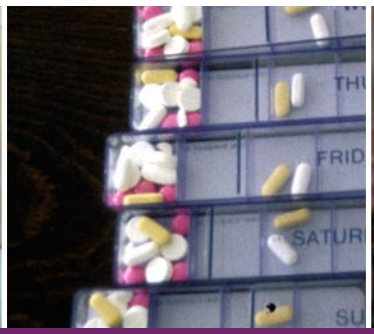
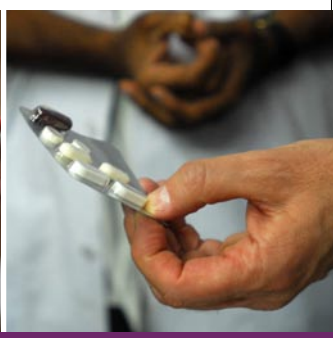
Pathway to Patients

Charting the Dynamics of the Global TB Drug Market

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

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1. Preface

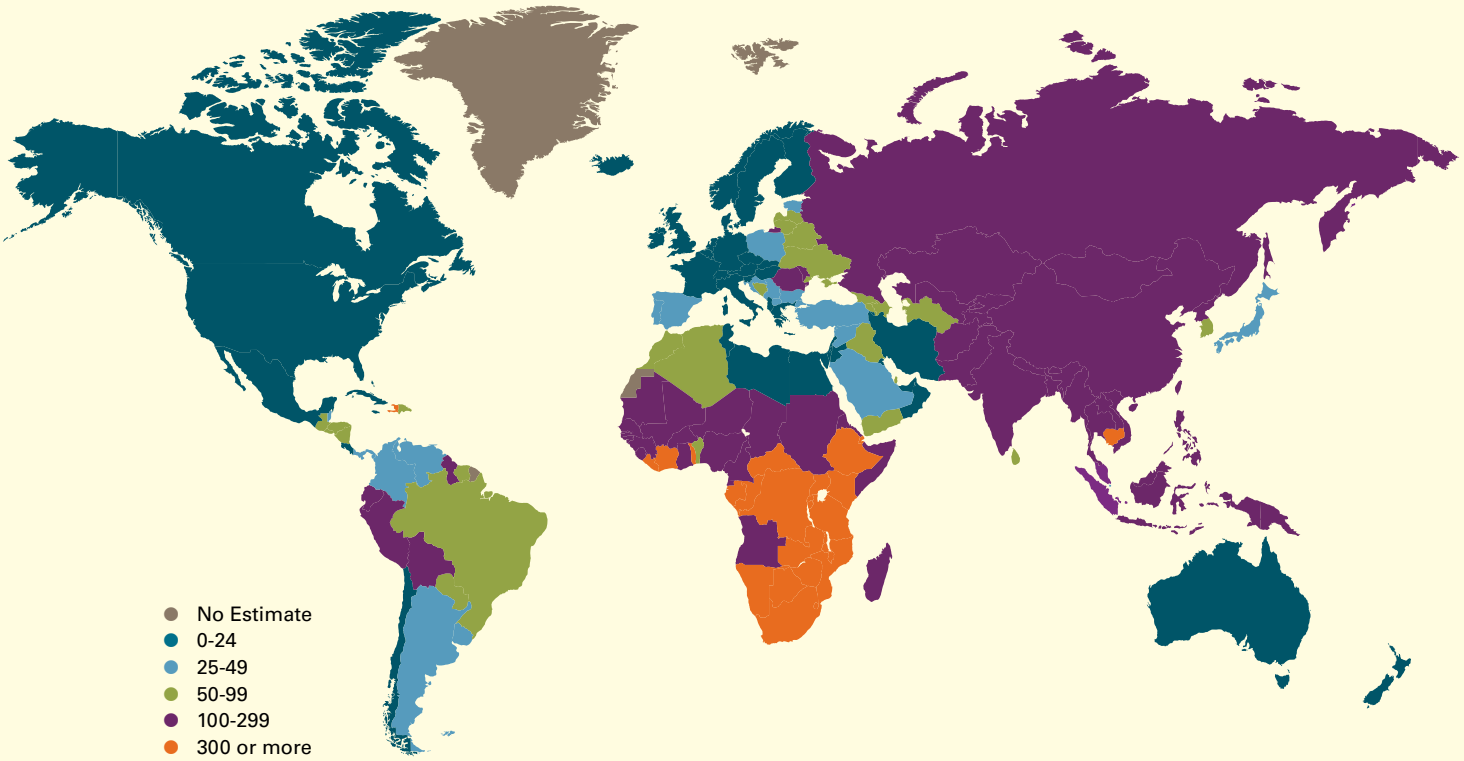
More than a century after the discovery of Mycobacterium tuberculosis (*M.tb*), the bacillus that causes tuberculosis (TB), and a half-century after the discovery of antibiotics to treat the disease, TB is second only to HIV as the leading infectious killer of adults worldwide.

TB kills someone every 20 seconds—about 4,400 people every day, or approximately 1.6 million in 2005 alone, according to the latest estimates from the World Health Organization (WHO).[1] It accounts for more deaths among women than all other causes of maternal mortality combined[2] and is the leading infectious cause of death among people with HIV/AIDS.[3]

The WHO estimates that one third of the world's population is infected with *M.tb*, which causes TB, with the greatest burden relative to population concentrated in the developing world, with high incidence of infection in sub-Saharan Africa, Asia and South America, as shown in Figure 1. Furthermore, today's TB epidemic is fuelled by a surge in HIV-*M.tb* co-infection and compounded by the growing emergence of drug resistant strains.

Apart from its devastating health consequences, the economic impact of the disease is staggering, making TB a significant contributor to world poverty. TB is estimated to absorb US$12 billion from the incomes of the world's poorest communities. In some countries, loss of productivity attributable to TB is in the order of four to seven percent of gross domestic product.[4]

Figure 1. Estimated Global TB Incidence (2005)



Source: *Global tuberculosis control: surveillance, planning, financing. WHO report 2007.* Geneva, World Health Organization.

1 *Global tuberculosis control: surveillance, planning, financing. WHO report 2007.* Geneva, World Health Organization.
2 Connolly M, Nunn P. Women and tuberculosis. World Health Stat Q. 1996;49:115-119.
3 Frequently Asked Questions *About TB and HIV.* World Health Organization. http://www.who.int/tb/hiv/faq/en/. Accessed 2/27/07.
4 *HIV/AIDS, Tuberculosis and Malaria: The Status and Impact of the Three Diseases.* The Global Fund to Fight AIDS, Tuberculosis and Malaria, 2005.

The current TB drug regimen, a product of the best scientific advances of the 1960s, works for active, drug-susceptible TB — as long as patients complete the six- to nine-month treatment. However, today's four-drug combination, taken ideally under direct observation by a healthcare worker or community member, is burdensome for patients and care providers alike and despite the enormous advances in provision of services over the past few years, many patients do not or cannot complete treatment.

The poor adherence and improper administration of existing antibiotics have led to the emergence of multi- and extensively drug resistant TB strains, known as MDR-TB and XDR-TB, respectively. Further, the global HIV/AIDS pandemic is fuelling an increase in TB, resulting in a dramatic rise in the number of co-infected individuals. An estimated one-third of the 40 million people living with HIV/AIDS worldwide are co-infected with TB. People with HIV are up to 50 times more likely to develop TB in a given year than HIV-negative people, and TB is one of the leading causes of death in HIV-infected people, particularly in low income countries.[5] In sub-Saharan Africa, up to 80 percent of tuberculosis patients are also HIV infected.[6] Unfortunately, the current TB drug regimen is not compatible with certain common antiretroviral therapies used to treat HIV/AIDS.

Critical to fighting this ancient disease is the development — and subsequent adoption — of affordable, new, faster and simpler drug regimens. After almost half a century of virtual inactivity, TB drug development has resurged. Bolstered by new scientific information on the bacillus, transforming international funding from philanthropic sectors and government donors, and the appearance of innovative business models designed to breach the drug development gap, the current global TB drug pipeline is the largest in history.

Experience has demonstrated that attrition rates are very high in drug development and it is expected that TB drugs will be no exception. However, the strength of the portfolio underscores the fact that even more new TB drug candidates and novel drug regimens are likely to be forthcoming within the next five to ten years.

Experience has also demonstrated that the uptake of innovation is a process that requires understanding of market forces, distribution channels, purchasing power and myriad other considerations. The promising new TB cures will be ineffective and the resurgent movement for TB drug development will have failed if the new treatments do not reach patients.

In 2006, the Global Alliance for TB Drug Development (TB Alliance) commissioned *Pathway to Patients: Charting the Dynamics of the Global TB Drug Market*. The study is the first comprehensive analysis of how today's TB drugs reach patients on a global scale. It includes an assessment of ten strategically selected countries — Brazil, China, France, India, Indonesia, Japan, the Philippines, South Africa, the UK and the US — as well as an appraisal of today's worldwide TB drug market value.

This compendium is a digest of information gathered from *Pathway to Patients* and details the pricing, purchasing, procurement and distribution mechanisms for first- and second-line TB treatments in these countries. In addition, the study updates the original global drug market assessment carried out by the TB Alliance in 2001 in *The Economics of TB Drug Development*.[7]

The research for *Pathway to Patients* was conducted in partnership with IMS Health, Inc., a global strategic consulting group focused on the pharmaceutical and healthcare industries. The project was financed by a grant from the Netherlands Ministry of Foreign Affairs' Department of Development Cooperation (DGIS) and with the support of the Bill & Melinda Gates Foundation. An abridged overview of these findings and a separate methodology document are available online at www.tballiance.org.

1.1 Introduction to the Project

Of the ten countries studied, six were chosen from among the 22 identified by the WHO as high burden countries (HBCs): Brazil, China, India, Indonesia, the Philippines, and South Africa. Together, these countries carry approximately 50 percent of the world's TB burden.[8] The project also encompassed four high income countries, France, Japan, the UK and US. Although the latter have a low burden of disease, they represent a significant value of the TB market because of higher cost of treatment. These countries are of particular interest to drug

5 *Frequently Asked Questions About TB and HIV.* World Health Organization. http://www.who.int/tb/hiv/faq/en/. Accessed 2/27/07.

6 Reid A, Scano F, Getahun H, et. al. Towards universal access to HIV prevention, treatment, care, and support: the role of tuberculosis/HIV collaboration. *Lancet 2006*; 6: 483-495.

7 *The Economics of TB Drug Development*. Global Alliance for TB Drug Development. October, 2001.

8 *Global tuberculosis control: surveillance, planning, financing. WHO report 2007.* Geneva, World Health Organization.

manufacturers because they account for 61 percent of the total global market for all pharmaceuticals.[9] Moreover, they were chosen because they reflect different geographies, different pricing and different health systems structures.

For the study, research on Indonesia and Japan was limited to determining market value and did not examine procurement and distribution.

1.2 Methodology[10]

The methodology used in the study allowed for both qualitative and quantitative analyses. Qualitative characterization of the TB market included mapping the flow of TB medicines from the supplier to the patient, the selection process for suppliers, and the role of public and private payers for first- and second-line TB medicines. Qualitative analysis also included the following steps:

1. Primary research was conducted through face-to-face interviews with global and country stakeholders by telephone and in person, including staff at the WHO, the Stop TB Partnership, and national and local staff from TB control programs of the countries studied

2. Secondary data were collected from a number of publicly available sources accessed through search engines and directly from the WHO website

3. Additional data and reports were collected from individual stakeholders following discussions

Quantitative characterization of the first- and second-line public TB drug markets focused on measuring the actual value (defined as market value) in the public and private sectors. Data were collected from several secondary sources:

1. IMS Health databases provided information on value and units sold in the private market in all countries where a private TB market exists (China, India, Japan, the Philippines and the US) and the public market in some countries (France, South Africa, the UK and the US)

2. Global organizations provided data on costs and supply of products both globally and at the country level

3. Product suppliers provided data on costs and sales of TB products sold

4. National TB control programs in the countries studied provided data on the number of patients treated in the public sector, funding for drug procurement, and costs per product and regimen in the public sector

For the private first- and second-line markets, IMS Health databases were used where available (e.g. India) to estimate value. Value estimates are based on the actual value of drugs sold in the private marketplace. Recognizing that many second-line drugs are used for indications other than TB, prescription data were used to adjust those figures so that they more closely reflected the value of second-line drugs used for TB specifically. First-line drug value figures were left unadjusted because the prescription data indicated that only a marginal fraction of those drugs in the countries studied were being used for indications other than TB.

Estimates of patient volume in the private sector could not be obtained for either first- or second-line drugs because patient adherence and treatment practices, as well as record keeping, varied greatly between and within countries. Therefore, patient volumes are only provided for public-sector programs.

The public-sector drug budget figures and the price per treatment regimen estimates described in this report may differ slightly from those reported in the 2006 WHO report *Global Tuberculosis: Surveillance, Planning, and Financing*. This is because research for the WHO report and for *Pathway to Patients* were gathered at different times. Figures reported to the WHO may have been based on projections for 2005, whereas the research in this study was primarily based on actual expenditures for 2005. Moreover, where 2005 data were not available for this report, researchers relied on 2004 data instead.[11] Because the figures are gathered using the same methodology from year to year, the combination of data from consecutive years was determined to be appropriate.

It should also be noted that the study did not seek to review or address the quality of TB treatment or the quality of procurement and distribution in any of the countries studied.

9 IMS Knowledge Link. http://www.imsknowledgelink.com.

10 For full information about the specific methodology used to determine the market estimates for each country and the global estimates, including individual drug cost figures and a list of the countries included in the global extrapolation, a separate methodology document is available online at www.tballiance.org.

11 Discussions with Kathryn Floyd, WHO, October 2006.

2. Global Procurement Services Agencies

A number of organizations known as procurement services agencies (PSAs) exist at the global level to assist countries and/or organizations in supplying drugs to their respective TB programs. These include agencies that are dedicated specifically to TB drug procurement, such as the Stop TB Partnership's Global TB Drug Facility (GDF) and Green Light Committee (GLC), or those that procure a range of products, such as Crown Agents or the IDA Foundation. In some countries non-government organizations (NGOs) also procure TB drugs, either for their own programs or for the geographic region in which they operate. *Pathway to Patients* focused on two of the PSAs engaged in procurement in HBCs: The GDF and the GLC.[12]

2.1 Global TB Drug Facility: Background and Role

Housed at the WHO headquarters in Geneva, Switzerland and managed by the Stop TB Partnership Secretariat, the GDF was initiated in 2001 in response to the difficulties experienced by countries in finding and funding stable TB drug supplies. Its stated mission is "to expand access to, and availability of, high-quality TB drugs to facilitate DOTS expansion."[13]

The GDF seeks to directly address several problems countries may face in the procurement of TB medication, including lack of financial resources, inefficient procurement mechanisms, poor quality assurance systems and inadequate in-country management and monitoring. For countries that lack the resources to fund drug procurement, the GDF offers in-kind grant services. For countries that can afford to purchase drugs, the GDF also offers direct procurement services. For all countries, it offers pre-qualification services to ensure adequate quality control mechanisms and provides in-country monitoring and technical support to improve and maintain high-quality drug supply, management, and distribution processes.

As described in this section, ordering TB medicines through the GDF is a multi-step process. The purchaser must approach the GDF with requests for TB drugs. The GDF then confirms the eligibility of the purchaser and forwards the order to a selected procurement agent. The procurement agent places the order with suppliers that have won an international competitive bid. Finally, the majority of orders are forwarded to the primary supplier named in the bid and, if necessary, a secondary supplier is used to provide additional volumes.

2.1.1 Customers

GDF customers fall into one of two categories, purchasers or grantees.

Purchasers (most often health ministries) obtain drugs from the GDF through direct procurement. In countries where the national government does not play a central role in procurement, state or provincial health ministries or NGOs such as Partners in Health (PIH) or Médecins Sans Frontières (MSF) may serve as primary purchasers.

Countries seeking to procure drugs through the GDF's direct procurement process must first be approved. Eligible countries or organizations include:

- Countries that implement WHO-recommended DOTS strategy in 90 percent or more of the population
- NGOs that support DOTS strategy in these countries
- Countries or NGOs approved by the GDF for TB drug grants
- Countries or NGOs approved for a grant for TB control by the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM)
- Organizations, donors and technical agencies supporting these countries or NGOs[14]

The value to clients of the GDF's direct procurement services varies depending on the capabilities and needs of each country. For the most part, the GDF's value proposition is measured in its ability to assist countries that do not have sufficient, reliable quality control, and/or efficient internal purchasing or production capabilities. For some countries, price and packaging are also viewed as an attribute.

