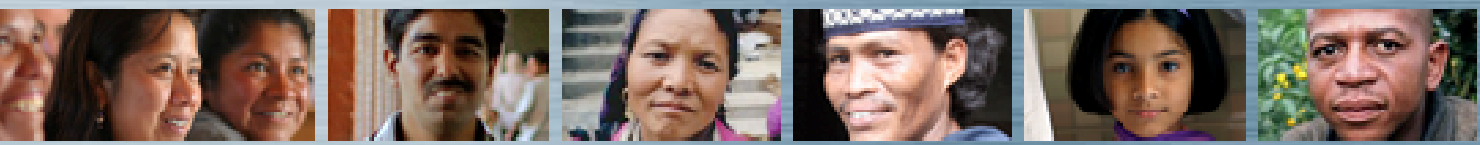
TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Analysis of the Global TB Drug Market and Country-Specific Case Studies of TB Drug Distribution Channels

Brazil Case Study



Prepared with IMS Consulting

November 2006

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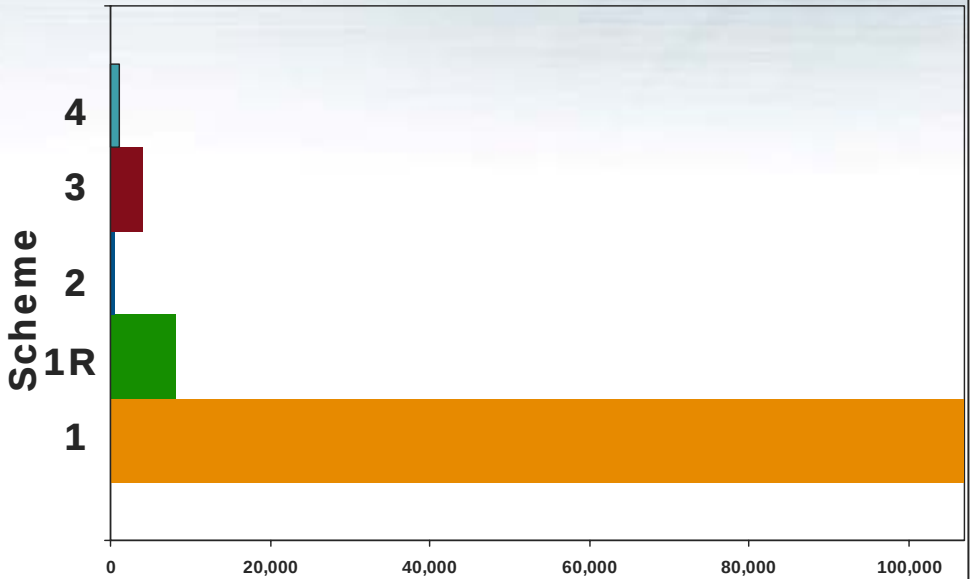
Most recent estimates from the MOH project about 120,000 total cases of TB in 2004

Number of cases of TB (2004)



Scheme 1: New TB Cases (Basic scheme)
Scheme 1R: Previously treated (Basic + Ethambutol)
Schema 2: TB Meningitis
Scheme 3: MDR-TB
Scheme 4: TB MR (R+I+ one other drug)

- In 2004:
  - 107,000 patients with TB (treated under Scheme 1)
  - 8,186 patients with TB who were previously cured or abandoned treatment (Scheme 1R)
  - 573 patients with TB meningitis (Scheme 2)
  - 4,093 patients who are resistant to RIF+INH (Scheme 3)
  - 1,070 who are resistant to RIF+INH+ at least one other drug used in Scheme 1 or 3 (classified as TB MR in Brazil and treated under Scheme 4)
- 45% of TB burden in Sao Paulo and Rio de Janeiro states
- In São Paulo State . . .
  - 21K total cases in state (17K within city)
  - 3K with TB/ HIV
  - 100 cases who are resistant to RIF+INH
  - 60% DOTS coverage and 30% in city (mostly south)

