
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</tbody>
</table>

**Accreditation bodies**

- United Kingdom Accreditation Service: http://www.ukas.com/
UNITED KINGDOM

Estimated in vitro diagnostics market (9)
- US$ 500-600 million
- Annual growth - 25% between 1996 -1998

Major markets (10)
- 85% of the UK population live in England. It is the commercial hub for the UK and accounts for the vast majority of medical devices procurement among the four economies. Exporters planning to sell directly to the NHS or NHS Trusts, as well as to private hospitals and clinics, would be well advised to use England as a primary market and springboard to the other UK markets. Around 12% of the population live in the capital, London. Other principal cities, with populations in excess of 500,000, include Birmingham, Leeds, Glasgow and Sheffield.

National regulatory policies for in vitro diagnostics (11)

Regulatory body/regulatory legislation
- European Union (EU) IVD directive
- UK competent authority: Medical and Health Products Regulatory Authority (MHRA)
  http://www.mhra.gov.uk
- All medical devices imported into and sold in the United Kingdom must conform to EU medical devices directives and display the Conformité Européene (CE) mark. The CE mark process for each class of IVD products can be found at www.us.tuv.com/product_testing/medical_devices/index.html
- The UK competent authority is the Medicines and Health care Products Regulatory Agency (MHRA). MHRA guidelines set out responsibilities for the purchase, deployment and maintenance of medical equipment and devices, both in hospitals and in the community.

Who registers the product?
- The IVD Directive requires all foreign manufacturers of diagnostic products to appoint an authorized representative in an EU nation in order to market a diagnostic product within the EU.

Is a detailed product dossier for performance required?

Classification of in vitro diagnostics
- Annex: Scheme 1.

Is local testing required to license the product?
- Yes, depending on IVD classification.

Are quality management systems/factory audits a required component of post-market entry?
- Yes. The national competent authorities have responsibility for monitoring the quality and reliability of diagnostic products at the post-market level.

- The MHRA is responsible for ensuring compliance with IVD regulatory requirements before product release, as well as for the post-marketing observation of such devices.

Movement towards regulatory harmonization
- Member of the Global Harmonization Task Force (through the EU).

Regulatory requirements for manufacturers/importers of TB-IVDs
- Low level of requirements for TB-IVDs that belong to Class “Annex III-other IVD”. Attachment of the CE-mark to the IVD is the manufacturers’ responsibility following self-declaration of conformity with the EC IVD Directive to the respective “competent authority”. They must prepare for an “intervention” inspection through health authorities including:
  i) evidence of an adequate quality management system - preferably ISO 13 485 - AND:
  ii) Technical documentation as proof for performance claims.
- Intervention inspections only occur in case of severe IVD failures on the market.

Import tariffs and other taxes (12)
- Both diagnostic instruments (HS Code 90181990000) and diagnostic reagents (HS Code 30063000) are duty-free.

Cost of registration (13)
- CE Mark registration costs range from US$ 5 000 to US$ 25 000 depending on the level of inspection required and the entire process.

Duration of registration process (14)
- Following application submission, average review time is 6-8 weeks.

Local manufacturing capacity (15)
- There is a long history of reputable IVD manufacturing. Furthermore, all of the major IVD companies have subsidiaries in the UK.

Local distribution (16)
- Before marketing a diagnostic product in the EU, the IVD directive orders that all foreign (non-EU) diagnostic products manufacturers appoint an authorized representative in an EU nation. Foreign companies without an EU subsidiary must either:
  i) cooperate with a local EU pharmaceutical manufacturer by licensing the foreign product/production know-how OR:
  ii) acquire an EU company.
Exporters of medical devices, equipment and supplies to the United Kingdom use a variety of methods to access the market, including engaging the services of an agent or distributor, marketing products through a procurement agency, and selling directly to the National Health Service (NHS) or private-sector hospitals and clinics.

There are around 50 medical device distributors currently operating in the UK. Many distributors specialize in certain types of medical device, although there are a number which distribute a wide range of products. Between them, most international medical device manufacturers are represented in the UK, many also distribute other companies’ products through the UK-based subsidiaries.

The NHS is the primary end-user of IVDs in the following settings: reference laboratories that conduct batteries of tests for physicians and hospitals; hospital operating rooms, emergency rooms, laboratories, near-patient, and patient bedside; physicians offices, and walk-in clinics.

The general public is the primary end-user of IVD’s in the following settings: pharmacies and supermarkets that offer in-store testing; individuals that purchase over-the-counter kits for self-testing.

**Procurement (17)**

The NHS and local authorities account for the vast majority of medical devices procurement in the United Kingdom. Local authorities tend to purchase supplies through their own purchasing departments or through a procurement agency such as the Office of Government Commerce (OGC), while the NHS procures goods mainly through the NHS Purchasing and Supply Agency, an executive agency of the Department of Health. [http://www.pasa.doh.gov.uk/suppliers/selling](http://www.pasa.doh.gov.uk/suppliers/selling)

The OCG produces a comprehensive catalogue featuring a wide range of products offered by more than 400 suppliers. There is also a growing number of private-sector supply agencies, which are gaining popularity in the UK health-care distribution market.