12 In early 2006, the GDF announced that it would converge with the GLC. Procurement functions of the GDF and GLC already have been combined. Plans to combine their application, review, monitoring, and evaluation functions are currently underway. For more information about the GDF/GLC convergence, see section 2.3 of this report.

13 Stop TB Partnership. http://www.stoptb.org/gdf/whatis/what_is.asp. Accessed 2/28/07.

14 As per "Global Drug Facility: An Introduction". Available in PDF format: www.stoptb.org/gdf/documents/FS%20GDF%20An%20Introduction_June06.pdf.

Grantees include countries that lack financial resources to procure TB medicines and instead receive in-kind grants in the form of free drugs. Grantees receiving drugs must meet all eligibility requirements for direct procurement as well as the following criteria:

- Annual per capita gross national income (GNI) under US$3,000
- A national plan and budget allocation for DOTS expansion to meet global TB control targets
- Technical guidelines demonstrating commitment to meet global TB control targets
- Completion of an annual report on DOTS performance (WHO TB collection form)
- Must have received a recent external national TB program review[15]

As shown in Figure 2, the GDF supplies first-line TB drugs to 13 of the 22 WHO-designated high burden countries. However, of the countries for which procurement was studied, only India and the Philippines currently use the GDF, and even for these countries, first-line drugs are also sourced through public tender processes.

2.1.2 Procurement Agent Selection Process

The GDF does not procure TB medicines on its own. Instead, it serves as a screener and broker between suppliers and purchasers. It first identifies agencies and organizations best suited to perform the TB drug procurement and distribution function.

Figure 2. WHO 22 High Burden Countries Based on GDF Supply

1. India	**12. Russian Federation***
2. China*	**13. Vietnam***
3. Indonesia	14. Tanzania
4. Nigeria	**15. Brazil***
5. Bangladesh	16. Uganda
6. Pakistan	**17. Thailand***
7. Ethiopia*	18. Mozambique
8. South Africa*	**19. Zimbabwe***
9. Phillipines	20. Myanmar
10. Kenya	21. Afganistan
11. DR Congo	**22. Cambodia***

* Do not purchase TB drugs or receive grants of drugs through the GDF

After forming contractual relationships with these organizations, the GDF seeks to match eligible countries with them. In doing so, it facilitates access to an uninterrupted supply of concessionally-priced, high-quality TB drugs.

Figure 3 on the opposite page describes the process through which the GDF selects a procurement agent. The procurement agent then becomes responsible for sub-contracting other partners for quality control and freight-forwarding functions.

Since the inception of the GDF, its primary procurement agent has been the Inter-Agency Procurement Services of the United Nations Development Programme (UNDP-IAPSO). In 2006, the service was re-bid and the German Agency for Technical Cooperation (GTZ) was selected as the new procurement agent, contracted for a period of two years.

2.1.3 Supplier Pre-Qualification and Selection Process

In order to be eligible to supply drugs to the GDF, suppliers must be assessed by the WHO. Manufacturing sites must comply with the WHO's Good Manufacturing Practices (GMP) standards. They must then meet WHO/PSM[16] pre-qualification requirements.[17] The selection process for approved suppliers is then carried out by the procurement agent through an annual international competitive bidding process.

Typically, the procurement agent selects two suppliers for each product — a primary and a secondary source. The primary supplier is usually awarded 65 percent of the annual supply and the secondary, 35 percent. Prices offered by the secondary supplier are typically higher. The award period for each product is typically one year and is specified in a Long Term Agreement (LTA).

2.1.4 Pricing

A number of factors can cause the cost of GDF-sourced treatments to fluctuate. Prices have increased in recent years, in part because they are not guaranteed or stabilized during the competitive bidding process.[18] Also, the cost of goods of some raw materials required to manufacture TB drugs has increased. Furthermore, as the GDF increases the number of countries it serves, it exhausts the supply from primary suppliers. It must then rely on the

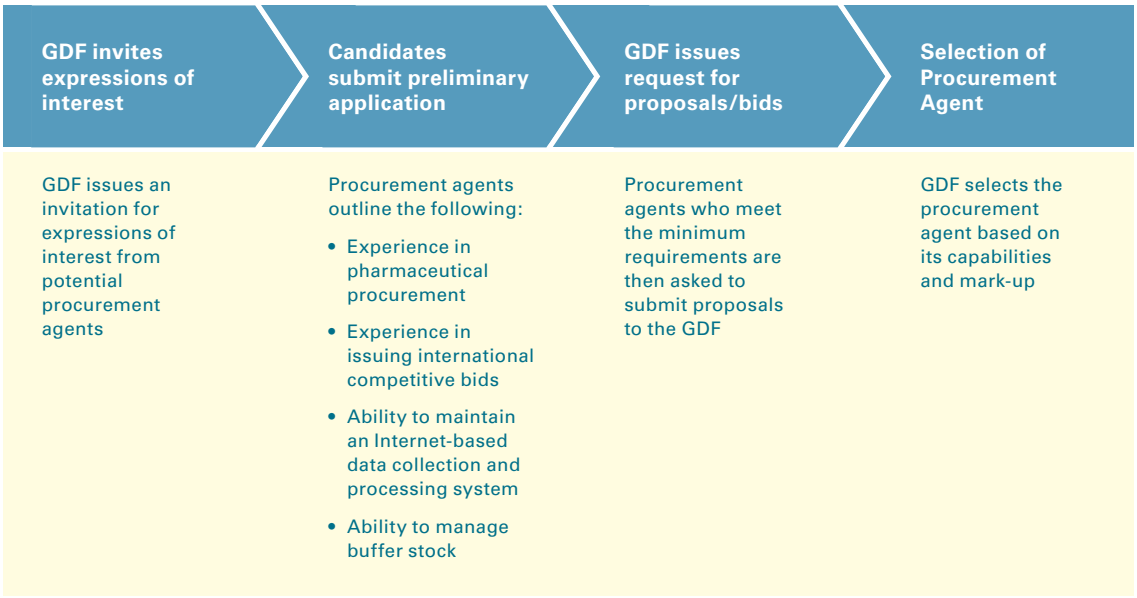
15 Stop TB Partnership Global Drug Facility: www.stoptb.org/gdf/applying/application_documents.asp.

16 Medicines Policy and Standards (PSM).

17 The specific prequalification standards for TB drugs are determined by the Procurement, Quality and Sourcing Project: Access to Anti-Tuberculosis Drugs of Acceptable Quality (TB Prequalification Project). This project was initiated in 2002 by the WHO Department of Medicine and Policy Standards: Quality Assurance and Safety of Medicines (PSM/QSM) to facilitate access to anti-TB drugs of acceptable quality through the assessment of products and manufacturers for adherence with WHO-recommended standards.

18 Stakeholder discussions with GDF, UNDP-IAPSO, 2006; information also available online in PDF format: www.stoptb.org/gdf/documents/GDFFactBrief_April2005.pdf

Figure 3: GDF Procurement Agent Selection Process



secondary supplier, thus increasing the average price of the standard first-line regimen.

2.1.5 Suppliers

In response to increases in prices and decreases in available supply, the GDF issued a new tender for additional manufacturers in March, 2005. The result was an increase in suppliers from three companies to four: Lupin, Cadila, Svizera, and Strides-Sandoz.[19]

2.1.6 Quality Control

Before products are shipped to the purchaser, orders must meet specific quality control standards determined by the GDF. The quality control process includes pre-shipment inspection (PSI) and laboratory batch testing of the product. Both steps are sub-contracted by the procurement agent. The GDF appoints a quality control agent who is responsible for ensuring that an order meets GDF standards. The batch test is conducted by a sub-contracted quality control laboratory.

Before an order is shipped, suppliers are required to notify a designated agent that the order is ready. The supplier must then submit a sample of the product to the GDF for quality control. A local agent is sent to the supplier facility to evaluate product packaging and labeling and report the results to the quality control agent. A sample of each product batch is then sent to a laboratory for testing. The laboratory also reports its results to the quality control agent.

Once it is confirmed that an order meets all of the GDF's specifications, the quality control agent notifies the procurement agent to release the shipment to a freight forwarder.[20]

2.1.7 Transport Process

Once the quality of the order has been assessed, a freight forwarder that has been contracted by the procurement agent is notified that the order is ready for shipment. The freight forwarder picks up the order from the supplier facility and, if all products in the country's order are being sourced from one manufacturer, the order is transported directly to the purchaser. If they are being sourced from multiple manufacturers, all products are transported to a consolidation point where orders are assembled prior to being sent to the purchaser. Once the order has been transported, the distribution of drugs becomes the responsibility of the purchaser.

The quality control and transportation processes are the same when the recipient is a grantee. However, under the direct-procurement mechanism, purchasers have the option of specifying where they would like their orders shipped, and are billed for this service. Conversely, when the GDF is processing a grant, the order is shipped to the country's port of entry only. Once orders have been received, the GDF usually conducts a follow-up assessment within four to six months to ensure the drugs are being used appropriately.

19 Tender procedures and criteria can be found online in PDF format: www.stoptb.org/gdf/assets/documents/GDFFactBrief_April2005.pdf
20 Stakeholder discussions with GDF, UNDP-IAPSO, 2006.

2.2 Green Light Committee: Background and Role

As noted in the introduction, cases of drug resistant TB are becoming increasingly common across the globe. Because the cost of treating these patients is a barrier to receiving care, a strategy known as DOTS-Plus was launched by the WHO in 1998. As part of this strategy, the GLC was formed in 2000 to serves as a global supplier of second-line drugs to treat MDR-TB. The GLC meets six times a year to assess applications from DOTS-Plus pilot programs, determines if a program is in compliance with the Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB, and provides access to affordably priced second-line TB drugs to approved programs.[21] [22]

2.2.1 Customers

The GLC accepts applicants from any program, agency or organization that fulfills several criteria.[23] They must:

- Ensure that the DOTS strategy is in place and is functioning well
- Secure government commitment and adequate funding
- Develop a coordinated project management plan
- Demonstrate that they have adequate laboratory resources
- Devise a rational treatment strategy
- Develop an adequate information management system
- Confirm that the drugs requested are registered in the country of the project
- Develop a drug management plan including transportation, registration, customs procedures, storage, distribution, monitoring and reporting

Each application must be completed with the following information:

- Location
- Size of patient cohort
- Anticipated start date and duration of program
- Time schedule for inclusion of patients during the pilot project
- List of all organizations involved
- Justification of the need for a DOTS-Plus pilot project

Projects must also facilitate a site visit upon request.

Each program is approved for a set number of patients. Once the program has met its quota, it must reapply for expansion. Through 2005, programs representing approximately 9,000 patients worldwide were approved by the GLC. More than half of those patients were in Peru alone.[24]

2.2.2 Procurement Agent Selection Process

The primary procurement agent serving the GLC today is the IDA Foundation (IDA)[25], which handles drug procurement, quality control, and transportation. IDA's primary responsibility is to ensure a high-quality and affordable supply of second-line drugs is available by negotiating prices directly with suppliers from a list of eligible manufacturers and drugs that have been assessed by the WHO and/or GLC. IDA plays a key role in quality control by assessing potential manufacturers and conducting its own quality control of procured drugs. In addition, IDA standardizes packing, labeling and product information specifications for generic drugs. Finally, IDA is responsible for transporting drugs to purchasers' ports of entry or airports.

2.2.3 Suppliers

Because many second-line drugs are patent-protected or are produced by a limited number of qualified suppliers, neither the GLC nor IDA currently use bids to procure its drugs. Instead, IDA approaches manufacturers who produce second-line TB drugs and forms agreements directly with them for reduced price products. During its interactions with potential suppliers, IDA attempts to negotiate the lowest price possible for generic drugs or, in the case of branded drugs, a concessional price that is affordable to its customers. The manufacturer may or may not specify a maximum volume of reduced price drugs that it will provide to the GLC.

2.2.4 Pricing

Table 1 on the opposite page describes the prices of second-line TB drugs offered through the GLC in 2006, as well as the companies that manufacture them.

2.2.5 Transport Pathway

The first step of GLC procurement is an application process that all potential purchasers must undergo.

21 Rajesh Gupta et al., *Increasing transparency in partnerships for health – Introducing the Green Light Committee,* Tropical Medicine and International Health, 2002; Stakeholder interviews, 2006.

22 As noted previously, the GLC recently converged with the GDF. Drugs procured on behalf of projects approved by the GLC will now be supplied through the the GDF procurement mechanism.

23 "Instructions for Applying to the Green Light Committee for Access to 2nd line Anti-tuberculosis Drugs", 2002. whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.369_eng.pdf

24 Data provided by the GLC, 2006.

25 GLC's most recent tender process was held in 2006. IDA, which already was serving as procurement agent, won that bid as well and new contract is currently being finalized.

DOTS-Plus pilot projects are required to submit applications to the GLC, which reviews them and decides whether to grant access to its price-negotiated second-line TB drugs. If the GLC approves the application, an approval letter is issued to the applicant outlining the number of patients for whom the program has been approved. Once GLC approval has been granted, pilot projects are permitted to work through IDA. Pilot projects then submit orders to IDA, and the agent works with its network of suppliers to fill orders. Once a supplier has filled an order, drugs are sent to an IDA warehouse.

2.2.6 Quality Control

As noted earlier, IDA conducts quality control assessments to ensure products meet GLC standards. After an order is placed and before the product is transported to an IDA warehouse, IDA evaluates product packaging and labeling and tests batches of its product orders. The product is then released for transport, and a freight forwarder contracted by IDA processes the shipment. Orders are sent directly to a country's port of entry — most commonly a major airport. Once the order reaches that location, the distribution of the drugs becomes the responsibility of the project coordinators.

2.3 Convergence of the Global TB Drug Facility and the Green Light Committee

In 2006, the Stop TB Partnership made a decision to combine the procurement responsibilities of the GDF and GLC.[27] Under this new model, the GLC will continue to review applications and grant access to its negotiated rates for second-line TB drugs, and the GDF will take responsibility for the selection of second-line drug procurement agents. The same processes and policies used for first-line drugs under the GDF will be followed for the procurement of second-line drugs. IDA will continue procurement on behalf of DOTS-Plus projects that have already been approved by the GLC, and a new procurement agent will purchase drugs on behalf of all other DOTS-Plus projects. Moving forward, the GDF will conduct a bid-and-tender process for second-line drugs that have multiple manufacturers, and will negotiate directly with manufacturers of drugs that are produced by only one company.

Table 1. Prices of Second-Line Drugs Through the GLC[26]

	UNITS	PRICE (US$)	SUPPLIER
Capreomycin, 1 gram powder for injection	1 vial	$ 3.21	Eli Lilly
Cycloserine, 250 mg	100 cap	$ 14.12	Eli Lilly
Cycloserine, 250 mg	100 cap bl	$ 50.96	Macleods Daman Plant
Ethionamide, 250 mg	100 tab	$ 10.21	Macleods Daman Plant
Amikacin 500 mg/2mL injection	100 amp	$ 23.15	Gland Pharma Ltd. Pally Factory
Kanamycin, 1 gram powder for injection	50 vls	$ 18.58	Panpharma
Ciprofloxacin, 250 mg	100 tab bl	$ 2.12	Micro Labs Ltd. (Brown & Burke)
Ciprofloxacin, 500 mg	100 tab	$ 3.81	Micro Labs Ltd. (Brown & Burke)
Ciprofloxacin, 500 mg	100 tab bl	$ 3.80	Micro Labs Ltd. (Brown & Burke)
Ofloxacin, 200 mg	100 tab	$ 3.49	Micro Labs Ltd. (Brown & Burke)
PAS acid sachet eq. to 4 gram aminosalicylic acid	30 sac	$ 48.18	Jacobus Pharma Company Inc.
Prothionamide, 250 mg	100 tab	$ 13.03	Fatol Arzneimitel
PAS sodium granules 60% (p-aminosalicylate sodium)	100 g	$ 9.74	Macleods Daman Plant
Ofloxacin, 200 mg	60 tab	$ 2.74	Macleods Daman Plant

26 Data provided by IDA, 2006.
27 Discussions with GDF, GLC and procurement agents, 2006.

2.4 Other Global PSAs

In addition to the GDF and GLC, there are a number of PSAs that play a role in global TB drug procurement. For example, while IDA procures second-line drugs for the GLC only, it also procures some first-line. Royal Crown Agents is a PSA that procures TB drugs on behalf of the state of Andhra Pradesh in India and plays some role in various regions around the world. The United Nations Children's Fund (UNICEF) has a PSA division that procures pediatric formulations of TB medicines.