Source: IMS interviews

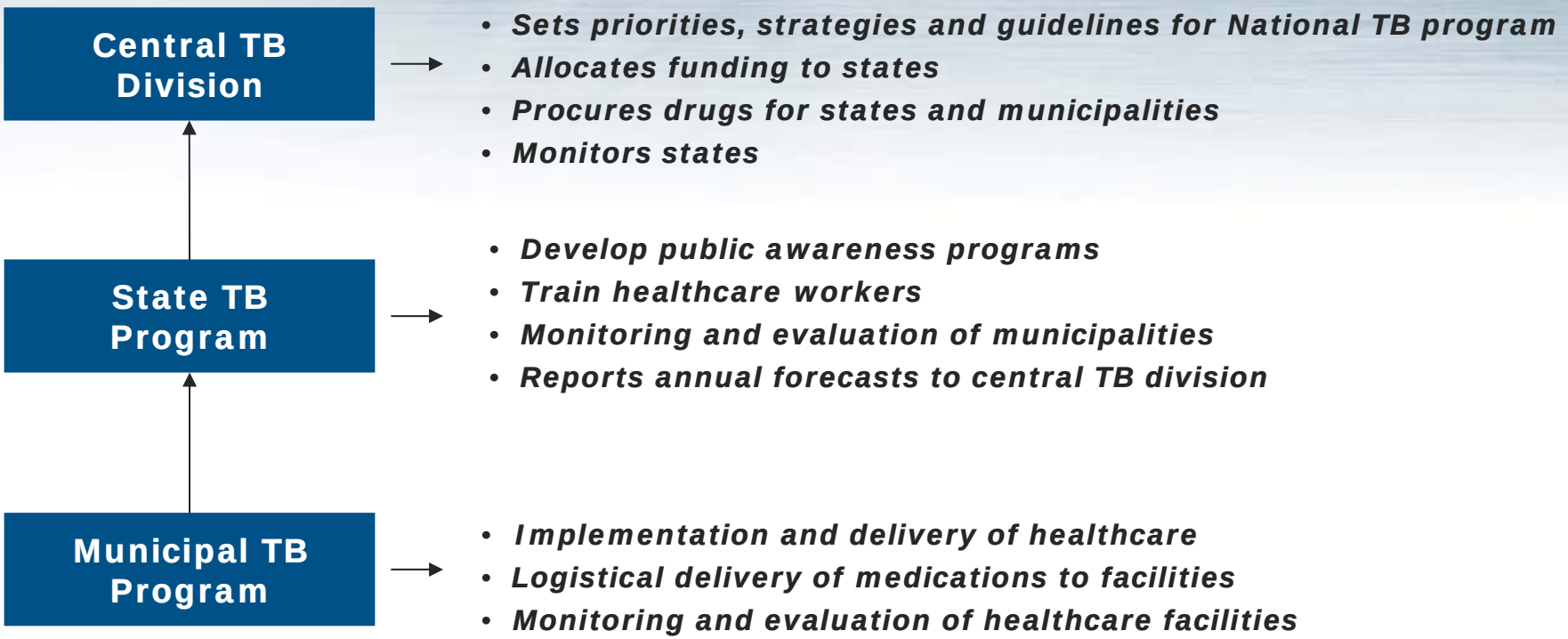
The MOH has defined TB based on several schemes and has developed treatment guidelines for each

Category	Definition	Treatment
Scheme 1: "Esquema basico"	New cases of pulmonary and extra-pulmonary TB	2RHZ/ 4RH
Scheme 1R: "Esquema basico + Etambutol"	Previously treated cases that were cured or abandoned basic treatment*	2RHZE/ 4RHE
Scheme 2: "Esquema para tuberculose meningoencefalica"	Cases of TB meningitis	2RHZ/ 7RH
Scheme 3: "Esquema para falencia de tratemento aos outros esquemas"	Patient who failed scheme 1R, or who is resistant to rifampicin and isoniazid	3ZSEEt/ 9 EEt
Scheme 4: "TB MR"	Patient who is resistant to rifampicin, isoniazid ad at least one other medicine from Scheme 1 or 3	Amicacin/ Ofloxacin/ Terizidone/ Ethambutol Clofazimine (until March 2006) Pyrazinamide (from March 2006) (4 oral drugs + 1 injectable for first 12 months; 4 orals for remaining 6 months)