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**Industry associations**

- **British in vitro Diagnostics Association (BIVDA)** is the national trade association for companies with major involvement and interest in the in vitro Diagnostics (IVD) industry. BIVDA represents both manufacturers and distributors who are active in the UK. [www.bivda.co.uk](http://www.bivda.co.uk)

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**Intellectual property rights issues (19)**

| Year in which country joined World Trade Oranization (WTO) and is therefore under the TRIPS agreement | 1995 |
| Year in which the country must be in accordance with TRIPS | 1996 |

---

a “Other” includes smear-negative pulmonary TB and smear-unknown.
b Includes patients previously treated for tuberculosis and relapses.
c May include microbiological TB-IVD; IVD for detection of TB-antigen and TB-antibodies; nucleic acid based TB-IVDs.
References:

b. Global Harmonization Task Force Website: http://www.ghtf.org/
c. The Medical Devices Market in the United Kingdom, December 2002, Market Research Centre and the Canadian Trade Commissioner Service, Department of Foreign Affairs and International Trade, www.infoexport.gc.ca
10. a. Espicom Business Intelligence.
b. Industry Canada Website: http://www.episcom.com
12. a. US Department of Commerce, Office of Microelectronics, Medical Equipment and Instrumentation.
c. The Medical Devices Market in the United Kingdom, December 2002, Market Research Centre and the Canadian Trade Commissioner Service, Department of Foreign Affairs and International Trade, www.infoexport.gc.ca
UNITED STATES OF AMERICA

Population (1) 284 043 000 * GNI (2) US$ 11 trillion * GNI/capita (3) US$ 37 870
Constitution-based federal republic; strong democratic tradition
50 states * 1 district with dependent areas

**Health system capacity and expenditures (4)**

- % GDP spent on health care: 14.6
- Per capita total health expenditure (US$): 5 274
- No. of hospital beds/1000 population: 3
- No. of doctors/1000 population: 2.8

**Total health expenditures**

Government: 44.9%
Private: 55.1%

Private prepaid plans as % of private expenditure on health: 65.7

**Laboratory infrastructure (6)**

- Estimated total no. of labs: 17 400
  (5000 independent; 5100 hospital based; 7300 physician office based)

**Accreditation bodies**
- National Voluntary Laboratory Accreditation Program
- American Association for Laboratory Accreditation:
  http://www.a2la2.net/index.htm
- Clinical Laboratory Improvement Amendments:
  http://cms.hhs.gov/clia/

**TB epidemiology (7)**

| Total estimated new TB cases | 13 409 |
| Total notified new TB cases | 14 861 |
| - DOTS | 14 861 (100%) |
| - Non-DOTS | 0 (0%) |

Total gap between estimated and notified new TB cases: Not applicable

Notified new "other" TB cases (DOTS):
- 5 303 (99%)
- 0 (0%)
- 0 (0%)
- 0 (0%)
- 5 558 (100%)
- 7 475

Total notified re-treatment cases: Not reported

% Multidrug-resistance in new cases: 1.1
% Multidrug-resistance in re-treatment cases: 5.2

Estimated % adult TB cases that are HIV co-infected (15-49 years): 27
TB laboratory network (8)

- National Reference Lab(s): Centers for Disease Control and Prevention-CDC, Atlanta. (Multiple state and local laboratories following national standards.)

<table>
<thead>
<tr>
<th>Smear laboratories</th>
<th>Total</th>
<th>Per million</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2566</td>
<td>9</td>
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<table>
<thead>
<tr>
<th>Culture laboratories</th>
<th>Total</th>
<th>Per million</th>
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<tbody>
<tr>
<td></td>
<td>1000</td>
<td>3.4</td>
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<thead>
<tr>
<th>DST laboratories</th>
<th>Total</th>
<th>Per million</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>260</td>
<td>0.9</td>
</tr>
</tbody>
</table>

**Estimated in vitro diagnostics market (9)**

- USS 12 billion
- Annual growth: 7%

**Major markets (10)**

Most marketers divide the country into the following regions (in order of importance):

- East North: Central Illinois, Indiana, Michigan, Ohio, Wisconsin.
- South Atlantic: Florida, Delaware, District of Columbia, Georgia, Maryland, N. Carolina, S. Carolina, Virginia, W. Virginia.
- West North Central: Iowa, Kansas, Minnesota, Missouri, Nebraska, N. Dakota, S. Dakota.
- West South Central: Texas Arkansas, Louisiana, Oklahoma.
- East South Central: Alabama, Kentucky, Mississippi, Tennessee.

**National regulatory policies for in vitro diagnostics (11)**

**Regulatory body/regulatory legislation**

- Under the Federal Food, Drug and Cosmetic Act, all medical devices that are marketed in the United States must comply with US Food and Drug Administration (FDA) regulations. The Office of In Vitro Diagnostic Device Evaluation and Safety consolidates all FDA regulatory activities for IVDs. 
  [http://www.fda.gov/cdrh/oivd/regulatory-overview.html](http://www.fda.gov/cdrh/oivd/regulatory-overview.html)
- Applications for FDA market clearance take two forms: Pre-market Notification - 510K and Pre-market Approval.
  - 510K clearance is used for tests and devices that are based on an existing technology and for a test that is already available (predicate products) 
  - Pre-market Approval (PMA, [www.fda.gov/cdrh/devadvice/pma/](http://www.fda.gov/cdrh/devadvice/pma/)) is applied to new tests, instruments and technologies.
- New tests can be cleared via the de novo process which is a relatively new provision of the Food, Drug and Cosmetic Act that allows new, unique, and low-risk medical devices to be evaluated under 510(k) procedures. 
  [www.amdm.org/AMDM/051502-DeNovo.html](http://www.amdm.org/AMDM/051502-DeNovo.html)
- Applications for FDA market clearance take two forms: Pre-market Notification - 510K and Pre-market Approval.
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  [www.amdm.org/AMDM/051502-DeNovo.html](http://www.amdm.org/AMDM/051502-DeNovo.html)
- The FDA also maintains an active complaints procedure and announces product recalls on the Internet.
- Initial importers are also subject to Medical Device Reporting Procedures (MDR) ([www.fda.gov/cdrh/devadvice/351.html](http://www.fda.gov/cdrh/devadvice/351.html)). Under these regulations, importers are required to report incidents in which a device may have caused or contributed to a death or serious injury as well as report certain malfunctions.