Additionally, regional procurement mechanisms exist that serve the Caribbean and Persian Gulf. This method of procurement is demonstrated by the Pan American Health Organization (PAHO), which was once responsible for the bidding process for manufacturers in Brazil. Finally, while they do not play a significant role in the countries included in this study, a number of NGOs such as MSF frequently procure TB drugs for their own programs and/or the regions in which they operate.

3. Country Case Studies

As noted in the introduction, a total of ten strategically-selected countries were included in the research for *Pathway to Patients*. In-depth qualitative analysis of national and global procurement and distribution systems in eight of these countries was conducted to provide the basis for understanding the market dynamics. Research on Indonesia and Japan was limited to determining market value. This section provides an overview of the role of national healthcare systems in controlling TB in the five high burden and three high income countries studied for in-depth qualitative analysis.

Table 2 provides the population, TB burden, and TB case notification statistics for the ten countries studied.

3.1 TB Control in the Context of National Healthcare Systems

All countries studied have a national, publicly-financed healthcare program through which a portion of or all drugs and medical services are provided free of charge to at least a segment of individuals and often to all citizens. TB control is one of several components of these national healthcare systems, and patients may choose to go to a public facility for treatment.

Table 2. Key Statistics for Focus Countries

	POPULATION	PROJECTED NEW TB CASES (TOTAL)	TB PREVALENCE (TOTAL)	TB CASE NOTIFICATION (TOTAL)
Brazil	184 million	109,672	141,115	86,881
China	1.3 billion	1,324,633	2,892,422	790,603
France	60 million	7,411	5,901	5,004
India	1.1 billion	1,824,395	3,394,040	1,136,506
Indonesia	220 million	539,189	605,759	210,229
Japan[28]	128 million	37,814	50,394	29,736
Philippines	82 million	239,459	378,094	130,530
South Africa	47 million	339,078	316,260	264,183
UK	59 million	7,101	5,497	7,039
US	295 million	13,877	14,517	14,517

Note: All data are 2004 numbers, as noted in WHO surveillance report released in 2006.

28 As noted, Japan and Indonesia were included in the market sizing exercise, only. In depth analysis of procurement and distribution were not performed.

The actual structure of each country's national healthcare system differs in many ways, including which patients have access, how patients enter the public sector, where patients are treated and by whom, what drugs and procedures are provided in the public sector, and what costs patients incur in the public system.

For example, in Brazil all patients have access to free healthcare across multiple facilities. This may include large public hospitals, outpatient clinics, or even private hospitals that have contracts with the national public health insurance program. In these facilities, inpatient procedures and pharmaceuticals are provided for free. Medication for some outpatient treatment is covered, including drugs for the outpatient treatment of TB, HIV and diabetes.

In South Africa, clinic visits for the treatment of TB and some other conditions are free for all patients, but hospital stays are billed according to a patient's income level. Individuals who are unable to pay for such services receive care free of charge.

In the US, there is no separate or centralized funding for the treatment of either drug susceptible or MDR-TB. Rather, TB treatments are funded by both public and private payers (e.g. Medicare, Medicaid, private health insurance.) For the uninsured, funding may be provided through either the federal, state or local health systems or through patient assistance programs sponsored by pharmaceutical companies who manufacture the drugs.

In addition, treatment and care for national health priorities (including HIV and TB) are provided to patients through the public sector at federal-, state-, and city-run health clinics.

3.1.1 High Burden Countries

Many similarities and differences exist across TB control programs in HBCs, including function of the program, structure of the program and division of responsibilities, and source of funding for TB control.

All HBCs studied have national TB control programs within their broader healthcare systems. These programs are responsible for defining TB control strategies and policies.

In high burden countries, TB control is typically administered by a dedicated department within the Ministry of Health (MOH) or equivalent agency, although the structure and reporting flow varies significantly by country.[29] In some countries, the national TB control program may report directly to the MOH, as is the case in Brazil and India. In other countries the TB control program reports to a communicable-diseases or infectious-diseases branch of the healthcare program. For example, in the Philippines, TB control is part of the communicable-diseases department, which reports to the health ministry. In South Africa, the TB control program falls under the TB, HIV/AIDS and Sexually Transmitted Infections Department, which is a subgroup of the Strategic Health Programs, under the MOH. In China, the national TB control program falls directly under the Chinese Center for Disease Control and Prevention and reports to the Office of TB Administration under the MOH's Department of Disease Control.

3.1.2 High Income Countries

In the high income countries studied, TB incidence is relatively low. For example, in 2004 there were 6,242 new cases of TB in France[30] and 6,837 in the UK.[31] In 2005 in the US, 14,095 cases of TB were documented by the US Centers for Disease Control and Prevention (CDC).[32]

In these countries, TB disease disproportionately affects specific populations — particularly low income and immigrant communities in urban areas. For example, in the UK, according to the Health Protection Agency (HPA), in 2004 almost 50 percent of the TB burden was concentrated in London, and most infected patients were immigrants from South Asia. Similar trends exist in France, where prevalence is highest in Paris where there is a concentration of high risk groups, including immigrants from endemic countries and people living in poverty.

In both of the European countries studied, TB control is an integrated function of the public healthcare system. For example, in the UK the National Health Service (NHS) provides universal coverage to all citizens. There is no stand-alone TB control program in the UK. Instead, the communicable-diseases branch of the health ministry is responsible for overseeing the surveillance, prevention, and control of TB, as well as other infectious diseases, including Creutzfield-Jacobs disease, diphtheria, hepatitis, flu, rubella, and polio. In France, the Directions Départementales des Affaires Sanitaires et Sociales (DDASS) — part of the Department of

29 Discussions with health ministries and national TB control programs in each country, 2006.
30 Superior Council for Public Hygiene Guidelines; Bulletin Epidemiologique Hebdomadaire.
31 Health Protection Agency; Office of National Statistics. www.hpa.org.uk/infections/topics_az/tb/menu.htm
32 *Trends in Tuberculosis – United States, 2005.* MMWR. 2006;55(11):305-308. US Centers for Disease Control and Prevention (CDC)

Health and Social Affairs — acts as a de facto TB control program and is responsible for surveillance and monitoring of TB cases. In the US, TB control is part of the National Center for HIV, STD, and TB Prevention, which is a unit of the Coordinating Centers of Infectious Diseases within the CDC.

Because TB is considered a public health threat, additional measures exist in all countries to ensure that physician or drug costs are not a barrier to treatment and that all patients have access to TB medicines. In France and the UK, all patients may receive TB treatment for free regardless of immigration status. Payment for drugs and treatment is more complicated in the US, however. While it is the responsibility of each state to provide treatment to every TB patient regardless of ability to pay, only patients without insurance coverage or who cannot afford to pay for physician office or drug co-payments are eligible for assistance. Payment assistance is determined using a sliding scale based on a patient's income. Hospitals typically refer patients who cannot afford treatment to state health departments or assist them in applying for emergency Medicaid coverage, if potentially eligible.

3.2 Overview of Key Trends Impacting TB Funding and Treatment in HBCs

Several emerging trends may affect how TB treatment is funded. First, some countries have significant private-sector activity in the treatment of TB. In these cases, governments are making a clear effort to shift treatment from the private to the public sector so that they can increase control and monitoring of patients and ensure appropriate and successful diagnosis, tracking, and adherence to TB treatment (*see Section* 3.4.4). Second, as MDR-TB becomes more prevalent and diagnosis more accessible, countries are beginning to include treatment of drug resistance in their national TB control programs. Currently, Brazil and South Africa provide second-line drugs, and China, India and the Philippines have recently piloted or will begin to pilot second-line treatment programs within the next year.[33]

3.3 HBC National TB Control Programs

3.3.1 Function

In all HBCs studied, national TB control programs were established to provide a central organization to help control TB through the public sector. Although there are slight differences between each country's program, the overarching goal is to effectively treat, monitor, and ultimately eliminate TB. From an organizational standpoint, these national TB control programs typically include:

- National, regional, or local budget lines allocated to TB control
- Established treatment guidelines
- Mechanisms of monitoring and evaluation
- Drug procurement and distribution mechanisms
- Treatment implementation, training, and logistical support

3.3.2 Financing

In Brazil, China, India and the Philippines, financing and resource-allocation decisions for TB control are set at the national level by one or more individual departments, including a central financing department, MOH, and/or national TB control program.

Additionally, in many countries (including China and the Philippines) the national TB control program is supplemented by regional (state or provincial) and local or municipal resources, though this is generally not a mandated requirement. For example, in the Philippines, local government units are expected to supplement national government funds by procuring some TB drugs, providing resources for raising awareness, and training pharmacists and physicians. However, a specific funding threshold is not mandated by the national government as a prerequisite. Instead, it is up to the local government to determine what part of the budget to allocate to TB control versus other healthcare, education, or social initiatives.

A similar model exists in Brazil. Although funding for the public sector is generally decentralized, Brazilian states and municipalities are not required to allocate specific funding for TB control. However, they do frequently provide funds to supplement programs. For example, officials may choose to implement DOTS in municipal public hospitals or provide financial incentives to patients who adhere to the DOTS program.

In China, local funding is more regulated. The level of funding provided by the national government is determined by a province's wealth, and all provinces are expected to contribute additional funds. With respect to drug procurement specifically, wealthier provinces are expected to procure drugs on their own.

33 Stakeholder discussions with national TB control programs.

Figure 4. National TB Control Program Responsibilities

LEVEL OF NTP	DESCRIPTION OF RESPONSIBILITIES
National	• Defining the policy and strategy of the country's TB control efforts • Allocating funding across TB control activities • Coordinating national level activities such as drug procurement • Overseeing regional TB control programs
Provincial/State	• Implementing the TB program within a specific geographic region, which may Cinclude planning, training physicians and healthcare workers, supervising facilities, and monitoring program effectiveness • Prioritizing activities Cwithin a specific geographic region Cand allocating additional funds to carry out many of the implementation activities (e.g., training, public awareness programs, DOTS incentives programs for patients and physicians) • Tracking drug supply needs and reporting to national level • Aggregating TB/ MDR-TB patient case reporting and reporting to national level registry • Monitoring local level implementation activities within specific geographic regions
Local Office e.g., city or metropolitan area	• Implementing on a local level, including public awareness, training, delivering drugs and equipment to facilities • Focusing on direct healthcare delivery, including diagnosing and treating patients

In South Africa, the financing of TB control differs from that of the other HBCs included in this study. The national government allocates an "equitable share of resources" for primary healthcare to each province, and the province is responsible for determining how much of this funding is allocated to TB control and how this money is used.

3.3.3 Structure

In the HBCs studied, TB control in the public sector is typically administered through a vertically structured program, with responsibilities defined at national, state or provincial, and local or municipal levels.[34] Figure 4 provides an overview of the responsibilities typically associated with each such level.

3.4 Treatment of TB Patients

This section describes typical patient treatment regimens in both the high burden and high income countries. Among the issues discussed are the use of fixed-dose combinations (FDCs); the role of public and private sectors in service provision, including typical referral pathways; and public-private mix (PPM) programs in TB control.

3.4.1 HBCs

In each of the HBCs studied, there are national diagnosis and treatment guidelines in place to inform the classification and treatment of TB patients by physicians in the public sector. In India and the Philippines, where many patients receive treatment in the private sector, prescribing practices vary widely.[35]

In general, active TB patients are categorized based on their sputum test results, symptoms, and other criteria, including whether their infection is extra-pulmonary or pulmonary and whether they have been previously treated. The first-line treatment regimen typically lasts six months, with an intensified two-month phase of treatment with a four-dose regimen of rifampicin (R or RIF), isoniazid (H or INH), pyrazinamide (Z), and ethambutol (E), and a continuation phase of treatment with rifampicin and isoniazid. In some countries streptomycin (S) is also prescribed for re-treatment cases.

For example, in India, first-line TB patients are categorized as follows:

- **Category I**: New smear-positive; seriously ill smear-negative; seriously ill extra-pulmonary
- **Category II**: Previously treated smear-positive (relapse, failure, treatment after default)
- **Category III**: New smear-negative; and extra-pulmonary, not seriously ill

There are some variations in national guidelines and protocols for treatment. One key example is the difference in regimens used to treat Category I and III patients. In some countries, such as India,

34 Stakeholder discussions with national, provincial/state and municipal/county level TB program administrators.
35 NTP, pharmacist and physician discussions in India and the Philippines; discussions with PhilTIPS in the Philippines, 2006.

ethambutol may not be used for Category III patients as it is for Category I patients, whereas in other countries, such as the Philippines and South Africa, the same regimen is used for Category I and III patients. In Brazil, ethambutol is not a part of the regimen for any new TB patients, whether smear-positive or smear-negative, and is only prescribed for previously treated smear-positive patients.

Variation also exists by country in dosing and administration. In Brazil, China and India, national guidelines follow the three-times-weekly or every-other-day approach. In the Philippines and South Africa, once-daily regimens are used.

3.4.2 High Income Countries

In high income countries, both active and latent TB patients are routinely treated. In France, the UK and the US, the four-dose regimen of isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE) is used in the intensive phase and a combination of rifampicin and isoniazid is administered in the continuation phase. These drugs are often administered in fixed-dose combinations (FDCs), which are popular in France and the UK where they comprise approximately 50 percent and 40 percent, respectively, of the volume of first-line drugs by unit.[36]

In both European countries studied, patients with latent TB are most commonly treated with a regimen of rifampicin and isoniazid for three months[37] or six months with isoniazid alone.[38] In the US, these patients are treated daily with isoniazid for nine months.[39]

3.4.3 Use of Fixed-Dose Combinations in Treatment Regimens

Views and practices regarding the use of FDCs in treatment differ widely by country. The governments of Brazil, the Philippines, and South Africa actively procure FDCs and include them as a key component of their public-sector TB programs. Perceptions around the advantages of using FDCs include ease of administration, ease of stock management, and an increase in adherence.[40] Conversely, neither China nor India uses FDCs in the public sector—although they are administered in the Indian private sector. Similarly, FDCs are not commonly used in the US, largely because physicians value their ability to titrate each separate agent.

3.4.4 Service Provision

All countries studied have a public sector in which patients can receive diagnostic and treatment services. In Brazil and South Africa, most TB treatment is provided by the government. In some countries, TB care can be obtained through the private sector and PPM facilities.

In Brazil and South Africa, most TB treatment is provided by the government. In contrast, in India and the Philippines, despite significant public sector programs, many patients prefer to seek diagnosis and treatment in the private sector for reasons that include perceived quality of care and maintenance of anonymity.

Private sector practices in TB pose a number of challenges to the public sector program. For example, patients entering the private sector may not be reported into the National TB program making it difficult to estimate the TB burden and track success in diagnosing and treating patients. Also, physician regimens differ from national guidelines and in many instances less effort is placed on treatment adherence. To address quality of care in the private sector, India and the Philippines have piloted PPM programs in an effort to reach more people with appropriate treatment and help provide an incentive to the private sector to adhere to the nationally approved regimen. Under this model, physicians who suspect a patient of having TB or initially diagnose a patient with TB can refer the patient to the public sector for further diagnosis and free treatment, or may continue to treat the patient him or herself, with drugs provided at no cost or subsidized by the government. (*The PPM model is described in greater detail in Section* 3.6.1).

3.5 Public Sector: Referral Pathway and Settings of Care

This section details the general referral pathway of a patient in the public sector and describes specific settings of care for the high burden and high income countries studied. Overall, there are three major sectors in which TB care is administered: the public sector, the private (for profit) sector, and through NGOs. In the countries studied, NGOs were not a significant service provider and therefore are not covered in depth in this report.

36 IMS MIDAS data for 2005.

37 France guidelines from Superior Council for Public Hygiene Guidelines; U.K. guidelines from National Institute for Health and Clinical Excellence, British Thoracic Society.

38 U.K. only guidelines from National Institute for Health and Clinical Excellence, British Thoracic Society.

39 CDC Targeted TB Testing and Treatment of Latent TB Infection. Available online in PDF format at www.cdc.gov/mmwr/PDF/rr/rr4906.pdf

40 Discussions with NTP and physicians in Brazil, the Philippines and South Africa, 2006.

3.5.1 HBCs

Generally, patients enter the public system in one of two ways: By visiting a public healthcare worker and being referred to a TB specialist or facility, or by visiting a private physician and being referred to the public healthcare system.