Source: IMS interviews

*Within the past five years; otherwise considered scheme 1 or new patients

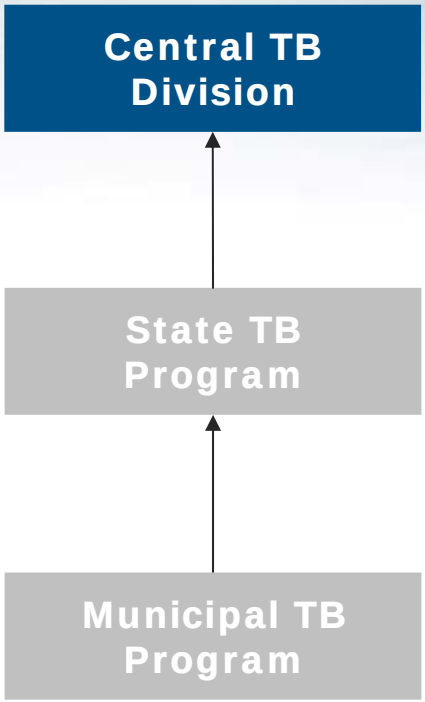
The National TB program sets the strategy, with implementation at the state and municipal level



Source: IMS interviews

The MOH is responsible for purchasing 100% of TB medicines and provides them free of charge for all patients

Level of PNCT

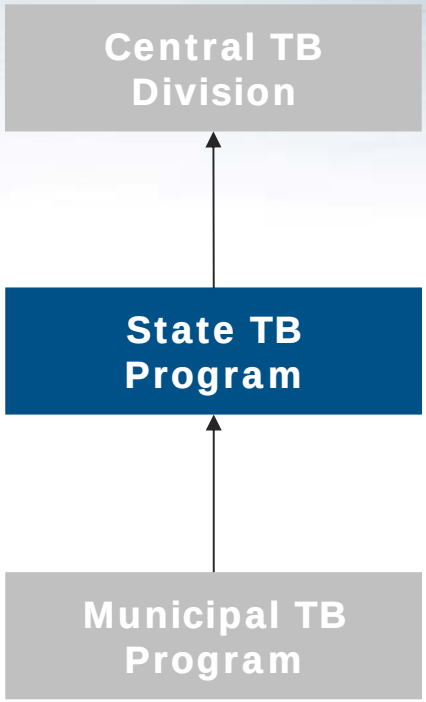


- TB patients are always treated in the public sector through the nation's TB program (PNCT)
- Since patients are guaranteed free access to such medications under government-sponsored programs, all sales are prohibited in the private sector
- Brazil offers a broad spectrum of 1st and 2nd line treatments

Source: IMS interviews

The state is responsible for supervising health regions and municipalities and ensuring access to care

Level of PNCT

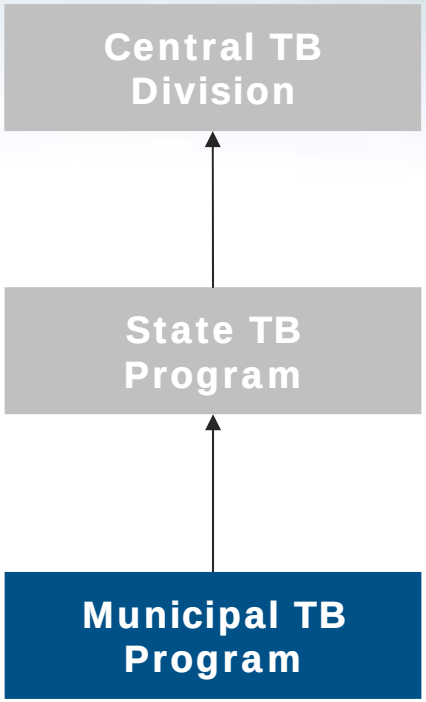


- Main role in coordinating the TB program
- Other than funding for drugs, most funds for TB program comes from federal government
- Responsible for ensuring healthcare workers are trained, for ensuring that patients have access to medicines and for developing public awareness campaigns
- Also responsible for supervising health regions and municipalities within their states
  - Some states provide financial incentives to ensure municipalities implement DOTS within their region
- May also be responsible for purchasing diagnostic equipment