**Who registers the product?**

- The manufacturer.

**Is a detailed product dossier for performance required?**

- Yes, depending on IVD classification.

**Classification of in vitro diagnostics**


**Is local testing required to license the product?**

- Yes, depending on IVD classification.

**Are quality management systems/factory audits a required component of post-market entry?**

- Yes, including: Enforcement action responses and/or corrective action plans, FDA-mandated Annual Certification Audits Recall strategies.
  i) Enforcement action responses and/or corrective plans
  ii) FDA-mandated Annual Certification Audits
  iii) Recall strategies.
- The FDA also maintains an active complaints procedure and announces product recalls on the Internet.
- Initial importers are also subject to Medical Device Reporting Procedures (MDR) ([www.fda.gov/cdrh/devadvice/351.html](http://www.fda.gov/cdrh/devadvice/351.html)). Under these regulations, importers are required to report incidents in which a device may have caused or contributed to a death or serious injury as well as report certain malfunctions.
The importers must maintain an MDR event file for each adverse event. All product complaints (MDR and non-MDR events) must be forwarded to the manufacturer.

- Under Medical Device Tracking requirements, certain devices must be tracked through the distribution chain.

**Movement towards regulatory harmonization**
- Member of the Global Harmonization Task Force.

**Regulatory requirements for manufacturers/ importers of TB-IVDs**
- Low level of requirements for microbiological IVD and IVD for TB-antigens and TB-antibodies (510k); highest level of requirements for nucleic acid-IVD (pre-market approval).

**Import tariffs and other taxes**
- All medical devices that are imported into the United States must meet Bureau of Customs and Border Protection (CBP) requirements in addition to FDA market clearance. The USITC Interactive Tariff and Trade DataWeb provides US tariff data. [http://dataweb.usitc.gov/](http://dataweb.usitc.gov/)

**Cost of registration**
- The review fees for 510(k) submissions are:
  - Small business fee: US$ 2 802
- FY 2005 device review user fees are:
  - Pre-market application (PMA, PDP, BLA): Standard fee: US$ 239 237
  - Small business fee: first application: fee waived; otherwise: US$ 90 910

**Duration of registration process**
- Average review time for 510K is 100 to 150 days and for a pre-market approval it is 1-2 years.

**Local manufacturing capacity**
- 80% of the major IVD manufacturers are based in the USA, including 9 of the top 15 companies.

**Local distribution**
- Foreign manufacturers should either form an alliance with an established US manufacturer with its own established sales force, or appoint a US agent to handle their marketing activities. In vitro diagnostics are traditionally handled by representatives or distributors in the US marketplace (www.hira.org; www.hida.org; www.imda.org; http://www.manaonline.org).
- Sales representatives and agents tend to demand a high commission, especially for new products or for products entering particular regions for the first time. Commission (for familiar products) is typically about 20% of profits. For sales to distributors (which are likely to be at a lower price than sales to actual users), the representative takes a commission rate of about 15%.

- Success in the market depends on convincing reimbursers (HMOs, private health insurance and Departments of Health and Human Services, of Justice, of Veteran Affairs or Federal Emergency Management Agency) to adopt the product for insurance coverage.

**Procurement**
- The US is a free market system, whereby reference laboratories, hospitals, government agencies, hospital buying groups establish preferential association with manufacturers for IVD products. This applies primarily to routine lab instruments and reagents for clinical chemistry, hematology, and microbiology.
- These may also be purchased via a tendering system. Each buying group establishes its own procedures. However, before a product can enter this free market, the challenge of reimbursement from the federal Medicare and Medicaid system and private payer groups such as health maintenance organizations (HMOs) and insurance groups must be overcome.
- For background information on the reimbursement environment in the US, visit the website of the American Association of Health Plans, www.aahp.org.
- In summary, the American Medical Association establishes the CPT and ICD coding structure applied by the US Centers for Medicare and Medicaid Services (CMS), to reimbursement requests for all Medicare and Medicaid patients. The CPT/ICD information is critical for reimbursement.
- Laboratory test systems, assays, and examinations must also have the Clinical Laboratory Improvement Amendments assessment in which they are assigned a category based on complexity as either “high,” “moderate” or “waived.” High and moderate classified tests can be performed only in labs that have been given a licence to perform more sophisticated tests.

**Intellectual property rights issues**
- Year in which country joined World Trade Organization (WTO) and is therefore under the TRIPS agreement: 1995
- Year in which the country must be in accordance with TRIPS: 1996
Industry associations

- The Medical Device Manufacturers Association (MDMA)
  www.medicaldevices.org/public

- Advanced Medical Technology Association (AdvaMed)
  www.AdvaMed.org

- American Association for Clinical Chemistry (AACC)
  www.aacc.org

- American Society for Microbiology (ASM)
  www.asm.org

References:

5. a. Karen’s data set and “Global Health care Markets.”
10. a. Department of Foreign Affairs & International Trade, Canada.
11. Department of Foreign Affairs & International Trade, Canada.
   b. Department of Foreign Affairs & International Trade, Canada.
   b. Global Harmonization Task Force Website: http://www.ghtf.org/
   c. Global Harmonization Task Force Website: http://www.ghtf.org/
TB diagnostics terms

**AFB**
Acid-fast bacilli.

**Anergic**
Lacking the normal immune response to a particular antigen or allergen.

**Antibodies**
Serum proteins formed in response to immunization and which are generally defined in terms of their specific binding to the immunizing antigen.