In many HBCs, patients suspected of having TB are referred to a public outpatient setting for diagnosis and treatment. Patients with TB are subsequently managed in the outpatient setting for the duration of treatment. In the rare case that a patient has MDR-TB, HIV or another serious concomitant disease, they may be referred to a special center or admitted to a hospital. Following are descriptions of public sector referral pathways and care settings in each of the five HBCs studied, followed by the three high income countries studied:

BRAZIL

In Brazil, patients will typically present in a public hospital ambulatory setting in their community, and will be referred to the pulmonology department at that hospital for sputum testing. Once diagnosed, patients will be managed in the hospital outpatient department. If the facility has been designated as a DOTS hospital by the municipal- or state-level authorities, the patient will be asked to return daily for treatment. If the facility is not DOTS-designated, the patient typically comes in on a regular basis either once a week or once a month for the next supply of pills. Patients who prefer to receive treatment at a family health program in their community or by a visiting healthcare worker may choose to do so if such services are available in their municipality.

CHINA

In China, patients typically present at a county or township hospital or to a village healthcare worker. Patients suspected of having TB are referred to a TB treatment dispensary—a local Chinese CDC unit or TB prevention institute, for free diagnosis, treatment and monitoring. At the county or township hospital level, healthcare workers may conduct X-rays and CT scans. Some facilities may have capabilities to conduct sputum microscopy testing as well. In such cases, patients are required to pay a consultation fee in addition to fees for conducting X-ray and sputum testing. Once a patient has been diagnosed with TB, the facility will record the patient into an Internet-based reporting system and refer the patient to the dispensary, where the patient is reported again. This may result in duplicative counting. Patients typically return to the CDC unit once a week or every two weeks for treatment and monitoring. In some rural areas patients live far from the TB dispensary, a village clinic physician will receive the medicines from the TB dispensary and administer directly to the patient once every one to two weeks. They are usually paid a monitoring fee to perform this service.

INDIA

In India, patients can present to any public health facility. If a patient is suspected of having TB, he or she is referred to one of the many designated microscopy centers located throughout the country. Once diagnosed, an ID card is filled out for the patient, a TB healthcare worker conducts an initial visit with the patient to inform him or her of the treatment regimen, and the patient is referred back to his or her original site of presentation to begin treatment. If the patient lives far from this treatment site, the TB healthcare worker attempts to locate a DOTS site that is closer to the patient's residence. A variation in this referral pathway is through the PPM model, which is viewed by government officials as an important way to leverage private-sector capacity. Through this model, patients present to private clinics and/or hospitals and, if suspected of having TB, are referred to public-sector microscopy centers. After diagnosis, patients may opt either to receive privately funded treatment, as they would from any other private-sector physician, or receive free drug treatment through the Revised National TB Control Program (RNTCP) under the supervision of their private-sector physician. This program has been increasing rapidly in scope, although it still involves a small fraction of private-sector practitioners.

PHILIPPINES

In the Philippines, patients may initially present at a public or private hospital or clinic. Patients are usually diagnosed first by X-ray and then following a sputum test, depending on the facility's capabilities and resources. In the public setting, patients who are diagnosed smear-positive are managed at a DOTS clinic that may be located at a large public hospital, a barangay (rural health unit), or even a PPM clinic at a private hospital. Those patients preferring to be treated in the private sector at non-PPM sites may do so, though they incur the cost of drugs as well as physician visits.

SOUTH AFRICA

Although some variation exists within South Africa, general TB control is a mandate of the public sector, and private-sector physicians are required to inform patients that they can receive free care in public facilities. Patients may then choose to receive care in the private sector at their own cost or present to the public sector. Patients in the public sector most frequently present to primary healthcare clinics. If suspected of having TB, patients are given a sputum smear test and the results are sent to a microscopy lab for confirmation. If drug resistant TB is not suspected and symptoms are not too severe, the patient begins DOTS treatment at the clinic, in the community under the supervision of a volunteer DOTS supporter, or in some cases, at his or her workplace. In exceptional circumstances, such as if the patient is migrant or must travel extremely long distances to healthcare facilities, he or she may be allowed to self-administer treatment.

Patients with severe symptoms or those who are suspected of having MDR-TB are referred to specialist centers or major hospitals, where they undergo a drug susceptibility test (DST) and are treated as an inpatient until they are no longer contagious. Where services are available, patients who are co-infected with HIV and TB are referred to a special HIV treatment site, where they receive care from a specially trained healthcare worker.

3.5.2 High Income Countries

FRANCE

In France, patients present most commonly in the emergency room and also to a general practitioner. In both cases, they are referred to a hospital for a chest X-ray. If a patient is suspected of having TB after the X-ray, he or she is referred to a specialist for sputum testing and subsequent treatment.

UK

Patients in the UK present to a general practitioner or the emergency room and are referred to the hospital outpatient setting for diagnosis by a chest X-ray. Patients who are suspected of having TB after the initial X-ray are referred to a hospital specialist in either the public or private setting, depending on their preference. That specialist confirms diagnosis through the result of a sputum test and subsequently manages treatment. The government also has a mandatory screening policy for immigrants from countries in which TB is endemic and who plan to stay in the country for more than six months. These individuals must have a chest X-ray when they enter the country.

US

Similarly, patients in the US typically present in the emergency room or to their general practitioner and are referred to a specialist for sputum and drug-sensitivity testing. Immigrants entering the country are required to receive TB testing prior to obtaining a visa and any suspected cases are immediately referred to the local health department upon entry. Those with latent TB are required to undergo nine months of prophylactic therapy with isoniazid.

3.5.3 Payment for Drugs and Services

In all HBCs studied, TB drug treatment in the public sector is free of charge. However, as previously noted, some patients may incur fees before being referred to specific facilities for diagnosis and treatment. For example, in China, patients seeking diagnosis in a county hospital or specialized hospital may pay consultation and diagnostic fees for the administration of X-rays and sputum tests. Once they are referred to a TB dispensary designated by the Chinese CDC, diagnostic procedures and treatment are free. In South Africa, patients receiving inpatient treatment for TB with the financial resources to pay for treatment are asked to pay a portion of the costs, based on their income level.

In the UK, patients in a public hospital will not pay anything if treatment is administered in an inpatient setting. In the hospital outpatient setting or in a retail pharmacy, patients pay the standard prescription charge—£6.65 (US$13) at the writing of this report. In France, TB is classified as an *affection de longue durée* (ALD) and is therefore exempt from all consultation fees, hospital charges and drug co-payments, irrespective of sector. All treatment and drugs are always 100 percent covered by social security and are free of charge. In the US, patients who do not have insurance or cannot afford co-payments are referred to a public clinic and receive treatment free of charge.

3.6 Private Sector: Referral Pathway and Settings of Care

Based on sales figures and information from primary and secondary sources, a significant portion of the population in India and the Philippines uses private healthcare facilities and systems for TB treatment.

In other countries, private-sector healthcare may be significant, but not for the treatment of TB.[41] In the case of TB, patients may present to any number of facilities and most likely will be diagnosed and treated on an outpatient basis. As outpatients, they will receive prescriptions for drug treatment which they must self-administer. Regulation in HBC private sectors is limited, and treatment practices vary considerably from physician to physician. It is not uncommon for patients to self-medicate, especially in areas where TB infection carries a social stigma.

The reasons that patients may choose to pay for treatment when free treatment is available vary considerably. Two of the most commonly cited reasons are that some patients perceive private treatment as being faster and better and that private treatment is more discrete.

3.6.1 Role of Public-Private Mix Programs in TB Treatment

In India and the Philippines significant private markets for TB treatment exist. The WHO piloted the PPM model to:

- Increase adherence by ensuring that cost is not an issue and by requiring that treatment is observed
- Facilitate the flow of patients between the two sectors in order to 1) ensure that patients diagnosed with TB are reported into the national registries for tracking and monitoring purposes; and 2) facilitate proper diagnosis and treatment based on the treatment guideline set in that country, including implementation of directly observational therapy

A PPM program was launched in India in 1995 in an effort to extend the capacity of the Revised National TB Control Program (RNTCP) as well as its scope of influence in the private sector. It was initially piloted in 14 cities and will soon be rolled out nationwide. Through the program, patients may initially consult with a private provider and still be eligible for free, directly-observed treatment. Patients who initially visit a private practitioner have the option of being diagnosed by their private physician or immediately being referred to the RNTCP for diagnosis. If diagnosed in the private sector, patients may remain in private care or move to the public sector. Those unable to afford private treatment are given a referral form and sent to the RNTCP for treatment. Those who prefer to be treated in the private sector may do so, however physicians can choose whether or not to waive the consultation fee.

A PPM program was launched in the Philippines in 1993 to address a variety of challenges that existed in the private sector. Private-sector physicians had a lack of knowledge regarding TB control challenges and development of drug-resistance. Physicians frequently used many different treatments, often not following the regimens recommended by the national TB control program. Furthermore, physicians did not follow up with patients on a regular basis to ensure adherence. Under the current PPM model, a PPM facility contracts with private physicians in the area. Private physicians affiliated with the PPM are asked to refer TB patients to a public health center unit when they are suspected of having—or are diagnosed with—TB. If the diagnosis for TB is confirmed, the patient remains in the public sector for treatment but may choose to also return to the private sector for periodic follow-up visits during treatment.

3.6.2 Payment for Drugs and Services in the Private Sector

As noted previously, a sizeable private market for first-line TB medicines exists in India, the Philippines and the US. In the private sector, patients are responsible for paying for consultation and diagnostic fees at the physician's office or hospital and are responsible for the cost of drugs at the pharmacy. As an exception to this, patients who are covered by private or public health insurance may not incur all fees associated with TB treatment. For example in the US, many patients have private insurance and thus pay an office co-payment and a drug co-payment rather than the full cost of services and drugs. However, the cost varies because there is a mix of public and private insurance coverage.

3.7 MDR-TB Control

Brazil and South Africa currently have national public-sector programs for treatment of MDR-TB and utilize domestic funding and in-country procurement mechanisms. China and India plan to implement and/or expand DOTS-Plus pilot projects as early as 2007. Meanwhile, patients who need to receive treatment for MDR-TB must do so in the private sector at their own expense. The Philippines receives funding for treatment of MDR-TB through GFATM grants and drugs through the GLC. In

41 In China, village doctors may provide TB care but they receive a payment from the government to do so and drugs are free to patients.

2005, treatment was provided for 250 patients and the country is now in the process of expanding treatment for up to 2,500 MDR-TB patients (see section 4.1.1).[42]

MDR-TB patients typically start to flow into national TB control programs much as they would for regular TB. However, once they are diagnosed with MDR-TB, they are referred to a specialized site that may or may not function exclusively for the treatment of TB. In South Africa, patients are usually sent to a specialist at a district or regional facility, and in the Philippines, patients are sent to either Makati Medical Center in Manila or another tertiary care center for treatment. Brazil's MDR-TB patients are sent to specialized TB reference centers.

The treatment of MDR-TB is a regular feature of TB control in high income countries, and—like the treatment of drug-susceptible TB—is fully integrated into the general healthcare system. In France and the UK, the treatment of such patients is primarily, if not exclusively, publically funded. In the US the funding of MDR-TB treatment depends on the patient's insurance coverage and whether he or she is eligible to receive assistance from the government. In the three high income countries studied, the primary difference between the treatment of drug-susceptible and MDR-TB patients is in the setting of care. In France and the UK, patients generally receive treatment on an inpatient basis at a hospital until they are no longer considered contagious and are healthy enough to finish treatment on their own. In the US, patients may also be treated on an inpatient basis at any hospital, or they may also be referred to one of the TB "Centers of Excellence" funded by the CDC.

4. Procurement and Distribution of TB Drugs in High Burden Countries

This section focuses on the financing of first- and second-line drugs as well as the public tendering process, a key procurement mechanism in the HBCs studied. Discussion of the public sector includes the demand forecasting process and distribution pathways of TB drugs. Finally, this section provides an overview of procurement in the private sectors of India and the Philippines, the two HBCs evaluated in *Pathway to Patients* in which the private sector plays a large role in TB control.

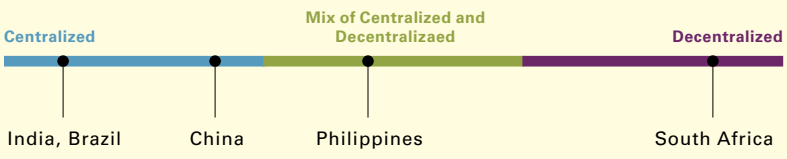
4.1 Financing for First-line TB Drugs

In all HBCs studied, the purchase of TB drugs is at least partially funded by the national government (see Figure 5). In Brazil, all funding for drug purchases comes from the national treasury. In India, donor funds from GFATM, the UK Department for International Development (DFID), the US Agency for International Development (USAID), and other agencies are paid to the central TB division and combined with domestic funding, as well as World Bank loans, to pay for TB drugs.

In China, the majority of funding comes from the national government. However, the governments of wealthier provinces—mostly located on the coast—are also responsible for providing funding for drugs supplied in their localities.

In the Philippines, national and regional levels of government share the cost of drug purchases. The national government has committed to purchasing Category I and II patient kits for the entire TB

Figure 5. Level of Centralization of Drug Funding in the Public Sector, HBCs



42 Discussions with national TB control officials in each country.

control program and local governments generally fund drug purchases for Category III patients.

In South Africa, provincial governments hold primary healthcare budgets, a portion of which are allocated to drug purchases for the public sector. Although drugs are tendered at the national level, the actual amount that is set aside for TB drug purchase is determined at the provincial level.

4.1.1 Financing for Second-line TB Drugs

Systems that support second-line TB drug financing are in their infancy in many countries. However, as the incidence of MDR- and XDR-TB becomes a growing concern, an effort has emerged to include second-line coverage as part of national TB control programs. At the writing of this report, only Brazil and South Africa had established funding for second-line medicines under their national TB control programs. The remaining countries studied have only recently begun pilot programs or have plans to initiate them over the next year.

In India, the RNTCP has begun a pilot program to include second-line drugs. The program, which funded treatment for 100 patients for 2006,[43] is expected to grow rapidly—although funding sources are in the process of being confirmed.

The Philippines has received GFATM funding for its pilot MDR-TB program. In 2005, the GFATM Round 2 grant provided funds to treat 250 patients through the GLC. Another 2,500 patients are expected to be treated between 2007 and 2011 with funds provided in the GFATM Round 5 grant.

Funds from a GFATM Round 5 grant will allow China to launch two pilot programs to treat approximately 4,000 patients, with plans to expand the number of projects to include 115 counties in six provinces by 2011.

Table 3. Procurement Mechanisms in HBCs

COUNTRY	PUBLIC TENDER[45]	GDF	GLC
Brazil[46]	●		
China	●		
India	●	●	
Philippines	●	●	●
South Africa	●		

4.2 Public Drug Procurement

4.2.1 Public Tender Process

Table 3 illustrates the modes of procurement in the public sector for each HBC included in the study.

Most of the public markets in the HBCs studied procure drugs through a bid and tender process. For second-line products, there may also be a direct negotiation between the governments and suppliers. The national TB control program (or a related agency within the government) determines the approximate volume of drugs that are needed by the public sector for the period of the tender contract, requests bids from drug manufacturers and selects suppliers who agree to provide drugs for a preset period of time, at a price determined in the bidding process. With the exception of South Africa,[44] all tender contracts in the HBCs studied are bid annually.

Although tenders are open to both national and international suppliers, nearly all of the countries included in the study prefer to source their drugs from locally-based companies when possible. Only two of the countries studied, India and the Philippines, use the GDF. In India, the GDF supplies approximately half of the drugs used by the public sector and in the Philippines, the GDF supplies all treatments for smear positive and re-treatment cases.

Moreover, with the exception of China, tenders in the five HBCs studied are administered at a national level, even if the financing for drugs comes from provincial budgets. In China the tendering system is split between the national and the provincial levels, depending on the origin of funds. If the Chinese government or external funders are providing the resources, the tender is administered by the national government. When provinces are providing the funding, tenders are issued by the provincial health ministry.