Source: IMS interviews

Implementation of the TB program, including adherence to DOTS, is determined largely by municipalities

Level of PNCT



- The "implementation" function that is responsible for diagnosing and treating patients
- Municipalities determine how their budget is allocated, including for implementation of DOTS, of family health programs or of other efforts
  - Those municipalities with budget to do so will provide incentive to patients for DOTS; for example they may offer food and/or reimbursement for public transport

Source: IMS interviews

The WHO recommends a 4-drug regimen for patients

Recommended TBCTA dose regimen for previously untreated patients

Category	Daily	3 times a week
Rifampicin	10 mg/kg (8-12; max of 600 mg)	10 mg/kg (8-12; max of 600 mg)
Isoniazid	5 mg/kg (4-6; max of 300 mg)	10 mg/kg (4-6; max of 300 mg)
Pyrazinamide	25 mg/kg* (20–30)	35 mg/kg* (30–40)
Ethambutol	Children 20 (15-25)* Adults 15 (15-20)	30 (25-35)*

For 55 kg person, 1650 RIF, 1650 INH, 5775 PYR, 4950 EMB weekly.

Ranking	Initial phase	Continuation phase
Preferred	INH, RIF, PZA, EMB daily, 2 months INH, RIF, PZA, EMB 3x/week, 2 months	INH, RIF daily, 4 months INH, RIF 3x/week, 4 months
Optional	INH, RIF, PZA, EMB2 daily, 2 months	INH, EMB daily, 6 months

**Not in continuation phase*

Source: Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC). The Hague: Tuberculosis Coalition for Technical Assistance, 2006.

However, the treatment regimen for utilized by the PNCT differs from the WHO recommended regimen in that ethambutol is not included in the basic regimen

PNCT TB Drug Treatment Regimen for Scheme 1

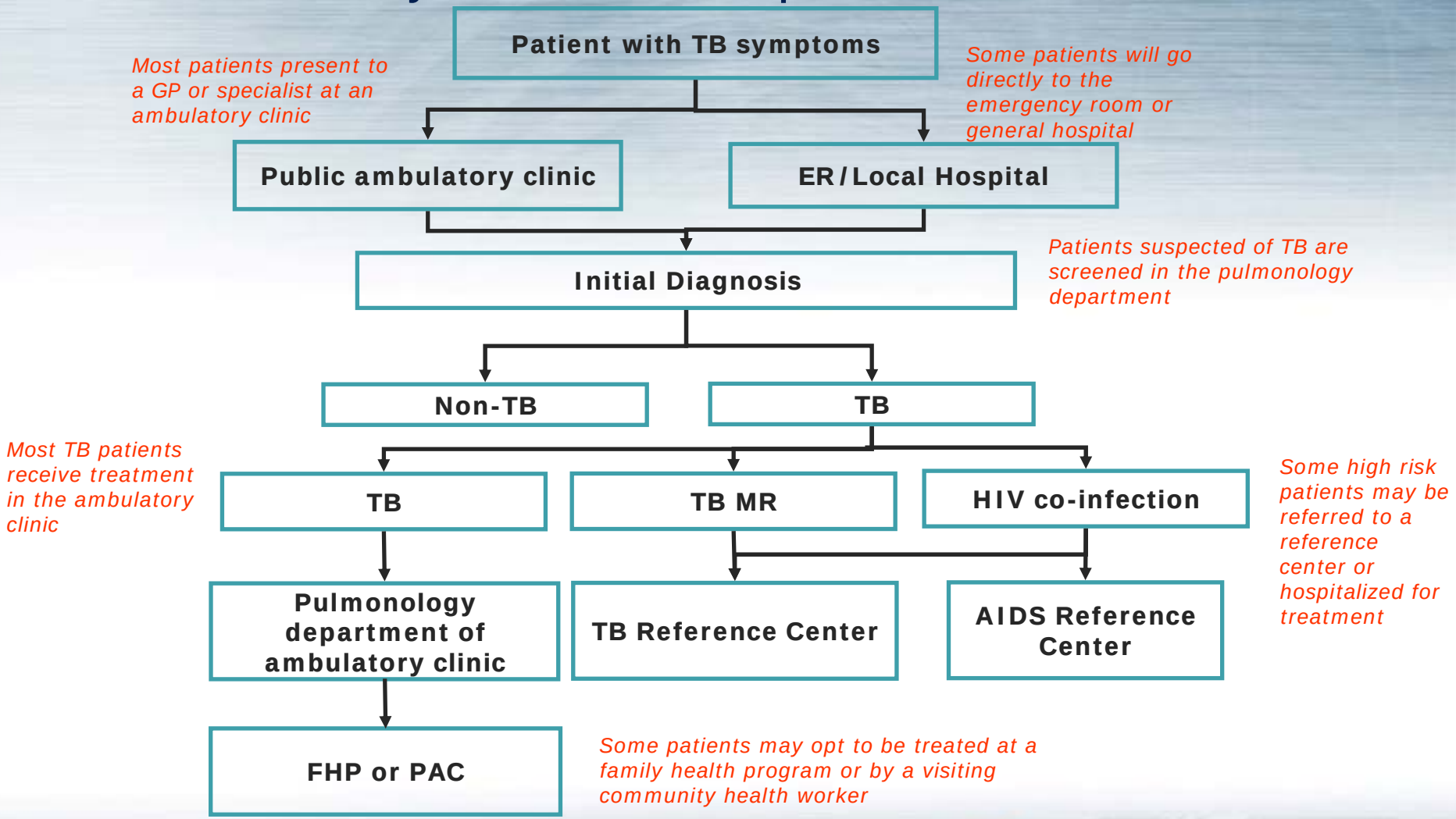
Category	PNCT Regimen (mg/day) for patient over 45 kg	WHO recommended for 45kg	WHO recommended for 70kg
Rifampicin	600 mg	450 mg	600 mg (because of max)
Isoniazid	400 mg	225 mg	350 mg
Pyrazinamide	2,000 mg*	1125 mg*	1750 mg*
Ethambutol	not used for previously untreated patients	675 mg*	1050 mg*