**Antigen**
Any foreign material that is bound by specific antibody or specific lymphocytes, also used loosely to describe materials used for immunization. Antigens may also be immunogens if they are able to trigger an immune response, or haptons if not.

**Bacillus (pl. bacilli)**
A straight rod-shaped bacterium.

**BCG**
Bacille Calmette-Guérin – an attenuated strain of *Mycobacterium bovis* used in the preparation of BCG vaccine that is used for immunization against tuberculosis and in cancer chemotherapy.

**Case detection**
A method of diagnostic testing that refers to finding active tuberculosis cases.

**Cell-mediated immune response**
A T cell-mediated reaction to antigen, which takes 24-48 hours to develop fully, and which involves release of lymphokines and recruitment of monocytes and macrophages.

**Culture**
Organisms grown on a medium so that they can be identified. A culture that is positive for *M. tuberculosis* contains tubercle bacilli, whereas a culture that is negative contains no detectable tubercle bacilli.

**Culture medium**
A liquid or solid nutrient preparation that permits the growth, in vitro, of microorganisms from clinical specimens.

**Cytokine**
Any of several regulatory proteins that are released by white blood cells and act as intercellular mediators in the generation of an immune response.

**DALYs**
Disability-adjusted life years

**DEC**
Disease-endemic country

**DNA fingerprinting**
A technique used to distinguish strains of bacteria or viruses. It involves enzymatic digestion of bacterial DNA and then separation of DNA fragments by gel electrophoresis.

**DOTS (directly observed therapy short-course)**
The WHO strategy for TB control which combines appropriate diagnosis of TB and registration of each patient detected, followed by standardized multidrug treatment with a secure supply of high quality anti-TB drugs for all patients undergoing treatment, individual patient outcome evaluation to ensure cure, and cohort evaluation to monitor overall programme performance.

**DOTS-Plus**
is a comprehensive management strategy under development and testing that includes the five tenets of the DOTS strategy. DOTS-Plus takes into account specific issues (such as the use of second-line anti-TB drugs) that need to be addressed in areas where there is high prevalence of MDR-TB. Thus, DOTS-Plus works as a supplement to the standard DOTS strategy.

**Drug-susceptibility testing**
Methods used to determine which drugs a strain of tubercle bacillus is susceptible to and which it is resistant to.

**ELISA (enzyme-linked immunosorbent assay)**
An assay (quantitative in vitro test) in which an enzyme is linked to an antibody and a coloured substrate is used to measure the activity of bound enzyme and, hence, the amount of bound antibody.

**Enhanced culture techniques**
Methods that do not use radioactive substances to indicate mycobacterial growth. Examples include:
- ESP II Culture System (Trek Diagnostics)
- MB/BacT (bioMérieux)
- MBRedox® (Heipha Diagnostika GmbH, subsidiary of Biotest Diagnostics Corp.)
- MGIT (mycobacterial growth indicator tube) - Middlebrook 7H9 broth and silicone sensor embedded in bottom of tube that turns fluorescent orange in the presence of mycobacterial growth
- TK MEDIA (SALUBRIS, Inc.)
Fluorescence microscopy
A technique for the detection of mycobacteria that uses illumination from either a quartz-halogen lamp or a high-pressure mercury vapour lamp. The advantage of fluorescence microscopy is that a low magnification objective is used to scan smears, allowing a much larger area of the smear to be seen and resulting in more rapid examination.

Haemoptysis
Expectoration of blood or of blood-stained sputum from the bronchi, larynx, trachea, or lungs.

HBC
High-burden country.

HIV
Human immunodeficiency virus.

Hypersensitivity
Altered reactivity to an antigen, which can result in pathologic reactions upon subsequent exposure to that particular antigen.

Immunocompetence
The capacity for a normal immune response.

Incidence
The frequency of new occurrences of disease within a defined time interval. Incidence rate is the number of new cases of a specified disease divided by the number of people in a population over a specified period of time, usually one year.

IVD
In vitro diagnostics.

Latent tuberculosis infection (LTBI)
(sometimes known as “dormant” tuberculosis)
A state in which viable mycobacteria present in the body do not cause active disease but have the potential to reactivate and cause disease. The latent focus may be the result of tuberculosis infection which has not progressed to cause disease, or of old tuberculosis disease that is not currently active, e.g. calcified nodes on chest X-ray. An adequate course of chemoprophylaxis (or anti-tuberculosis treatment) is believed to effectively prevent a latent focus from reactivating in most patients for at least 20 years.

Mantoux test
See Tuberculin skin test.

M. tuberculosis complex
Consists of 4 mycobacterial species with such high genetic relatedness, that they are referred to as a ‘complex’ - M. tuberculosis, M. bovis, M. africanum and M. microti. With the exception of M. tuberculosis, the species rarely cause human disease.

Multidrug-resistant tuberculosis (MDR-TB)
TB that is resistant to isoniazid and rifampin; more difficult to treat than drug-susceptible TB.

Mycobacterium tuberculosis TB (MTB)
An infection, most commonly affecting the lungs, caused by the bacterium M. tuberculosis and transmitted from person to person by an aerosol of organisms suspended in tiny droplets that are inhaled. The immune defences of healthy people usually prevent TB infection from spreading beyond a very small area of the lungs. If the body’s immune system is impaired because of infection with HIV, ageing, malnutrition, or other factors, the TB bacterium may begin to spread more widely in the lungs or to other tissues, such as the larynx, lymph nodes, brain, kidneys, or bones (extrapulmonary TB).

Negative predictive value
The probability that a person with a negative test is a true negative (i.e. does not have the disease).

Nucleic acid or molecular amplification
A method for amplifying DNA or RNA that facilitates rapid detection of microorganisms.