In most cases, before a drug manufacturer can participate in a bid and tender process, it must be pre-qualified or meet a number of criteria set by the tender administrator. One commonly used criterion is whether a manufacturer is local to the country issuing the tender. Most of the countries studied preferred to source their drugs from local companies when possible. Procuring drugs directly from local suppliers often offers national TB control programs and governments the benefit of lower prices, as is the case in China and India.

43 The program is administered in the states of Gujarat and Maharashtra with the first cohort scheduled to begin in early 2007. The LRS Institute in Delhi also has had a small self-funded program with approximately 150 patients.

44 South Africa bids on a bi-annual basis.

45 For some second-line drugs, procurement is done through direct negotiation with suppliers rather than through a tender process.

46 In 2005 due to internal manufacturing problems, Brazilian national suppliers were unable to meet the total demand for first-line TB drugs, and were assisted by PAHO. Generally, Brazil produces 100 percent of its national drug supply.

However, procuring drugs locally does not always result in cost-savings. The publicly sanctioned TB treatment regimens in other countries studied, notably Brazil, the Philippines and South Africa, actually cost more than similar regimens offered on the global market or through the GDF. The cited rationale for procuring drugs at these higher prices was a desire to support local industry as well as ensure the quality and safety of products. Some of the HBCs studied have turned to international competitive bids or the GDF for their drug procurement needs when quality or sufficient volumes could not be assured by local suppliers, or because of donor preference.

While some elements of the pre-qualification of suppliers were similar among the HBCs studied, other criteria used in manufacturer pre-qualification varied widely. For example, in India, potential suppliers must have WHO-GMP certification, meet a minimum threshold of annual revenues, and demonstrate prior experience in manufacturing large quantities of TB drugs.[47] In China, manufacturers must be certified by the State Food and Drug Administration before they can submit bids in the public tender. In Brazil, the invitation for bids in the public tender is issued only to state and military laboratories.

4.2.2 Demand Forecasting

Ensuring a continuous supply of drugs for patients is an important aspect of TB control. Each of the HBCs studied has developed different strategies to ensure that sufficient supplies will be on hand for patients even in the event of manufacturing delays or emergencies. These strategies typically require an assessment of the rate of TB drug utilization, anticipation of needs for the upcoming tender period, and the maintenance of a "buffer stock" at each level of the supply chain. This demand forecasting is usually conducted at the level at which the tender is being administered.

Demand forecasting is usually performed by a person or division within the national TB control program, as is the case in Brazil.[48] Every year, the Brazilian Ministry of Health forecasts the needs of the program for the following year using figures from state reports that are based on projections by each municipality. The ministry then augments these figures with a buffer stock of 25 percent. Similarly, in China, forecasting is conducted by the Statistics and Surveillance Office within the National Center for TB Control and Prevention. The TB prevention institutes at the county, prefecture and provincial levels report the supply and distribution of drugs — as well as the number of new patients detected — to the national government, which uses those figures to forecast the demand for the entire program and allocations of drugs for each province. In India, forecasting is conducted by the Central TB Division and the Ministry of Health and Family Welfare with the assistance of a private agency called Strategic Alliance. All levels of the TB control program are required to submit standardized reports that indicate patient numbers, inventory levels, and drug-utilization rates. These reports feed into the forecasting process, which determines the drug supply needs of the program at national, regional, and local levels.

In South Africa, by contrast, forecasting is not performed by a person or agency dedicated solely to TB control.[49] Because TB control in South Africa is integrated into the general primary care system, a division within the Ministry of Health called Pharmaceutical Planning and Policy forecasts demand for nearly all drugs used in the public healthcare system. This division also negotiates supplies of certain second-line TB drugs whose volumes do not warrant a public tender. Using historical utilization reports from provincial government depots, this agency determines the annual need for the entire healthcare system and inserts these figures into the public tender. However, the actual ordering of the drugs during the tender contract period is performed by the provincial depots that serve as the first point of delivery. Once the price is set by the national tender, the responsibility for procurement falls at the provincial depot level, which is responsible for contacting manufacturers to place orders and providing payment.

In the Philippines, tracking patients and forecasting supply are done through a bottom-up approach. Local health sites report to rural health units, which report to the provincial and regional levels. Data are collected at the national level, analyzed at the DOH, and used for funding allocation, future planning and policy development.

4.2.3 Distribution Pathways

Public distribution systems for drugs within the countries studied are quite diverse. However, quality assurance was identified as a challenge faced by all

47 As noted in Section 2.1.3 GMP refers to Good Manufacturing Practices. Additional information available on the WHO website at www.who.int/medicines/areas/quality_safety/quality_assurance/gmp/en/index.html.

48 Stakeholder discussions with Brazil MOH and NTP, 2006.

49 Stakeholder discussions with South Africa MOH and NTP, 2006.

programs. Accordingly, each country has a series of checkpoints to test the quality of drug orders before they are released to other parts of the supply chain.

In the countries studied, quality testing is usually first conducted at the production site. Once an order has been manufactured and is ready for delivery, the agency that has placed the order is notified. A sample of the batch is sent to a laboratory—either a government laboratory or a private laboratory that has been contracted by the government—and is tested before the order is shipped. If the results of the batch test indicate that the order is not of sufficient quality, follow-up tests are conducted to confirm the results of the initial test. During this time, the order is held at the manufacturing site. If negative results are confirmed, an order is frozen and manufacturers are required to replace the product. If the results of a secondary batch test are satisfactory, the order is released for distribution and delivered to an initial point of delivery—usually a government depot—where the final packaging of drugs is conducted if necessary. An additional batch test may be conducted at this level before the order is shipped, either to other depots or the various healthcare facilities where products are distributed.

TB drugs purchased by the public sector tend to flow through a series of public depots or warehouses before reaching the facilities that administer them to patients. The frequency with which drug orders are submitted and shipped varies by country. The countries studied follow one of two models of distribution: the push system or the pull system. Figure 6 represents how drugs are ordered and distributed in the public sector though the push and pull systems.

Under the push system, drugs are ordered by one central agency or division and then "pushed" or delivered at regular intervals to other parts of the supply chain. This push system is found in most provinces in China. TB medicines flow to facilities at pre-specified supply levels and arrive at facilities at regular intervals, typically four times a year.

In the Philippines, drugs to treat Category I and II patients flow through a push system and are delivered twice a year to a port of entry, with supplies sent to regional warehouses on either a monthly or quarterly basis. Second-line drugs are also ordered on an intermittent basis by the Tropical Disease Foundation for distribution in its facility.

Under the pull system, the flow of drugs is driven primarily by orders from depots and/or facilities further along the supply chain. Countries operating on such a model include Brazil, the Philippines (for Category III drugs) and South Africa. Through this system, bulk supplies of drugs are ordered by and held in regional depots until they are requested by facilities. Orders may vary widely in size and frequency, depending on the needs of the facility or depot.

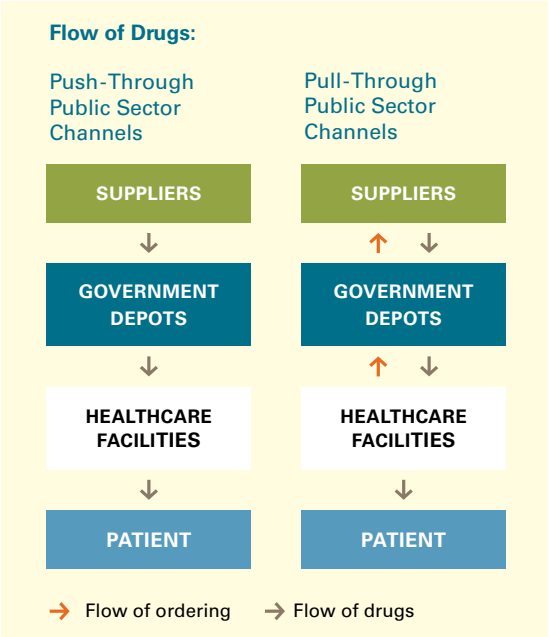
India has a hybrid system through which the central unit procures drugs and determines annual requirements for the country as a whole. The amount supplied to states and districts is determined based on monitoring of drug stocks.

4.3 Private Drug Procurement: First- and Second-line Drugs

In Brazil, China and South Africa, the distribution of TB drugs in private facilities or pharmacies is either discouraged or prohibited for quality control reasons.

In India and the Philippines treatment in the private sector is utilized by a broader segment of the population. In these countries, the private sector plays a significant role in the procurement and distribution of TB drugs.

Figure 6. Flow of Drugs Through the Public Pull vs. Push Systems in High Burden Countries



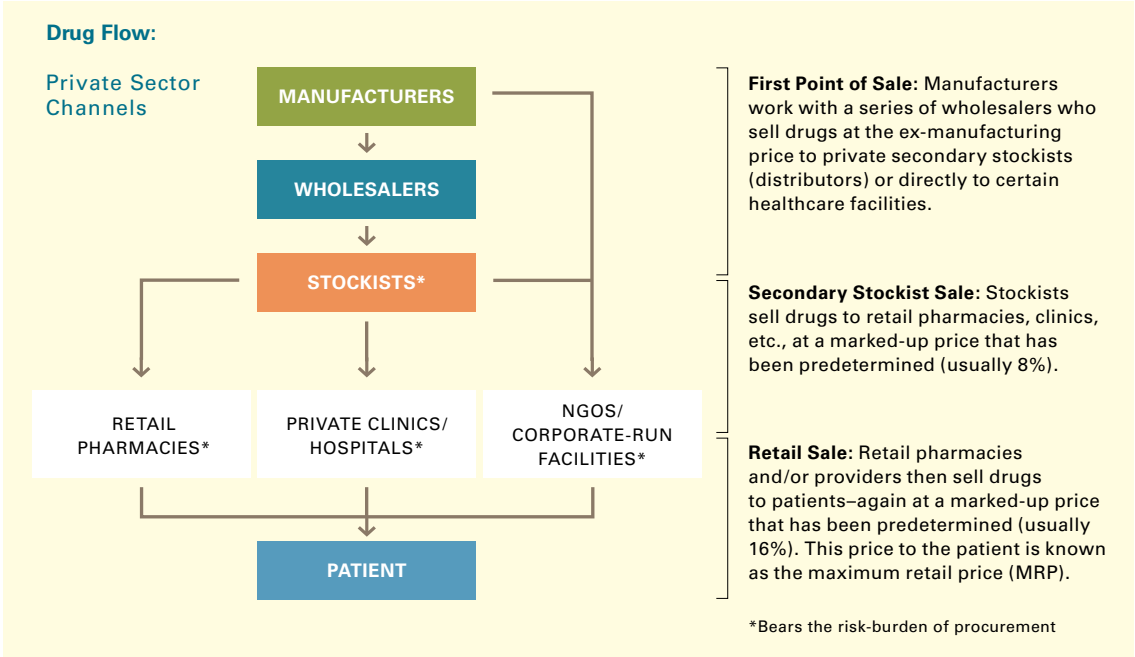
The flow of drugs in the private sector is quite different from that of the public sector. In India, for example, treatment in the private sector is not free of charge, though prices are relatively low and often controlled. Patients in the private sector are more likely to receive a prescriptions or are advised to purchase certain TB drugs rather than be administered medication in a facility. If this is the case, a patient must obtain drugs from a retail pharmacy,where they are paid for either out-of-pocket or through funds from an insurance plan, if the patient has one. As in India, in the Philippines, patients may approach a pharmacy directly and purchase TB medicines without a prescription. Patients may also visit a doctor who provides an initial supply of medication and a prescription to obtain drugs from a retail pharmacy, where they are paid for out-of-pocket.

Another difference between the private and public sectors is in the decentralization of distribution. For example, in the private sectors in India and the Philippines, manufacturers often sell their products to several wholesalers who resell those drugs to the many retailers throughout the country. Most procurement and distribution is performed either by large and complex networks of massive pharmacy chains or by "mom-and-pop" pharmacies that serve specific regions.

Another significant difference between the private and public sectors in India and the Philippines is the manner in which drugs are priced and procured. Rather than using a bid and tender process for price setting, manufacturers set a price at the launch and negotiate volume discounts or rebates on an individual client basis. Wholesalers or distributors purchase drugs from manufacturers at an "ex-manufacturing" price. They then sell their drugs to retail pharmacies or facilities at a marked-up price. These facilities subsequently sell drugs to patients at a Cmargin. As an example, Figure 7 describes how drugs most commonly flow from manufacturer to patient in India's private sector.

Although the structure of private-sector procurement and distribution was fairly similar among the countries studied, the number of "middle-men" who process drug orders, and the price mark-ups these intermediaries charge, vary widely. Private-sector prices and mark-ups in India and South Africa are highly regulated, although additional margins may sometimes be negotiated through volume discounts and rebates. Figure 7 describes the private sector price mark-up structure in India and the average mark-up at each stage of the drug-flow process. In other countries, notably China, the mark-up structure is so unpredictable that it would be misleading to state definite numbers.

Figure 7. India Private-Sector Mark-Up Structure



5. Procurement and Distribution of TB Drugs in High Income Countries

5.1 Financing of TB Drugs

As noted in Section 3.1.2, TB control in the high income countries studied is not a separate program but rather an extension of the existing healthcare system. Financing of TB drug treatment follows the same financing patterns as that of other drugs.

5.2 Procurement of TB Drugs

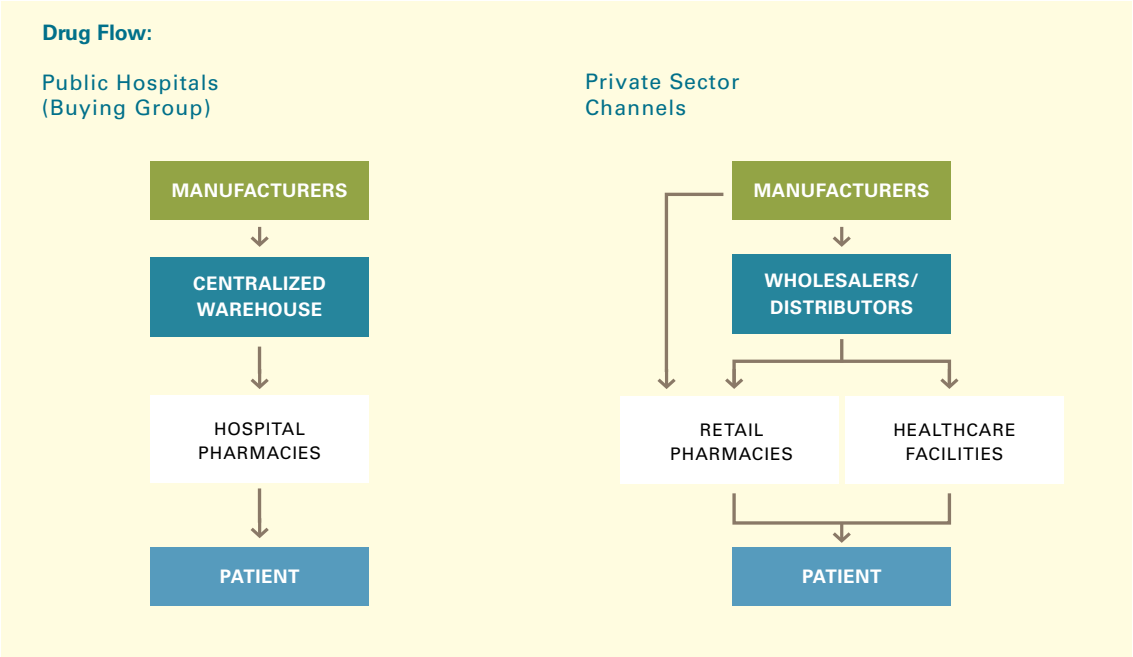
While procurement of TB drugs in the public sectors of the HBCs studied is mostly centralized, it is decentralized in the public sectors of high income markets. In some cases, drugs are priced through a public tender system. For example, in the UK, any orders valued at or above £100,000 (US$197,000) must be priced though public tender by the primary care trusts.[50] In France, each individual hospital negotiates price and order supplies directly with the wholesaler. The only exception to this is for hospital buying groups in Lyon and Paris, the two largest cities, which may use purchasing collectives to negotiate volume discounts. However, most frequently, the prices of drugs are directly negotiated by funders (e.g., private insurance plans in the US) and/or wholesalers that supply healthcare facilities and retail pharmacies.