Details on the 1st line Regimen

Initial phase is 2 months. Continuation phase is 4 months. Pyrazinamide (and ethambutol) not used in continuation phase.

Source: Brazil MOH; Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC). The Hague: Tuberculosis Coalition for Technical Assistance, 2006. See appendix for full treatment regimens for all schemes.

TB patients typically present and remain treated at a public ambulatory clinic /or hospital



Source: IMS interviews

Patients can receive TB treatment at a community health center or a Family Health Program (FHP) rather than the hospital out-patient department from rural areas

- Efforts to improve the availability and quality of primary care have been under way for some time with the development of the Family Health Program (FHP), which was launched in 1994, mainly in rural areas
- The Family Health Team includes a GP, 1 dentist, 2 nurses and 2 community agents with responsibility for between 600 and 1000 families in specific municipalities
- Priority areas include diabetes, women's health, pediatrics, hypertension, TB and leprosy
- More than 11000 teams are now working in rural communities and small towns, and the program has reached ~ 60 million people
- No pharmacy capacities exist at the FHP, and therefore, nurse will receive a month's supply of TB medicines at a time to administer to the patient
- A new push to expand the program is now underway including expanding among urban areas, where there 30%-50% patients are initially attended in hospitals

Source: IMS interviews; IMS Health Market Prognosis

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On an annual basis, the MOH projects the supply of drugs it must procure for TB and for multi-drug resistant TB

Estimate of supply for 2006

TB

	Planned	Buffer stock	Total
Isoniazid 100 mg	8, 291, 000	4,145,500	7,495
Isoniazid 100 mg + Rifampicin 150 mg	6,104,000	1,221,000	7,325,000
Isoniazid 200 mg + Rifampicin 300 mg	32,875,000	6,575,000	39,450,000
Pyrazinamide 500 mg	22,130,500	4,426,000	26,556,500
Pyrazinamide oral 3%	57,806	11,544	69,350
Pyrazinamide oral 2%	209,300	41,850	251,150
Rifampicin 300 mg	6,575,000	1,315,000	7,890,000
Streptomycin 1g	149,300	59,050	208,350
Etambutol 400 mg	6,341,450	1,154,050	7,495,500
Etionamide 250 mg	916,050	182,950	1,099,000