Passive case finding
Detection of individuals with the disease of interest upon self-presentation to health facilities.

Peritoneum
The lining of the abdominal cavity.

Phage
A virus for which the natural host is a bacterial cell.

Pleural space
The small potential space between the parietal and visceral layers of the pleura.

Polymerase chain reaction (PCR)
A type of nucleic acid amplification test.

Positive predictive value
The probability that a person with a positive test is a true positive (i.e. does have the disease).

PPD
Purified protein derivative: a mixture of proteins from heat-killed M. tuberculosis, injected intradermally to
test for TB infection. See Tuberculin skin test.

**Prevalence**
The ratio (for a given time period) of the number of occurrences of a disease or event to the number of units at risk in the population.

**Sensitivity**
The ability of a diagnostic test to detect disease when it is present, measured as the proportion of diseased individuals whose test results are positive (true positives divided by false negatives plus true positives).

**Serological test**
A blood test that detects the presence of antibodies to a particular antigen.

**Smear microscopy**
A thin tissue or blood sample spread on a glass slide for examination under a microscope. If a person is "smear-positive", this means the laboratory has found some TB bacteria on the smear. The test was first developed in 1882–83.

**Specificity**
The ability of a diagnostic test to rule out disease when it is not present, measured as the proportion of normal individuals whose test results are negative (true negatives divided by true negatives plus false positives).

**Tuberculin skin test**
A method of testing for TB infection, carried out by using a needle and syringe to inject liquid tuberculin (PPD-S; PPD RT/23) between the layers of the skin (intradermally), usually on the forearm. The reaction to this test, usually a small swollen area (induration), is measured 48 to 72 hours after the injection and is classified as positive or negative depending on the size of the reaction and the patient's risk factors for TB.

**TK MEDIA**
See Enhanced culture techniques.

**Virulence**
The relative capacity of a pathogen to overcome body defences.
CHAPTER 3


* Diagnostics for tuberculosis: global demand and market potential *
CHAPTER 4


7 Gift TL et al. The rapid test paradox: when fewer cases detected lead to more cases treated: a decision analysis of tests for Chlamydia trachomatis. Sexually Transmitted Diseases 1999, 26:232–240.


17 Plotkin SA. Why certain vaccines have been delayed or not developed at all. Health Affairs, 2005, 24:631–634.


CHAPTER 5


6 Miles M, Feulner EJ, O’Grady MA. 2005 I


Diagnostics for tuberculosis: global demand and market potential


ANNEX

Regulation of in vitro diagnostics: a global perspective

The Special Programme for Research and Training in Tropical Diseases (TDR) sponsored by UNICEF, UNDP, World Bank and the World Health Organization, completed a global survey of diagnostics regulation in 2001, sending questionnaires to all 191 of the WHO’s Member States and obtaining responses from just over half. The results presented herein showed great variability in the type and rigour of regulation, with the majority of poorer countries not regulating the sale of diagnostic devices at all. By extension, an in-depth review of published documents on in vitro diagnostics (IVD) regulatory policies and other market entry issues, was carried out in fourteen countries. The countries were selected on the basis of their geographic setting, economic status, IVD market size and burden of tuberculosis. The reviews were complemented by input from several credible diagnostic company representatives with ground experience in the respective countries. Our hope is that an improved understanding of the regulations surrounding IVD registration, procurement and distribution in various countries will assist tuberculosis diagnostic test developers and marketers.

The following tables and graphics summarize the results of the Global survey of the regulation of medical devices and outline how IVDs are defined, classified and registered in major TB diagnostic test markets. The 14 country reviews will be published, in a series, in the near future, but key regulatory requirements, post-market entry requirements, procurement and distribution are highlighted in the “Country Profiles” section of this document and in the on-line database of the United States Department of Commerce (http://www.ita.doc.gov/td/mdequip/regulations.html).

Ultimately, the lack of regulatory oversight in many countries underscores the need for a regulatory harmonization process to streamline and standardize regulation of in vitro diagnostics for infectious diseases. The Global Harmonization Task Force has published and disseminated harmonized guidance documents for basic regulatory practices for medical devices, including a proposed harmonized scheme for medical device classification. WHO/TDR, in cooperation with WHO’s Health Technology and Pharmaceuticals Department, is developing a technical framework for its own regulatory-quality diagnostics evaluation system and has entered into discussions with regulators from advanced developing countries on strengthening their own capacity.

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1 Australia, Brazil, Canada, China, France, Germany, India, Indonesia, Japan, Russian Federation, South Africa, Uganda, United Kingdom, USA
2 Jean-Francois de Lavison (International Affairs, bioMérieux); Michael Towns (VP Medical Affairs, BD Diagnostic Systems); Roseann Gartner (International Regulatory Affairs Manager BD Diagnostic Systems); Carolyn Jones (Associate VP Technology and Regulatory Affairs, AdvaMed); Thomas Silier (President & CEO, SALUBRIS, Inc.); Neil Mehta (President & CEO, Premier Medical Corporation).
3 Founded in 1993 by the Governments and industry representatives of Australia, Canada, the European Union, Japan and the USA to harmonize national standards in order to minimize regulatory barriers, facilitate trade and improve access to new technologies.
4 See www.GHTF.org document SG1/N015R18
Global Survey of the Regulation of Medical Devices, 2001

The survey comprised the following questions:

1. Are medical devices regulated in your country?
2. If so, what is the name and address of the agency (government, other public institution, or professional association or industry) in your country specifically charged with regulating medical devices?
3. Are in vitro diagnostic devices for infectious diseases (e.g. HIV serology, dipstick diagnostic tests for malaria, hepatitis serology) also regulated? If no, go to question 16.
4. If yes, note the name and address of the person or group responsible if different from above.
5. Does a list of approved devices exist? If yes, please provide on a separate sheet.
6. Does regulation of in vitro diagnostic devices for infectious diseases include the performance of laboratory or clinical evaluations by the government or one of its contractors?
7. If so, which diagnostics?
8. If in vitro diagnostic devices are regulated, how is this regulation enforced?
9. How is the regulation of in vitro diagnostics financed?
10. Is financial sustainability a problem?
11. Is there a legal provision for the collection of fees?
12. Are fees collected?
13. Is there sufficient physical infrastructure (laboratory facilities and equipment, transportation, materials) to carry out this work?
14. Is there sufficient administrative and technical infrastructure (clearly written guidelines, assigned responsibilities, local technical expertise, standardized reagents, defined laboratory procedures) to carry out this work?
15. What are the main constraints?
16. Does the government purchase any infectious diseases diagnostic tests for national control programmes (including blood safety)?
17. If so, which?
18. Are infectious diseases diagnostics (e.g. HIV, TB, STDs, hepatitis, etc) in common use in the private sector?
19. Is the misuse or sale of unregulated diagnostics a problem in your country?
20. If yes, is this problem recognised by the ministry of health?
Results are summarized in the following tables and graphics:

**Q1: Are medical devices regulated?**

<table>
<thead>
<tr>
<th>Region</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFRO</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>AMRO</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>EMRO</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>EURO</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>SEARO</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>WPRO</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>

**Q3: Are in vitro diagnostic devices for infectious diseases regulated?**

<table>
<thead>
<tr>
<th>Region</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFRO</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>AMRO</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>EMRO</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>EURO</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>SEARO</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>WPRO</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>

**Q6: Does regulation include clinical evaluation?**

<table>
<thead>
<tr>
<th>Regulation includes clinical evaluation</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO answer</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>68%</td>
<td></td>
</tr>
</tbody>
</table>

**Q8: How is the regulation enforced?**

<table>
<thead>
<tr>
<th>Regulation enforcement</th>
<th>Persuasion</th>
<th>Punishment fine</th>
<th>Warnings</th>
<th>Sanctions</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO answer</td>
<td>18%</td>
<td>18%</td>
<td>15%</td>
<td>18%</td>
</tr>
</tbody>
</table>

5 http://www.who.int/about/regions/en/index.html
Q9: How is the regulation financed?

- Regulation free of industry: 30%
- Government funded: 70%

Q11: Legal provision?

- NO: 11%
- YES: 23%

Q12: Are fees collected?

- NO: 13%
- YES: 20%

Q13: Is physical infrastructure sufficient?

- NO: 14%
- YES: 23%

Q14: Is administrative and technical infrastructure sufficient?

- NO: 10%
- YES: 26%

Q15: Main constraints

- Financial: 17%
- Human resources (expertise): 23%
- Physical resources (equipment, specimens, etc.): 30%
- Regulation (procedure): 30%

Q16: Does government purchase infectious diseases diagnostic tests?

- NO: 17%
- YES: 66%
- NO answer: 2%

Q18: Are infectious diseases diagnostics in common use in private sector

- NO: 38%
- YES: 57%
- NO answer: 5%

Q19: Is misuse of unregulated diagnostics a problem?

- Yes, but recognized: 31%
- No answer: 7%
- Yes, but NOT recognized: 5%
- No problem: 57%

Q20: If yes is the problem recognized?

- Yes, but recognized: 31%
- No answer: 7%
- Yes, but NOT recognized: 5%
- No problem: 57%
Definition of in vitro diagnostics
IVDs are broadly defined as devices that analyse human body specimens in order to provide information for the diagnosis, prevention, or treatment of a disease.

Classification
Between countries, IVDs differ in their legal classification within the set of medical products:

<table>
<thead>
<tr>
<th>Classification of in vitro diagnostic</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical diagnostics</td>
<td>Canada</td>
</tr>
<tr>
<td>Medical devices</td>
<td>Australia, Brazil, China, Indonesia, Russian Federation, USA</td>
</tr>
<tr>
<td>Pharmaceuticals</td>
<td>Japan, China, India</td>
</tr>
<tr>
<td>In vitro diagnostic medical devices</td>
<td>European Union</td>
</tr>
<tr>
<td>NA</td>
<td>South Africa, Uganda</td>
</tr>
</tbody>
</table>

In many, but not all, countries, IVDs are subclassified according to rule-based or risk-based criteria. This in turn impacts on regulatory and registration procedures.
### European Union Member States