The distribution of TB drugs in high income countries operates almost entirely by the pull system.[51] This is likely because the volume of TB drugs needed is small and the procurement and distribution systems are often decentralized. In these markets, the volume and frequency of drug orders are determined on a real-time basis and buffer stocks are kept at small levels, if at all. Furthermore, the pull system is easily supported by the infrastructures in high income markets. Facilities and retail pharmacies often have electronic stock maintenance programs that provide alerts when new products need to be ordered. The small size of orders and the ease of transportation allow facilities and retail pharmacies to quickly replenish their stocks, if necessary.

5.3 Flow of Drugs

The distribution of drugs in high income countries also differs significantly from that in HBCs. Unlike the HBCs studied, which maintain completely

Figure 8. Comparison of Typical Drug Flow in High Income Countries



50 Primary care trusts are responsible for setting healthcare budgets for all NHS Hospital Trusts and general practitioners (GPs) in their area and allocating resources across settings.

51 In the US, some states also use a push system, with the state providing free supply and distribution of drugs to regional or local health units.

separate distribution routes for the public and private sectors, TB drugs in the high income markets studied flow through overlapping distribution routes, regardless of how the drugs are funded. Rather than passing through a series of government depots, TB drugs in the high income markets flow through the same channels as any other legal medicines — from manufacturers to wholesalers, to facilities or retail pharmacies, and finally to patients. In some cases, drugs may flow through a centralized warehouse that serves a region or purchasing group. For example, in Paris certain hospital retail pharmacies are permitted to consolidate their orders. Figure 8 on the previous page provides a comparison of the typical flow of TB drugs through centralized warehouses vs. wholesalers in high income countries.

6. Cost of Treatment of TB in Both High Burden and High Income Countries

6.1 Prices of TB Drug Regimens

TB drug prices in the public sector can vary significantly by country based on supply sources used and the process through which drugs are procured. In the HBCs studied, and in some cases France and the UK, procurement of drugs in the public sector is administered through a public bidding process in which manufacturers bid to supply TB medicines. Price is thus determined as part of the bidding process. In other countries, prices may be negotiated by each facility, either with wholesalers or directly with manufacturers.

Prices also vary because supply sources differ by country. For instance, in China and South Africa, local manufacturers are utilized as a result of the bidding process. In Brazil, raw materials are procured through a bidding process and drugs are produced by state laboratories. In the Philippines, the NTP procures from the GDF and prices are established during the GDF/manufacturer bidding process. Additional drug supply in the Philippines is procured by local government units from local and multinational manufacturers, through which drug prices are significantly higher. In India, the NTP procures from a combination of local suppliers and the GDF. Examples of how prices for various TB drug regimens can vary between the countries studied are illustrated in Tables 4 and 5 on the following page.

6.2 Public and Private Pricing

Prices of drugs also differ significantly between the private and public sectors in both burden and high income countries. In the HBCs studied that have sizeable public and private TB sectors (i.e., India and the Philippines), drug procurement in the private sector is more expensive than in the public sector. This is likely due to supply sources — for example, whether drugs are procured from the GDF, from local manufacturers, or from multinational drug manufacturers. Differences in drug procurement costs between the public and private sectors also stem from the varying procurement processes. These include national bidding, local bidding, or direct negotiations with manufacturers. Moreover, price mark-ups occur regularly along the supply chain in private-sectors.

Tables 6 and 7 on the following page provide examples of the costs of various TB drug regimens in the public vs. private sectors in India and Philippines. In the Philippines, prices differ because the public sector is able to utilize the GDF and obtain direct supply at a low negotiated price. Private sector drug procurement operates through the traditional pharmaceutical pathway and faces additional mark-ups that occur along the supply chain.

In the public sector in India, drugs are procured through two major pathways, the RNTCP and the non-RNTCP. The RNTCP utilizes the GDF for about 50 percent of patients. For the other half, the RNTCP obtains drugs through a centrally-administered bid and tender process to choose manufacturers and drive down costs. The few public facilities that

Table 4. Select Public-Sector Prices in HBCs[52]

	CATEGORY I	CATEGORY II	CATEGORY III	SOURCE
Brazil	$41 (Scheme 1)	$69 (Scheme 1R)	$62 (Scheme 2)	Drugs traditionally produced internally through state, military or national laboratories.
China	$8-17	$14-27	$8-11	Sourced from national manufacturers. Procured through competitive bidding process. Prices differ based on bid (central, JICA or WB funds).
India	$10	$18	$8	GDF (loose drugs)
Philippines	$18	$33	$18	Categories I and III procured by the national TB program from GDF (patient kits and FDCs); Category II procured from local government units and patients from local manufacturers.
South Africa	$47	$127	$47	Sourced from multinational manufacturers with production facilities in South Africa (Sanofi-aventis and Sandoz).

Note: In South Africa, smear negative and extrapulmonary are treated as Category I.

Table 5. National TB Control Programs Public Sector Prices in Studied High-Income Countries[53]

	ACTIVE	SOURCE
France	$270.92	Local and Multi-national manufacturers
UK	$489.83	Local and Multi-national manufacturers
USA	$409.79	Local and Multi-national manufacturers

Table 6. Private vs. Public Costs of a Full Course Treatment in the Philippines (Drugs Only)

	TREATMENT CATEGORY	COST OF DRUGS IN THE PRIVATE SECTOR ($)	COST OF THERAPY USING GDF PRODUCTS ($)
Philippines	Category I	$135.36	$17.89
	Category II	$315.84	$32.50
	Category III	$135.36	$17.89

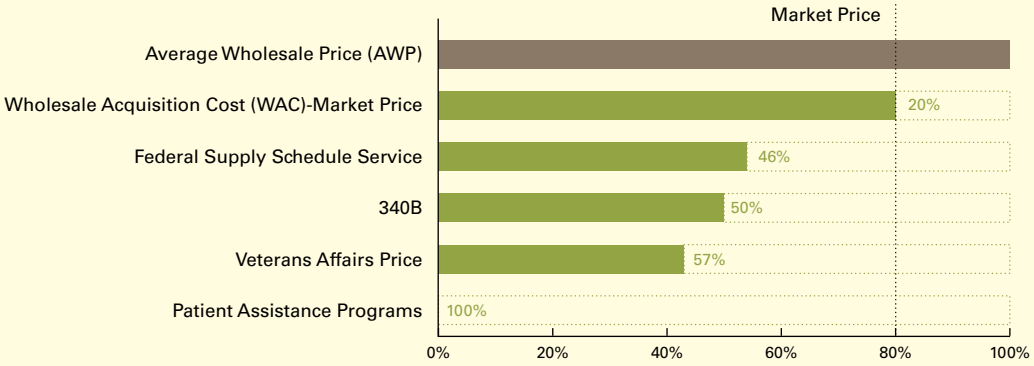
Table 7. Private vs Public Cost of Full Course of Category I Treatment in India (Drugs Only)

	TREATMENT CATEGORY	COST OF DRUGS IN THE PRIVATE SECTOR ($)	COST OF THERAPY USING GDF PRODUCTS ($)
India	Category I	$135.36	$17.89

Note: All amounts in US$.

52 Prices refer to cost of full drug treatment regimen.
53 Prices refer to cost of full drug treatment regimen.

Figure 9. Prices in the US Across Different Settings[54]



are not procuring their drugs through the RNTCP negotiate directly with manufacturers to obtain the lowest price possible, or through a bid and tender process similar to that used by the RNTCP. Private market drugs are purchased through wholesalers, stockists and retailers and face high mark-ups at each level.

Prices for TB drugs in the US — the only high income country studied with a sizable private TB market — differ based on whether payers are private insurance companies or a publicly administered program such as Medicaid. In the private sector, manufacturers set a list price and insurance plans negotiate with manufacturers for rebates. However, in the public sector prices are partially set by the federal government. The government's price level is required to be set at or below the best price offered to commercial plans which is typically at or below the Wholesale Acquisition Cost (WAC) price, and manufacturers bid at that price or less for government business. As a result, prices differ across different settings, as shown in Figure 9.

7. Value Estimates For First- and Second-Line TB Drugs

A key objective of *Pathway to Patients* was to collect sufficient data to project a global estimate of the market for first-line TB drugs, based on the value of the TB drug market in each of the countries studied.

This section describes the first- and second-line TB drug market value estimates calculated for each of the ten countries studied and on a global aggregate level. A brief description of the methodology used to determine both the country and global estimates is provided, as well as information on each high burden and high income country. Value estimates for first- and second-line drug markets are provided by country and, where available, patient volume numbers are also included. Finally, based on an extrapolation, the study estimates the global market value for first-line TB drugs. Because MDR-TB patient regimens vary significantly, it was impossible to quantify treated MDR-TB patients and estimate a global market value for second-line TB drugs.

7.1 Overview of Methodology

The methodology used to determine the value of the TB drug market in each country included in *Pathway to Patients* varied according to the data available. The value of the public markets was in most cases sourced directly from discussions with stakeholders — usually government officials or key funders — or from financial reports issued by NTPs. For South Africa, figures for the public sector were sourced from the two suppliers chosen through the government tender. When reliable patient figures and

54 *States, and the 340B Drug Pricing Program*, 2006 edition. Average Wholesale Price (AWP) defines the list price published in RedBook, currently used only as a reference to negotiate discounts. Wholesaler Acquisition Cost (WAC) is typically at 20 percent below AWP; usually referred to as the market price. Federal Supply Schedule Price, VA Price, and 340B are all set discounted prices calculated based on Medicaid best price available for all federally covered entities.

drug prices were available, a bottom-up calculation was conducted to validate top-line figures.

Private-sector figures were sourced from IMS Health databases and segmented by product into the first- and second-line market. Because preliminary analysis of first-line prescription data indicated that almost all first-line drugs for TB were used exclusively for TB treatment, figures for these drugs were left unadjusted. However, prescription data—available for most countries in the study—were used to adjust second-line figures.[55] The percentage of prescriptions written for TB for each drug was multiplied by the top-line sales figure for the drug to calculate the second-line TB drug market value.

For more information about the specific methodology used to determine the market estimates for each country and the global estimates, including individual drug cost figures and a list of the countries included in the global extrapolation, a separate methodology document is available online at www.tballiance.org.

7.2 Country-by-Country Estimates

For the ten countries studied, public and private sector value data for first- and second-line drugs were determined using IMS and program data (see Table 8). First-line value is defined as the total value of the first-line regimen (rifampicin, isoniazid, ethambutol, and pyrazinamide). Volume is defined by the number of patients, rather than units, since regimens may vary by country and actual adherence may differ as well.

Estimating patient volume in the private sector is extremely challenging because treatment regimens offered may vary significantly and actual adherence is unknown. Therefore, estimates on private-sector volume were not considered reliable enough to include in this report.

However, the total value of the second-line market in the public and private sectors in the countries studied was calculated. In the instances where volume data are collected for second-line patients in the public sector (e.g., Brazil and the Philippines), volume calculations were developed for the second-line market. For the private sector, volume was not calculated because of significant variation in treatment regimens and adherence. Such variation rendered estimates too uncertain to yield a confident

Table 8. First- and Second-Line Market Values in Each Country Studied

	FIRST-LINE PUBLIC	FIRST-LINE PRIVATE	SECOND-LINE PUBLIC	SECOND-LINE PRIVATE
Brazil	$4.9 million	NA	$5.0 million	NA
China	$20 million	Unknown*	NA	$25 million
India	$24.25 million	$61.2 million	Unknown**	$8.4 million
Indonesia	$5.75 million	$8.96 million	NA	$2.7 million
Philippines***	$2.16 million	$28.9 million	$58,600	$13,100
South Africa	$18.31 million	$940,000	$1.71 million	$850,000
France	$3.6 million	NA	$4.0 million	NA
Japan	$11.3 million	NA	$1.99 million	NA
UK	$4 million	NA	$4.5 million	NA
US	$16.2 million		$4.01 million	

* China first-line private market sales could not entirely be extricated from public sales, so exact figures are not available at this time.

** Some of India's public-sector facilities may procure second-line drugs directly, but figures for such sales were not available. Interviews suggest that such purchases are unusual.

*** Figure does not include Category III drugs, which are procured primarily by Local Government Units. The estimated value of Category III drugs is US$908,865.

Note: All figures in US$. NA = not available

55 Not available for China or the Philippines.

global second-line value projection. Following are TB drug market value estimates for the ten countries studied (See Figure 10).

BRAZIL

The Brazilian TB drug market is valued at approximately US$10 million, all of which is accounted for in the public sector. The value of the total market is nearly evenly split between first-line drugs (US$4.9 million) and second-line drugs (US$5 million). However, due to the much higher cost of second-line treatment, the first-line market is much larger in terms of patient volume. There are approximately 115,000 first-line TB drug recipients in Brazil and only 5,000 patients who receive second-line drugs.

CHINA

The combined first- and second-line TB drug market in China is valued at US$45 million. The first-line market is predominantly a public market.

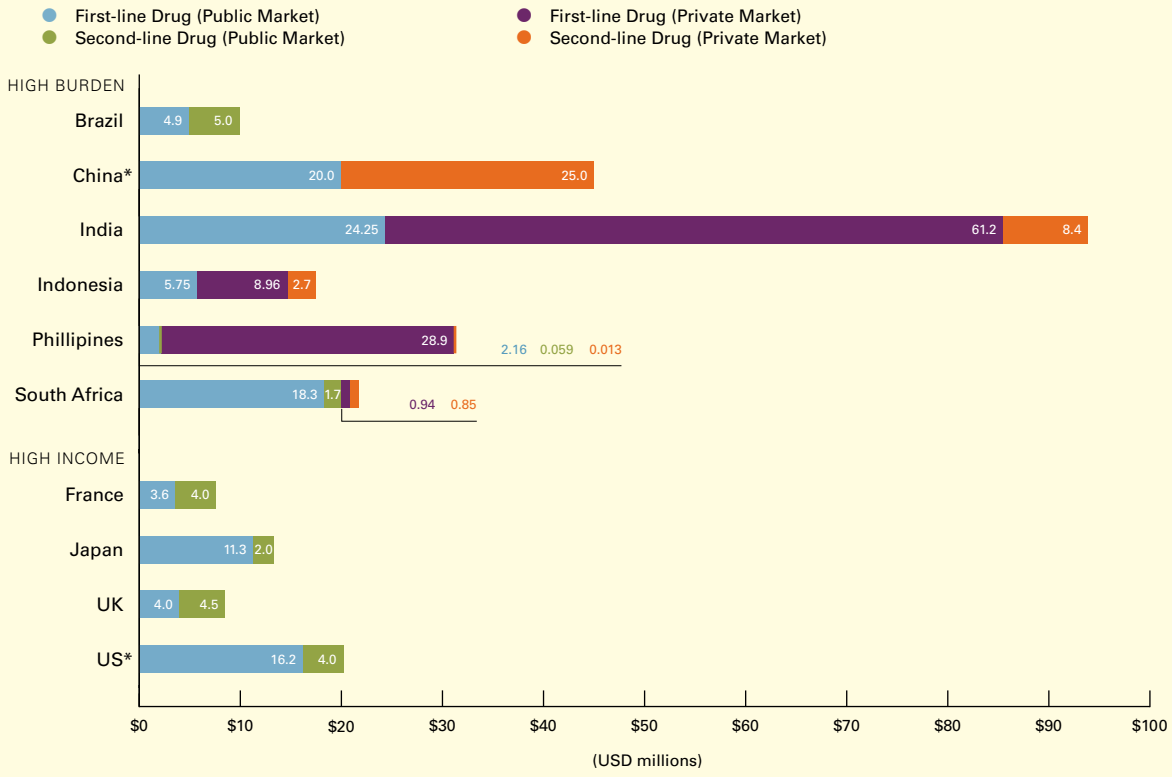
Public-sector reports from 2005 indicate that 789,189 patients were treated and approximately US$20 million was spent on first-line drugs. The total value for first-line drugs procured through national tenders was approximately US$10.8 million. An additional US$8.9 million accounts for drugs funded locally. This includes expenditures by both the private and public sectors, though research indicates that the majority of "locally procured" drugs are financed by the public sector.

Unlike the first-line market, the second-line market in China is exclusively private. Its value is approximately US$25 million.

INDIA

The total TB drug market in India is valued at approximately US$94 million, about 74 percent of which is represented in the private sector. India's market is predominantly first-line, valued

Figure 10. First- and Second-line TB Drug Market Value by Country



* Although exact figures are unknown, the majority of first-line treatment is financed by the public sector. In the US, this is also true for second-line treatments.

at US$85.45 million, with both public and private payers. Payers representing the public sector, which initiates treatment in 1.5 million patients per year, purchase approximately US$24.3 million in TB drugs. The private sector, whose patient numbers cannot be estimated with accuracy, accounts for the remaining US$61.2 million.