Multi-drug resistant

	Planned	Buffer stock	Total
Isoniazid 100 mg	64,800	16,200	81,000
Isoniazid 100 mg + Rifampicin 150 mg	4,000	1,000	5,000
Isoniazid 200 mg + Rifampicin 300 mg	6,400	1,600	8,000
Pyrazinamide 500 mg	129,600	32,400	162,000
Rifampicin 300 mg	58,400	13,900	69,500
Streptomycin 1g	12,000	3,000	15,000
Etambutol 400 mg	836,794	209,200	1,046,000
Amicacina 500mg/2ml	62,400	15,600	78,000
Amicacina 1 g/ 4 ml	31,200	7,800	39,000
Claritromicina 500 mg	29,200	7,300	36,500
Ofloxacino 400 mg	581,868	145,600	728,000
Terizidona 250 mg	19,040	4,760	23,800

Source: MOH Estimates 2006

It accounts for a planned level of stock and a reserve stock which it stores at a central warehouse in Brasilia

	Planned	Buffer stock	Total
Isoniazid 100 mg	1, 000	4,145,500	95
Isoniazid 100 mg + Rifampicin 1	4,000	1,221,000	00
Isoniazid 20 Rifampicin 3			
Pyrazinamid			
Pyrazinamid			
Pyrazinamid			
Rifampicin 3			
Streptomycin 1g	149,300	59,050	208,350
Etambutol 400 mg	6,341,450	1,154,050	7,495,500
Etionamide 250 mg	916,050	182,950	1,099,000

- Each year the MOH projects need for upcoming year
- Estimates are built from the bottom up
  - Each municipality reports forecasts and stock to state
  - State reports to national MOH
- Supply delivered directly to state

- The MOH allocates an extra 25% buffer stock on top of the planned level of supply
- This reserve is kept at the MOH warehouse as a reserve supply

Source: MOH estimates 2006

The MOH then negotiates directly with national and state laboratories to produce 1st and many 2nd line drugs

Estimates for 2006

	Price per unit	Supplier
Isoniazid 100 mg	.0164	LAFEPE/LQFAE/LFM
Isoniazid 100 mg + Rifampicin 150 mg	.0992	LAFEPE/LQFEX
Isoniazid 200 mg + Rifampicin 300 mg	.1654	LQFEX
Pyrazinamide 500 mg	.1213	FURP/LAFEPE/LQFAE/ LQFEX/LFM
Pyrazinamide oral 3%	1.9500	LFM
Pyrazinamide oral 2%	.8299	FURP
Rifampicin 300 mg	.1415	LAFEPE/NUPLAN/LQFEX
Streptomycin 1g	.9630	FURP
Ethambutol 250 mg	.1014	FIOCRUZ/FURP/IQUEGO
Etionamide 250 mg	.2948	LQFEX
Ofloxacino 400 mg	.3899	LFM
Terizidona 250 mg	4.6060	FLOMED

Source: MOH estimates 2006

Majority of products are produced by national and state labs including:

1. **Farmanguinhos (national lab under Fiocruz)**
2. **Military labs include army (LQFEX), navy (LFM) and air-force (LQFAE)**
3. **State labs include**
   - **FURP (Sao Paulo)**
   - **LAFEPE (Pernambuco)**
   - **Nuplan (Rio Grande de Norte)**
   - **Iquego (Goias)**

The MOH uses a bid and tender process with labs to secure supply on an annual basis

The MOH issues a bid…

- After building the annual forecast, the MOH issues a bid to state and military labs to fill next year's supply
- The MOH bases expectations on each lab's production capabilities from the previous year's production levels

Conduct negotiations…

- The MOH then reviews accepts bids directly with the state, military and national labs on the <u>production level and timing of delivery</u>
- Price is not a part of the negotiation process, rather the MOH determines the price they are willing to pay primarily based off of the previous year
- State labs have some ability to "turn down" the MOH if they do not have capacity, and have done so in recent years due to the price of raw materials

Finalizes order

- Once the MOH finalizes the negotiation with the lab, orders are sent directly from lab to the state / national warehouse
- The MOH determines to which destination each lab's supply will go

Source: IMS interviews

State labs negotiate with external suppliers for raw materials through a bid and tender process