<table>
<thead>
<tr>
<th>Scheme number</th>
<th>Method for classifying in vitro diagnostics</th>
<th>Conformity assessment route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Annex IIa IVD</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Group</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV 1</td>
<td>Notified body approves design dossier and ISO 9001 quality system (Annex IV&lt;sup&gt;a&lt;/sup&gt;), and can impose batch-release controls. OR: Notified body approves registration file (Annex V&lt;sup&gt;a&lt;/sup&gt;) and ISO 9002 quality system (Annex VII&lt;sup&gt;a&lt;/sup&gt;), and can impose batch-release controls. From 31 July 2006 only ISO 13 485:2003-11</td>
</tr>
<tr>
<td></td>
<td>HIV 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HTLV I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HTLV II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatitis B,C,D</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blood typing products</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>IVD products</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Irregular antierythrocytic antibodies</td>
<td>Notified body certifies ISO 9001 quality system (Annex IV&lt;sup&gt;a&lt;/sup&gt;). From 31 July 2006 only ISO 13 485:2003-11 OR: Notified body approves registration file (Annex V&lt;sup&gt;a&lt;/sup&gt;) and provides EC verification (Annex VI&lt;sup&gt;a&lt;/sup&gt;) OR: Notified body approves registration file (Annex V&lt;sup&gt;a&lt;/sup&gt;) and certifies ISO9001 quality system (Annex VII&lt;sup&gt;a&lt;/sup&gt;). From 31 July 2006 only ISO 13 485:2003-11</td>
</tr>
<tr>
<td></td>
<td>Rubella</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Toxoplasmosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlamydia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phenylketonuria</td>
<td></td>
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<td></td>
<td>HLA tissue groups</td>
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<td></td>
<td>Prostate-specific antigen</td>
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<td></td>
<td>Self-tests for blood glucose</td>
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<td></td>
<td>Anti-Kidd</td>
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<td></td>
<td>Evaluation of risk of trisomy 21</td>
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<tr>
<td></td>
<td><strong>Annex IIb IVD</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td><strong>Group</strong></td>
<td></td>
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<tr>
<td></td>
<td>All self-testing products (for use in a home environment) except blood glucose monitors</td>
<td>Notified body approves design dossier (Annex III.6&lt;sup&gt;a&lt;/sup&gt;) OR: Any of the conformity assessment procedures for products of Annex IIa&lt;sup&gt;a&lt;/sup&gt; and Annex IIb&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td><strong>Annex III</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Manufacturer submits EC declaration of conformity with technical documentation (Annex III&lt;sup&gt;a&lt;/sup&gt;) (no Notified body required)</td>
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<td><strong>Annex III</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
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<td><strong>Group</strong></td>
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<td><strong>IVD products</strong></td>
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<td></td>
<td><strong>Annex III</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td><strong>Annex III</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
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</tbody>
</table>

### India

<table>
<thead>
<tr>
<th>Group</th>
<th>IVD products</th>
<th>Conformity assessment route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical</td>
<td>HIV, HBsAg, HCV &amp; blood grouping reagents</td>
<td>Form-40, Form 9, registration of the manufacturing site, a registration certificate and a product dossier and testing by National Institute of Biologicals (NIB) in India.</td>
</tr>
<tr>
<td>Non-critical</td>
<td>all other kits</td>
<td>Import Licence - Form 10</td>
</tr>
</tbody>
</table>

### Canada

<table>
<thead>
<tr>
<th>Class</th>
<th>IVD products</th>
<th>Conformity assessment Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Microbiological media used to identify or infer the identity of i) a microorganism OR: ii) a cultured microorganism</td>
<td>Do not require a licence, but still are subject to the safety and effectiveness requirements of the regulations</td>
</tr>
<tr>
<td>II</td>
<td>IVD that is intended to be used to detect the presence of, or exposure to, a transmissible agent or for patient management</td>
<td>Must obtain a device license which requires basic information. Must be registered to at least ISO13488:1996 by a Canadian Medical Devices Conformity Assessment System (CMDCAS)-accredited registrar</td>
</tr>
<tr>
<td>III</td>
<td>Near-patient IVD: a device that is intended for use outside a laboratory, for testing at home or at the point of care, such as a pharmacy, a health care professional’s office or the bedside; also, see group II</td>
<td>Must obtain a device licence. The application requires product history (including design philosophy, marketing history, marketing and compliance records); risk assessment, preclinical and clinical data, supporting safety and effectiveness; and chemistry, manufacturing, quality systems information and labelling. Must be registered to ISO 13485:1996 by a CMDCAS-accredited registrar</td>
</tr>
</tbody>
</table>

b Unless (i) the transmissible agent causes a life-threatening disease and there is a risk or propagation, then classify as Class IV OR (ii) the IVD detects “serious” disease, STDs, infectious agents found in CSF or blood or there exists the risk that mistaken test result would cause disability/death of patient or patient’s offspring, then classify as Class III.