As is the case in China, the second-line market in India is found only in the private sector, though spending by the public sector in this area will begin to increase in the next three to five years as DOTS-Plus pilot projects are implemented. The second-line market is currently valued at US$8.4 million.

INDONESIA

The total Indonesian TB drug market is valued at US$17.4 million, about two thirds of which is spent in the private sector (US$11.7 million), and a third of which is spent in the public sector (US$5.75 million). As in other HBCs, first-line drugs account for most of the market, with sales figures at approximately US$14.7 million, or 85 percent of the total. The first-line market is split 61 percent and 39 percent between the private and public sectors, respectively.

Indonesia's public program does not distribute second-line drugs at this time. The second-line market is entirely private and has an estimated value of US$2.7 million.

PHILIPPINES

As in India, the value of the TB drug market in the Philippines is predominantly private. The value of the combined first- and second-line market is approximately US$31.13 million, 93 percent of which is accounted for in the private sector. The first-line market, valued at US$31.1 million, is almost entirely private. The public sector, in which about 135,000 patients are treated per year, accounts for US$2.16 million per year. This figure does not include Category III drugs, which are procured primarily via public tender by Local Government Units (LGUS). The estimated value of Category III drugs is US$908,865. The second-line market, which accounts for less than US$100,000 per year, is dominated by public-sector expenditures (approximately US$58,600). Presently, the private sector only spends approximately US$13,100 per year on second-line drugs. However, treatment of MDR-TB is expected to grow over the next five years.

SOUTH AFRICA

The value of the South African TB drug market is estimated at approximately US$21.8 million, nearly all of which is spent in the public sector on first-line drugs. Of the US$19.25 million first-line market in South Africa, almost 95 percent (US$18.31 million), is purchased in the public sector. Proportionally, the private sector plays a larger role in the second-line market, representing about one third, or US$850,000, of the US$2.56 million market.

HIGH INCOME MARKETS

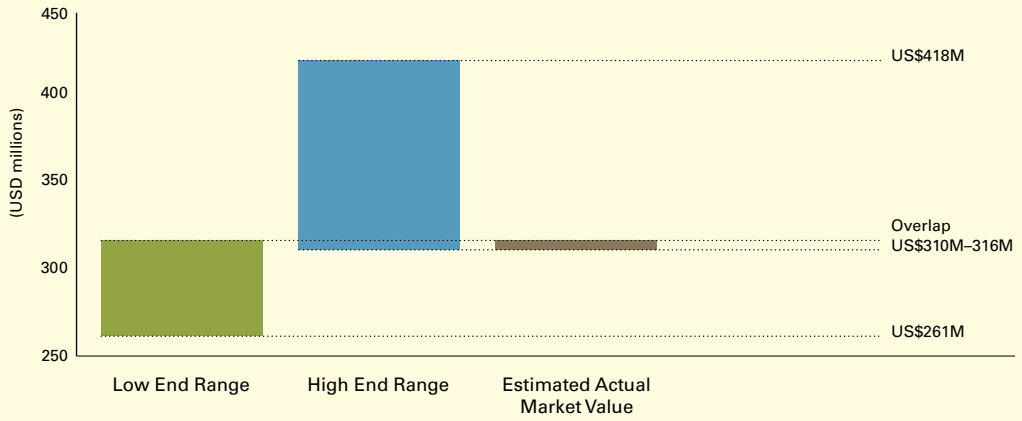
Sales and patient figures for the high income markets studied in *Pathway to Patients* were more easily accessed than data for HBCs. However, pricing of treatment regimens was difficult to ascertain, which made it difficult to validate through bottom-up calculations.

Of the high income countries studied, Japan had the highest incidence of TB infection. In 2004, there were approximately 30,000 newly registered cases and the percentage of patients with MDR-TB was less than one percent. The value of the Japanese drug market, which is entirely public, is estimated at US$13.3 million, with US$11.3 million representing the first-line market.

The French and British TB drug markets are also entirely public and are valued at approximately US$7.6 million and US$8.5 million, respectively. The market value in France is split between first-line treatment (US$3.6 million) and second-line treatment (US$4 million). As in France, the total British TB drug market is split between first-line treatment (US$4 million) and second-line treatment (US$4.5 million).

The US reported approximately 14,000 new cases of TB in 2005, less than one percent of which were MDR-TB. The total US market value for TB drugs is approximately US$20.21 million, 82 percent of which is represented by first-line treatment (US$16.2 million) with the remaining US$4.01 million representing second-line treatment.

Figure 11. Global Estimate Ranges of First-Line TB Drug Market



Low end range defined based on case notification approach; High end range based on incidence.

7.3 Global Estimates

First-line treatment

As noted earlier, the six high burden countries studied represent approximately 60 percent of TB disease in the 22 high burden countries and all ten countries studied account for approximately 50 percent of the total global TB burden.

Researchers were able to extrapolate the first-ever estimate of the global market based on original research by using the data of the countries studied to yield the following projections on a worldwide scale:

1) A low end estimate, based on DOTS notification rates (actual number of cases reported each year) and a range of actual and average price per patient regimen costs, suggests that the value of the global first-line market is between **US$261M–316M**.

2) A high end estimate, based on the WHO's global incidence figures (total projected number of new cases) and a range of actual and average price per patient regimen costs, suggests that the value of the global first-line market is between **US$310M–418M**.

Assuming that current case notification rates do not always reflect the full number of patients being treated, and that incidence rates reflect the absolute maximum number of patients that can be treated, the overlap of the two ranges is the closest estimate of the actual first-line market, indicating that the total value of the global market for first-line TB drugs is approximately **US$315M** (see Figure 11).

Second-line Treatment

The study found that a number of factors prevent making a similar, global estimate of the second-line TB drug market. According to the Stop TB Partnership's Global Plan to Stop TB 2006-2015, less than two percent of estimated culture positive MDR-TB patients are treated appropriately. Cases of MDR-TB are not consistently reported, particularly if they are not treated in the public sector. There are a number of potential treatments included in second-line regimens, and there is variance in prescribing practices, length of regimen as well as adherence rates. Similarly, costs also vary dramatically across countries and there is no realistic "average cost" for second-line regimens. Therefore, researchers felt it is inappropriate to apply the methodology used to project the first-line global estimate to a second-line worldwide estimate.

However, looking only at the ten countries studied, the research found that the estimated value of the second-line TB drug market in those countries is approximately US$54M.

8. Additional Considerations

Pathway to Patients provides in-depth insight into issues that affect the dynamics of today's TB drug market. These findings help map factors that will have direct and indirect impact on market dynamics between now and the time novel drug regimens are approved and ready for introduction into the global marketplace. However, this analysis also suggests the need for additional research or explanation.

Quality of TB services, programs and processes

As mentioned in the introduction, this research did not review or address the quality of TB services or the procurement and distribution in the countries studied. Instead, it sought only to describe them. Issues related to the degree to which those systems function effectively — such as whether the quality of care is effective, whether patients are receiving DOTS, whether demand forecasting is accurate, or whether adequate levels of buffer stocks are always on hand — were not addressed.

TB control programs in decentralized systems

The characterization of the TB control programs of highly decentralized healthcare systems, such as those found in China and South Africa, would benefit from additional study. In those countries, the implementation of TB control varies widely from province to province and a more robust analysis of each program, including a region-by-region study, was not possible within the time constraints of this project. Future studies of such programs should include a comprehensive regional analysis to ensure that the nuances of local variation are captured.

Data discrepancies regarding value and volume estimates

In most cases, the different data sources from which figures were pulled either corroborated with one another or could be checked with an alternative calculation. However, in a few instances, such as in China, stakeholder discussions yielded numbers that did not align, and/or researchers were unable to triangulate on the actual figures through a bottom-up calculation. A systematic audit of each of the sources used would help to further refine estimates in future market sizing attempts.

Market segmentation of private-sector data

The segmentation of private-sector data into first-line and second-line markets also posed a challenge. In most countries, IMS Health private-sector databases are aggregated by product and not indication, so the first-line market includes drugs that are used in second-line treatment and vice versa. Therefore, available prescription data did not always allow researchers to distinguish between the first- and second-line use of any given drug. Improved ability to allocate each drug's sales and volume to its respective use might change the characterization of the market.

Lack of estimates for private-sector patient volume

Estimating the patient volume in the private sector was not possible. The reasons stemmed from variations in treatment regimens, lack of information about adherence, and lack of data available regarding flow of patients between private and public sectors. A survey of prescribing practices and adherence in HBCs with a significant private sector would allow for the development of a relatively reliable volume estimate for each country.

Inherent imprecision in extrapolating

Finally, while the market estimates of the countries included in the scope of the research provided the basis for extrapolation to other countries, it is clear that such comparisons are not a perfect proxy. For instance, Russia's grouping into the HBCs was based on its TB incidence, but the prices of its TB drugs are significantly higher than in other HBCs. The "rest of world" extrapolation also has a degree of uncertainty. Drug prices for countries in the "rest of world" category were also determined based on information from HBCs studied. Thus, more specific pricing and utilization information from these countries would allow for a more exact estimate.

9. Predicting Future Market Dynamics

Understanding the structure of the TB drug market, including procurement and distribution systems in high burden countries, is essential for planning the introduction of new TB drug regimens.

Potential Market Changes

This study provides in-depth insights into issues that affect the dynamics of the TB drug market today and helps map factors that will have direct and indirect impact on these dynamics between now and the time novel drug regimens are approved and ready for introduction into the global marketplace. The analysis also suggests the need for additional research into a number of evolving factors that may alter the flow of TB drugs, highlighting that a better understanding of all of this closer to the new products roll-out would facilitate adoption of and access to new TB drugs when they become available.

The Global Plan calls for expanded, equitable access for all to quality TB diagnosis and treatment by 2015. Therefore, efforts undertaken over the next decade to achieve the Global Plan, including the introduction of new tools to diagnose, treat and prevent the disease, along with policy and funding considerations, are expected to increase significantly the number of patients being treated for TB.

New Diagnostics

New, faster and more reliable diagnostic tools for TB are in the pipeline, and should begin to enter the market over the next several years. The Global Plan calls for point of care diagnostics by 2010 that will allow rapid, sensitive and inexpensive detection of active TB. Two years later, Stop TB envisions a diagnostic toolbox that will accurately identify people with latent TB infection and those at high risk of progression to disease. New diagnostics, once developed, should lead to increases in case finding that will result in an increase in demand for treatment.

New Drugs

The goal of the Global Plan is to have a new short (one–two months) TB regimen(s) by 2015. A number of trials are currently underway that could, by 2010, potentially shorten the regimen to three–four months. Shortened treatment with novel drugs offers the potential to enhance patient adherence, decrease default rates, curtail costs to the healthcare system and patients, and substantially improve outcomes for those infected, especially for patients co-infected with HIV and TB. If realized, these advantages are expected to increase the need and demand for new TB drugs.

The expansion of drug resistant TB worldwide is affecting market dynamics. This is expected to increase because countries are beginning to include treatment of MDR-TB and XDR-TB as part of their national TB control programs. Expanding the coverage of drug-resistant TB will increase the market demand for second-line drugs.

Patient access to novel therapies will require national and international adoption of new treatments and extensive "retooling" of TB programs to accommodate changes in the regimen. A number of elements, including cost, availability and ease of administration will have a direct impact on adoption of new therapies. Fully understanding these and other factors will be critical for implementation of new shorter regimens worldwide.

New Vaccine

While numerous factors lead to the potential of increased numbers of patients being treated, resulting in larger demand for TB drugs, others could lead to a longer-term decrease in market demand. Specifically, the Global Plan calls for a new, safe, effective and affordable vaccine to be available by 2015. The current vaccine is 85 years old, works only in children, and is not always effective. A new preventive vaccine that works to protect all age groups has the potential, if widely adopted and used, to provide a positive impact on TB control and, in the long-term, a significant reduction in the number of those requiring treatment.

It will be important to understand the potential effects of a successful vaccine on TB drug demand and the market. Further study of this interface will be possible when more is known about the profile of a new vaccine.

Policy Influences

Policy changes have the potential to increase the number of patients treated, thereby affecting the market dynamics and highlighting the need for

close monitoring of these changes in the years ahead. An example is China's recent decision to include treatment of smear negative patients as a part of its national TB control program, which adds patients and increases the amount of drugs needed by the public program. Similarly, the expansion of public sector funding for treatment of drug resistant TB in markets like India, China and the Philippines, albeit slow, will increase the number of patients receiving second-line drugs and, over time, will change the value dynamics of that market.

In the past 15 years, public sector TB programs have dramatically expanded in many high burden countries. In those countries with large private sector markets, like India and the Philippines, there is a slow trend of patients moving from private to public sector treatment, largely due to government implementation of WHO-recommended "public-private mix" programs. This could result in a decrease in the value of the private market, but an increase in value of the public tender market.

Funding Influences

With widespread commitment to the Global Plan and the introduction of new financing mechanisms and commitments by the UN, G8, and donor and high burden countries, it is expected that TB control programs will continue to expand and strengthen over the next ten years. However, the extent to which the drug market responds to this expansion will depend on a number of variables.

In the countries studied, most funding used for TB drugs, whether from the public or private sectors, comes from domestic sources. Some high burden countries, however, are dependent on external donor funding to enhance their national commitment, especially for second-line drugs and pediatric TB medication. New funding schemes, such as the Global Fund for AIDS, TB and Malaria (GFATM) and UNITAID, an international drug and diagnostics purchase facility, may offer increased access to second-line TB medications over time. Thus, markets — especially for second-line drugs — will continue to be susceptible to trends and changes in funding.

10. Conclusions

Pathway to Patients studied the TB drug marketplace in ten countries, providing a comprehensive understanding of country-specific data and an analysis of procurement and distribution systems in eight of these countries and at the global level. The study points to the variability of the market dynamics among the countries studied, the complexities of the issues faced, and the fragmented nature of the market.

The Market

The study's current global estimate for first-line TB drugs is approximately US$315M per year, including high income country sales. This projection is consistent with that offered in the 2001 study *The Economics of TB Drug Development*[56] which, using a different methodology, estimated the first-line market in 2001 at approximately US$350M.

While the total market estimate is not inconsiderable, the TB marketplace is highly fragmented because it is shared by more than four drugs and a multiplicity of suppliers. This fragmentation is not likely to change. First, successful treatment of TB will most likely require a combination therapy. Second, as the study suggests, domestic drug production facilities may be integral to market entry for new TB drugs in most countries studied and likely in others.

At present, there is also a limited commercial market for second-line TB drugs. While the MDR and XDR-TB markets have revenue-generating potential, current access in most countries is primarily restricted to the private sector, with prices that severely limit access for most patients with drug resistant TB. Tapping this market would require a significant expansion of public sector treatment programs, as well as government- or donor-sponsored purchase and procurement.

In the high income countries studied, the total TB market is relatively small, with pricing and procurement following the same pricing systems as other pharmaceuticals. France, Japan, the UK and the US combined — accounting for 61 percent of the total global pharmaceutical market[57] — purchase less than US$50M worth of TB drugs.

56 *Executive Summary for The Economics of TB Drug Development.* Global Alliance for TB Drug Development. October, 2001.
57 IMS Knowledge Link. http://www.imsknowledgelink.com.

Lessons Learned from High Burden Countries

The study suggests that careful planning will be needed to accelerate the adoption of any new TB drug regimen in the high burden countries. Research confirms the preference of many countries to purchase TB drugs directly from local suppliers and not from the global marketplace. Although the GDF services a number of countries, especially those that lack local manufacturers or quality assurance capacity, most purchasers for the public sector markets studied show a strong preference for procurement from domestic manufacturers. It will be essential to research this issue further, including other high burden countries, before developing roll-out plans for new TB drugs.

The study also suggests that the launch of any new drug regimen will require a phased roll-out in high burden countries. Drug approval by regulatory authorities is only the first step toward adoption. The national TB program must then decide if it will include the new therapy as part of the treatment regimen. Thus, access to public sector markets will require an understanding of the processes by which new regimens are adopted by national TB programs as well as the public tender systems and their requirements.

Even after adoption, national roll-out leading to actual patient access will take time because countries will need to understand the impact of a new regimen on service delivery and existing supply. Also, buffer stocks of existing medications must be exhausted from both the GDF and national stores. Planning for appropriate production will require an understanding of how long it would take post-approval for high burden countries to implement a change in therapy. Collaboration with disease control programs and donor agencies which have worked on supply chain issues in other areas, such as malaria and HIV, would be helpful in such planning.