Process today:

1. **State labs issue bids to suppliers annually for raw materials**

   Two major standards considered:

   1. **Strength in accordance with Brazilian treatment regimens**
   2. **Quality compliant with Brazilian Pharmacopeia***

2. **State labs review and accept proposals from suppliers for a negotiated supply**

3. **If more raw materials are needed within the year, a lab can go directly to supplier for more if within 25% of the agreed range**

   - **If needed supply exceeds this range, lab must issue a new bid**

2006 and Beyond

- **MOH starting to create a network of labs through the MOH to act as a pooled procurement mechanism and assist in price negotiations with suppliers of raw materials**

* USP or European or British Pharmacopoeia would be used if data is unavailable in Brazilian pharmacopoeia

Source: IMS Health Interviews

If there is a gap in supply between what the state labs can produce and the annual forecast, the PNCT will look into other options internally and then externally

Description of process:

1 National TB Drug Producer Public Labs Networks

- *First option for TB drug production is the National Public Labs Network*
- *Farmanguinhos is the lab with the highest capacity and is leading a process of development of FDCs, but bids are open to the public labs network*

2 National private manufacturers

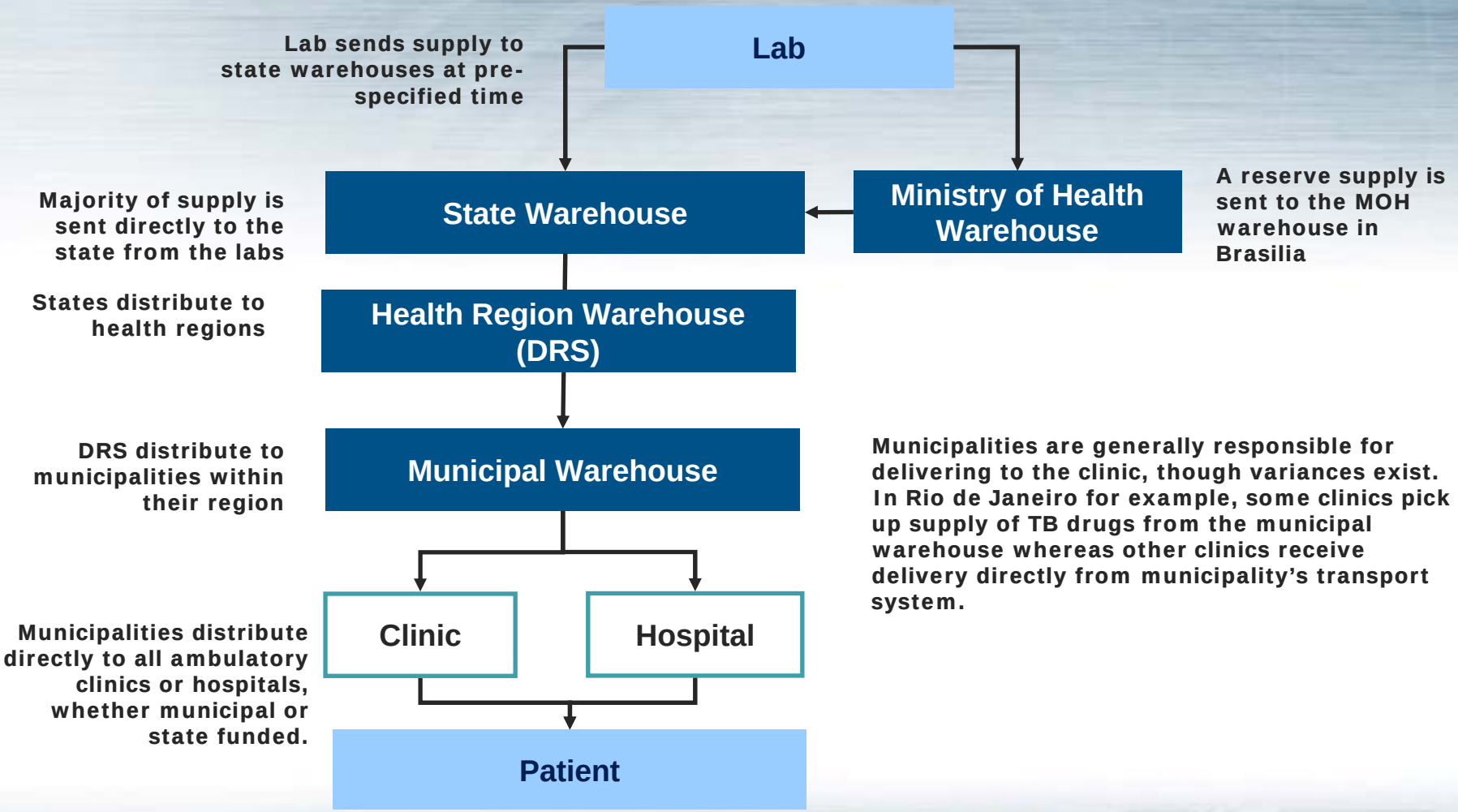
- *If Farmanguinhos cannot provide adequate supply, then the MOH would issue a bid for private manufacturers in Brazil*
- *Manufacturers have to be pre-qualified by the Brazilian regulatory agency, ANVISA*