c Unless intended to be used for the management of patients suffering from life-threatening diseases or there exists the risk that an erroneous result will lead to a patient management decision resulting in an imminent life-threatening situation for the patient, then classify as Class III.
<table>
<thead>
<tr>
<th>Scheme number</th>
<th>Method for classifying in vitro diagnostics</th>
<th>Australia</th>
<th>Conformity assessment for commercial IVDs</th>
<th>China</th>
<th>Indonesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>“Listing”: (i) Administration, formula/specification; (ii) Specification of raw materials; (iii) Laboratory test result, if needed; (iv) Labelling.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>“Pre-market approval” – Class I requirements, plus (i) Special testing of effectiveness, specificity and sensitivity for diagnostic products; (ii) QA test for electro medical devices; (iii) Laboratory test results, as required; (iv) Labelling.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>“Pre-market evaluation” – Class II requirements, plus (i) Laboratory test results from notified lab for crucial requirements; (ii) Study on the safety, quality and efficacy of the product.</td>
</tr>
<tr>
<td>1</td>
<td>No public health risk/low personal risk</td>
<td>Manufacturers will be required to notify the range of IVDs manufactured and to self-declare that their manufacture complies with the essential principles.</td>
<td>Class 1: Safety and effectiveness can be ensured through routine administration. Registration with State Drug Administration (SDA) with submission of the following documentation: 1. Qualification certificate of the medical device (MD) producer 2. Declaration of conformity 3. Quality standard/assurance certificate 4. Letter of authenticity 5. Qualification certificate of the applicant 6. Certificate issued by the country (region) of origin that approved or permitted such MD product to enter the market of that country (region) 7. Technical specifications of the MD product that applies for registration and corresponding means of test 8. Instruction manual of the product 9. Catalog/UPN number 10. Model designations 11. Component/raw material/vendor specifications 12. Final functional procedure and data 13. Labels 14. Manufacturing flow chart or manufacturing procedure 15. Product description/indication for use 16. A type test report on the MD issued within one year by the MD quality testing institutions certified by the SDA (Classes 2 and 3 only) 17. Clinical trial reports from more than two clinical trial bases. The clinical trials shall be conducted in compliance with the Provisions on Clinical Trials for MD Products. Only products that have not been approved by the originating country need local clinical trials; otherwise, the clinical trial report from the originating country is acceptable 18. A statement of guarantee on quality of the product issued by the producer who must make a commitment in such a statement that the product to be registered and sold in China will have the same quality as the same product sold in the country (region) of origin; 19. A letter of authorization which designates after-sale service agencies in China, a letter of commitment and the business licence of such entrusted agencies 20. A statement of guarantee on the authenticity of the materials submitted. The above-mentioned documents must be submitted in a Chinese language version.</td>
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<td></td>
<td>Class 1: Minimal potential for harm to the user</td>
</tr>
<tr>
<td>2</td>
<td>Low public health risk/moderate public health risk</td>
<td>Manufacturers will be required to make a pre-market application to the Therapeutic Goods Administration (TGA) and include evidence that the IVD design supports the use of the IVD in the way proposed by the manufacturer. Manufacturers will be required to have quality systems in place and have their systems certified by the TGA, unless other acceptable certification is in place.</td>
<td>Class 2: Further control is required to ensure their safety and effectiveness</td>
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<td></td>
<td></td>
<td>“Listing”: (i) Administration, formula/specification; (ii) Specification of raw materials; (iii) Laboratory test result, if needed; (iv) Labelling.</td>
</tr>
<tr>
<td>3</td>
<td>High personal risk/moderate personal health risk</td>
<td>The TGA will perform an assessment that all the documentation is present and appears to have been assembled with sufficient rigour, but will not normally evaluate the material in depth. However, the TGA would retain the right to question any deficiencies or discrepancies noted. Manufacturers will be required to have quality systems in place and have their systems certified by the TGA, unless other acceptable certification is in place.</td>
<td>Class 3: Implanted into the human body, or used for life support or sustenance, or pose potential risk to the human body and thus must be strictly controlled with respect to safety and effectiveness</td>
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</tr>
<tr>
<td>4</td>
<td>High public health risk</td>
<td>Full pre-market evaluation by the TGA requiring the manufacturer to submit a detailed application relating to the design and manufacture of the IVD. Manufacturers will be required to meet manufacturing standards and have their quality systems certified by the TGA, unless other acceptable certification is in place.</td>
<td>Class 4: High risk</td>
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</tbody>
</table>

Medical devices (MDs) are subclassified into Classes 1, 2 and 3. MDs classified as medical devices are Class 2.
### Scheme number

<table>
<thead>
<tr>
<th>Class</th>
<th>Japan</th>
<th>Japan approval process</th>
<th>United States</th>
<th>Device requirements by class (<a href="http://www.fda.gov">www.fda.gov</a>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>General medical device – extremely low risk</td>
<td>Pre-distribution notification and approval for marketing authorization not required</td>
<td>Application form requirements: product name, generic name, intended use, material, product specifications, usage method; manufacturing and QC data, storage conditions, plus Summary Technical Documentation (STED) and data subsets. STED: Development history; overseas usage; manufacture and QC data; safety data; stability; performance risk analysis; clinical data reliability review; site inspection and document review (ISO13485); post-approval inspection</td>
<td>Device classification for in vitro diagnostics can be found at <a href="http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCdr/CfRSearch.cfm?CFRPart=866">http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCdr/CfRSearch.cfm?CFRPart=866</a></td>
</tr>
<tr>
<td>2</td>
<td>Controlled medical device – low risk</td>
<td>Pre-distribution notification is required. Third party certification system will be introduced</td>
<td>General controls alone are insufficient to ensure safety and effectiveness, and existing methods are available to provide such assurances.</td>
<td>Pre-market notification: may include special labelling requirements, mandatory performance standards and post-market surveillance. Not all Class II devices require pre-market notification.</td>
</tr>
<tr>
<td>3</td>
<td>Specially controlled device – middle and high risk</td>
<td>A licence system for distribution is being introduced. Minister’s approval for marketing authorization is required for high-risk devices i.e. all TB diagnostics.</td>
<td>Insufficient information exists to ensure safety and effectiveness solely through general or special controls. Usually those that support or sustain human life are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.</td>
<td>Pre-market approval: Scientific review process to ensure the safety and effectiveness of Class III device. All clinical evaluations of investigational devices, unless exempt, must have an approved Investigational Device Exemption (IDE) before the study is initiated. In vitro diagnostic devices are exempt from the IDE requirements provided they meet the following requirements: 1. the testing is non-invasive 2. does not require invasive sampling 3. does not introduce energy into a subject AND: 4. is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic device or procedure (21 CFR 812.2(c)(3)).</td>
</tr>
<tr>
<td>Scheme number</td>
<td>Method for classifying in vitro Diagnostics</td>
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</table>
| 5 Brazil      | Group A: disposables and accessories (low risk - equivalent to Class I in Brazil Medical Device Classification Scheme)  
Group B: IVD for non-infectious diseases (medium risk - equivalent to Class II in Brazil Medical Devices Classification Scheme)  
Group C: IVD for infectious diseases - excluding Group D (high risk - equivalent to Class III in Brazil Medical Device Classification Scheme)  
Group D: IVD for blood transfusion, STD & blood group identification |
| 6 Russian Federation | No standardized subclassification of IVDs |
| 7 Uganda, South Africa | No formalized regulatory procedures  
See 'Country Profiles' for more information regarding product approval. |
Global demand and market potential