Lessons Learned from High Income Countries

TB is detected throughout the high income countries studied, although most diagnosed and treated cases are concentrated in the major cities. In these economies, a number of medical specialties and subspecialties treat TB, with physicians deciding which treatment regimens to use. Combined with other factors, this dynamic suggests that new TB drugs and regimens will require an awareness building campaign and/or substantial marketing efforts to reach these doctors.

Summary Observations

Although this study found some similarities across markets, the critical finding with the supply chain for TB drugs was the variability by country. There has been a recent call for a global "infomediary" to gather and organize market data for low and middle income countries, across disease areas, and act as an intermediary between those who supply the information, such as national TB control programs, and those who want the information to assist suppliers with demand forecasting, reduce delays and ensure consistent supply.[58] This research suggests that a global "infomediary" could be extremely helpful to the development and roll-out of new TB drugs, by providing efficient and cost-effective information sharing.

This study provides unique insight into the complexity of today's global TB market. Just as research and development into new compounds requires many stages before a drug is ready for regulatory approval and use, preparing the world for rapid universal adoption and use of new TB treatments will require the understanding of market dynamics, perceived benefits of the new regimens, manufacturing and supply chain issues, operational changes necessitated by new therapies, donor policies, price elasticity of demand and other attributes that would justify the change in treatment regimen.

Given the market intricacies revealed in this research, it is safe to conclude that providing the proper pathway for a new generation of faster and easier-to-use TB drugs to reach the patient will require a targeted and informed country-level and global strategy.

58 Center for Global Development, Global Health Policy Research Network. *Consultation Report of the Global Health Forecasting Working Group*. February, 2007.

II. Appendices

11.1 Partial List of Acronyms

APHA	American Public Health Association
ARVs	antiretrovirals
AWP	average wholesale price
BMGF	Bill & Melinda Gates Foundation
CDC	U.S. Centers for Disease Control and Prevention
China CDC	Chinese Center for Disease Control and Prevention
CIDA	Canadian International Development Agency
DFID	U.K. Department for International Development
DGIS	Directorate-General for International Cooperation (of the Netherlands Ministry of Foreign Affairs)
DOH	Department of Health
DOTS	directly observed therapy, short course
EMB	ethambutol
EU	European Union
FDC	fixed-dose combination
GDF	Global Drug Facility
GFATM	Global Fund to Fight AIDS, TB and Malaria
GLC	Green Light Committee
HBC	high burden country
HR	isoniazid, rifampicin
HRE	isoniazid, rifampicin, ethambutol
HRZE	isoniazid, rifampicin, pyrazinamide, ethambutol
IAPSO	Inter-Agency Procurement Services Organization
IBEF	India Brand Equity Foundation
IDA	International Dispensary Association
INH	isoniazid
JICA	Japan International Cooperation Agency
JSI	John Snow International
KNCV	Royal Netherlands Chemical Society
MDR-TB	multi-drug resistant tuberculosis
MRC	Medical Research Council
MRP	maximum retail price
MSH	Management Sciences for Health
NCTB	National TB Control Program (China)
NDTI	National Disease and Therapeutic Index
NGO	non-governmental organization
NPA	IMS Health's National Prescription Audit
NSP	IMS Health's National Sales Perspective
NTP	national TB control program
OPPI	Organisation of Pharmaceutical Producers of India
PAHO	Pan American Health Organization
PDI	Pharmacy DOTS Initiative
PhilCAT	Philippines Coalition Against Tuberculosis
PhilTIPS	Philippines TB Initiatives in the Private Sector
PIH	Partners In Health
PPM	public-private mix programs
PZA	pyrazinamide
RIF	rifampicin
RNTCP	Revised National TB Control Program (India)
TAC	Treatment Action Campaign
TB	tuberculosis
ICD-10	International Classification of Diseases
UNICEF	United Nations Children's Fund
UNDP	United Nations Development Programme
USAID	U.S. Agency for International Development
WAC	wholesaler acquisition cost
WB	World Bank
WHO	World Health Organization

11.2 List of Manufacturers (By Country)

Brazil

The majority of drugs are produced by National and State Laboratories

National:
- Farmanguinhos (under Fiocruz)

Military:
- Army (LQFEX)
- Air Force (LQFAE)
- Navy (LFM)

State:
- FURP (Sao Paulo)
- Iquego (Goias)
- LAFEPE (Pernambuco)
- Nuplan (Rio Grande de Norte)

China

Manufacturers awarded national tender:
- Shenyang Hongqi Luoshan Sanjiu
- Guoyao Guorui

Hospitals can procure from any approved manufacturer.

France

Manufacturers of first-line drugs:
- Ethambutol (GenoPharm; SERP; GSK)
- Isoniazid (Laphal)
- Pyrazinamide (Sanofi-aventis)
- Rifampicin (Sandoz; Sanofi-aventis)
- Rifampicin + isoniazid (Sanofi-aventis)
- Rifampicin + isoniazid + pyrazinamide (Sanofi-aventis)

Manufacturers of second-line drugs:
- Ciprofloxacin (Sandoz)
- Clavulanic acid (Sandoz)
- Levofloxacin (Sanofi-aventis)
- Ofloxacin (Sanofi-aventis, Sandoz)

India

- Cadila Pharma
- Concept Pharma
- Lupin
- Macleods
- Overseas Healthcare
- Sandoz-Novartis
- Shreya Life Science
- Themis Medicare
- Wockhardt

Japan

- Cycloserine (Meiji Meuiseka)
- Ebutol (Kaken Seiyaku)
- Ethambutol (Sandoz Japan)
- Iscotin (Daiichiseiyaku)
- Pyramide (Sankyo)
- Rifampicin (Sandoz Japan, Nipro Pharma)
- Rifandin (Daiichiseiyaku)
- Rimactane (Novartis Pharma Japan)
- Streptomycin Sulfmei (Meuiseka)
- Tubermin (Meuiseka)

Philippines

- Biomedis
- Duncan Pharm Phil
- Medichem
- Natrapharm
- Pascual Labs
- Patriot Pharma
- Pediatrica Lab
- Sandoz
- Terramedic Inc.
- United American
- Westmont
- Wyeth

South Africa

Manufacturers awarded national tenders:
- Sandoz
- Sanofi-aventis

Manufacturers of second-line drugs:
- Be-tabs Pharmaceuticals
- Biotech Laboratories*
- Bizshelf Pharmaceuticals
- Caps Pharmaceuticals*
- Pfizer Laboratories*
- Sandoz
- Sanofi-aventis
- International Suppliers

* Suppliers of streptomycin, which is also used in first-line treatment of relapse patients

11.3 Prices of Drugs for Select Countries and Purchasers

China

Price per regimen for centrally financed drugs (2005)

REGIMEN	INTENSIFIED PER UNIT RMB	INTENSIFIED # PER WEEK	INTENSIFIED # OF MONTH	CONTINUATION PER UNIT RMB	CONTINUATION # PER WEEK	CONTINUATION # OF MONTH	TOTAL COST RMB	TOTAL COST USD
CAT I HRZE HR	2.10	3	2	0.82	3	4	81	$ 10.13
CAT II HRZE HRE	2.10	3	2	1.52	3	6	138	$ 17.26
CAT III HRZ HR	1.25	3	2	0.82	3	4	66	$ 8.65

COST PER REGIMEN (ASSUMING 3 MONTHS INTENSIFIED PHASE) REGIMEN	INTENSIFIED PER UNIT RMB	INTENSIFIED # PER WEEK	INTENSIFIED # OF MONTH	CONTINUATION PER UNIT RMB	CONTINUATION # PER WEEK	CONTINUATION # OF MONTH	TOTAL COST RMB	TOTAL COST USD
CAT I HRZE HR	2.10	3	3	0.82	3	4	115	$ 14.37
CAT II HRZE HRE	2.10	3	3	1.52	3	6	185	$ 23.13
CAT III HRZ HR	1.25	3	3	0.82	3	4	84	$ 10.55

Price per regimen for JICA funded centrally procured drugs (2005)

REGIMEN	INTENSIFIED PER UNIT RMB	INTENSIFIED # PER WEEK	INTENSIFIED # OF MONTH	CONTINUATION PER UNIT RMB	CONTINUATION # PER WEEK	CONTINUATION # OF MONTH	TOTAL COST RMB	TOTAL COST USD
CAT I HRZE HR	1.57	3	2	0.62	3	4	67	$ 8.41
CAT II HRZE HRE	1.57	3	2	1.14	3	6	120	$ 14.94

COST PER REGIMEN (ASSUMING 3 MONTHS INTENSIFIED PHASE) REGIMEN	INTENSIFIED PER UNIT RMB	INTENSIFIED # PER WEEK	INTENSIFIED # OF MONTH	CONTINUATION PER UNIT RMB	CONTINUATION # PER WEEK	CONTINUATION # OF MONTH	TOTAL COST RMB	TOTAL COST USD
CAT I HRZE HR	1.57	3	3	0.62	3	4	86	$ 10.79
CAT II HRZE HRE	1.57	3	3	1.14	3	6	139	$ 17.33

Price per regimen for DFID/WB funded centrally procured drugs (2005)

REGIMEN	INTENSIFIED PER UNIT RMB	INTENSIFIED # PER WEEK	INTENSIFIED # OF MONTH	CONTINUATION PER UNIT RMB	CONTINUATION # PER WEEK	CONTINUATION # OF MONTH	TOTAL COST RMB	TOTAL COST USD
CAT I HRZE HR	2.44	3	2	0.93	3	4	103	$ 12.88
CAT II HRZE HRE	2.44	3	2	1.76	3	6	185	$ 23.12

COST PER REGIMEN (ASSUMING 3 MONTHS INTENSIFIED PHASE) REGIMEN	INTENSIFIED PER UNIT RMB	INTENSIFIED # PER WEEK	INTENSIFIED # OF MONTH	CONTINUATION PER UNIT RMB	CONTINUATION # PER WEEK	CONTINUATION # OF MONTH	TOTAL COST RMB	TOTAL COST USD
CAT I HRZE HR	2.44	3	3	0.93	3	4	133	$ 16.56
CAT II HRZE HRE	2.44	3	3	1.76	3	6	215	$ 26.82

Philippines

The cost of First- and Second-Line TB drugs in the private sector

	DRUG	MANUFACTURER	DOSE	COST PER PILL
FIRST LINE DRUGS	Myrin P	Wyeth	HRZE	$ 0.23
	Myrin	Wyeth	HRE	0.18
	Tritab	Unilab	HRE	0.20
	Quadtab	Unilab	HRZE	0.18
SECOND LINE DRUGS	Ciprofloxacin	Local	300 mg	$ 0.34-1.50
	Clarithromycin	Local	300 mg	1.88

South Africa

Sandoz private-sector prices (US$)

SANDOZ TRADE NAME	PACK SIZE	SEP PRICES (VAT EXCLUDED)	SEP PRICES (VAT INCLUDED)
Rimactane 150	100	$ 16.50	$ 18.81
Rimactane 300 Vials	1	17.29	19.71
Rimactane 450	100	29.03	33.09
Rimactane 600	100	54.15	61.73
Rimactazid 150/75	60	7.00	7.98
Rimactazid 300/150	40	6.20	7.07
Rimactazid 60/30	40	5.27	6.00
Rimactazid Paed 60/60	80	11.92	13.59
	120	17.88	20.38
Rimcure Paed 3-FDC	80	15.93	18.16
	120	23.90	27.24
	500	99.57	113.51
Rimstar 4-FDC	40	4.60	5.24
	60	6.90	7.87
	80	9.20	10.49
	100	11.50	13.11
	500	57.50	65.55
Sandoz Ethambutol HCl 400	100	12.67	14.44
Sandoz Pyrazinamide 500	100	14.72	16.78

Sanofi-aventis private-sector prices (US$)

SANOFI-AVENTIS TRADE NAME	PACK SIZE	SEP PRICES (VAT EXCLUDED)	SEP PRICES (VAT INCLUDED)
Rifafour e-275	40	$ 4.43	$ 5.05
	60	6.64	7.57
	80	8.86	10.10
	100	11.65	13.29
	500	55.35	63.10
Rifinah 300 mg	40	5.83	6.65
Rifater Junior	40	7.00	7.98
	40	5.78	6.58

11.4 Interview Lists

GLOBAL STAKEHOLDERS

Marcos Espinal
Executive Secretary,
Stop TB Partnership Secretariat

Peter Evans
Consultant,
Independent consultant to GDF

Kathryn Floyd
Acting Head of TB Monitoring and Evaluation,
WHO

Christina Foley
TB Advisor, CIDA

Ernesto Jaramillo
MDR-TB Working Group Secretariat,
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12. Acknowledgements

The TB Alliance would like to acknowledge the many people whose time, effort and enthusiasm, made this unprecedented research project possible.

We are very grateful to our project advisors: Mona Ashiya, Sarah Ewart, Jordan Lewis, Marieke Korsten, Robert Matiru, Jim Rankin and Doris Rouse, and the members of our research team: Nina Schwalbe and Heather Ignatius from the TB Alliance, and Alyse Forellina, Alexis Geaneotes, Michelle Lee, Lauren DiCola, Tarek Raafat, and Clare Walker from IMS Health.

The *Pathway to Patients* research team would like to acknowledge the continuous support of TB Alliance officers Maria Freire, Mel Spigelman, Karen Wright, Al Hinman and Bradley Jensen; the research & development team's Ann Ginsberg, Zhenkun Ma, Christo van Niekerk, and Khisi Mdluli; and the communications and policy teams' Cuyler Mayer, Derek Ambrosino, Stephanie Seidel, and Asmita Barve for their review, writing and publication support.

The TB Alliance would also like to thank the following for their contribution: Ken Castro, LS Chauhan, Daniel Chin, Gavin Churchyard, Katherine Floyd, Petra Heitkampp, Mandisa Hela, Jeff Hoover, Michael Howley, Hajime Inoue, Fabienne Jouberton, Joel Keravec, Hannah Kettler, Afranio Kritski, Elisabetta Molari, Sonal Munsiff, Lindiwe Mvusi, Pierre-Yves Norval, Antonio Ruffino Netto, Ikushi Onozaki, Nitin Patel, Suvanand Sahu, VS Salhotra, Thelma Tupasi, Rosalind G. Vianzon, Jan Vosken, Diana Weil, Fraser Wares, Wang Xiaomei, and Charles Yu.

Finally, this project would not have been possible without the generous financial support of The Netherlands Ministry of Foreign Affairs' Department of Development Cooperation (DGIS) and the Bill & Melinda Gates Foundation.

DESIGN: IDEAS ON PURPOSE, NEW YORK, NY
PHOTOGRAPHY: COVER (FAR LEFT), COVER (SECOND FROM RIGHT), JOHN-MICHAEL MAAS; COVER (SECOND AND THIRD FROM LEFT), BACK COVER (SECOND FROM RIGHT), GARY HAMPTON; COVER (FAR RIGHT), BACK COVER (FIRST TWO FROM LEFT), ATUL LOKE

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

About the Global Alliance for TB Drug Development

The Global Alliance for TB Drug Development (TB Alliance) is a not-for-profit, product development partnership accelerating the discovery and/or development of new TB drugs that will shorten treatment, be effective against susceptible and resistant strains, be compatible with antiretroviral therapies for those HIV-TB patients currently on such therapies, and improve treatment of latent infection.

Working with public and private partners worldwide, the TB Alliance is leading the development of the most comprehensive portfolio of TB drug candidates in history, and is committed to ensuring that approved new regimens are affordable, accessible and adopted.

The TB Alliance operates with the support of the Bill & Melinda Gates Foundation, Irish Aid, the Netherlands Ministry of Foreign Affairs (DGIS), the United Kingdom Department for International Development (DFID), and the United States Agency for International Development (USAID).

For more information on TB drug development and the TB Alliance, please visit **www.tballiance.org**.

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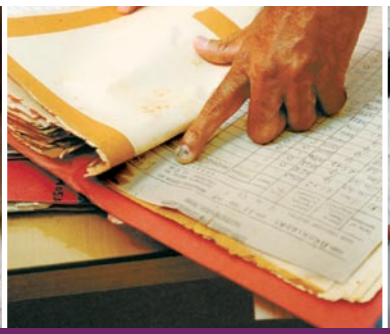


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