3 International manufacturers

- *The last option would be to look for external suppliers*
- *Some 2nd line drugs including amicacin and terizidone, are procured regularly from external suppliers*
- *Most recently, FDC's of rifampicin and isoniazid were procured through external suppliers in India*

Source: IMS interviews

1st line drugs produced by state labs are distributed directly to state warehouses



Source: IMS interviews

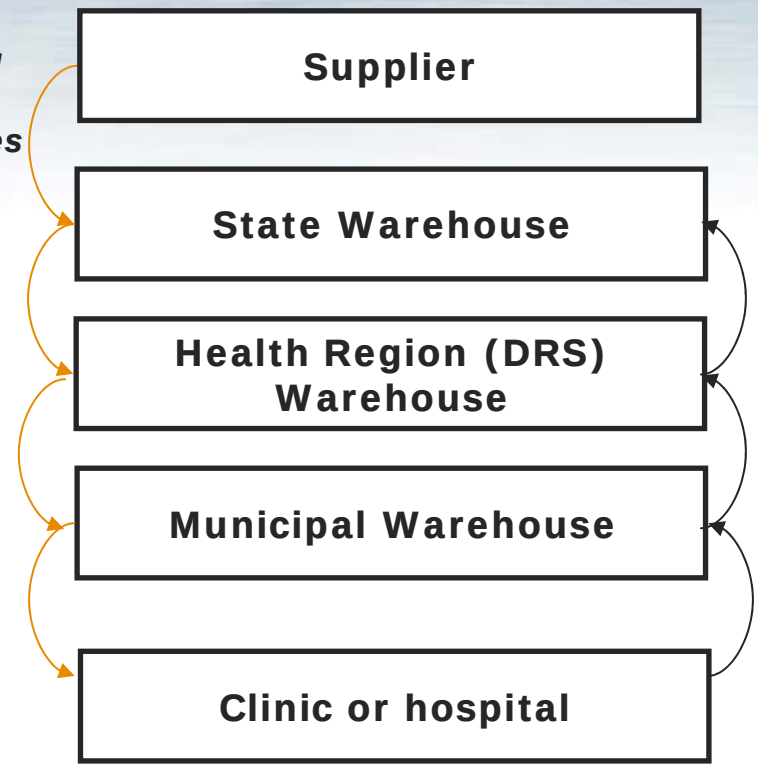
Though some variations exist in timing, TB medicines are generally released to the state who is then responsible for distributing within to the municipalities

Drugs procured by the MOH government are initially shipped to state warehouses every 3 months**

Drugs are shipped the health region warehouse on a regular basis (usually every 2-3 months)

Drugs are shipped directly to municipal every month

Drugs are shipped directly to clinic or hospital on a monthly basis



Reports stock and need every three months to the MOH

Report stock and needs every 1-3 months* to state

Report stock and needs each month to municipal warehouse

*** A larger state like Sao Paulo is divided into 24 health regions, so drugs are shipped direct to supplier to the regions rather than a central state warehouse.*

**For example, in Sao Paulo municipality orders on a monthly basis and Rio de Janeiro orders every two months.*

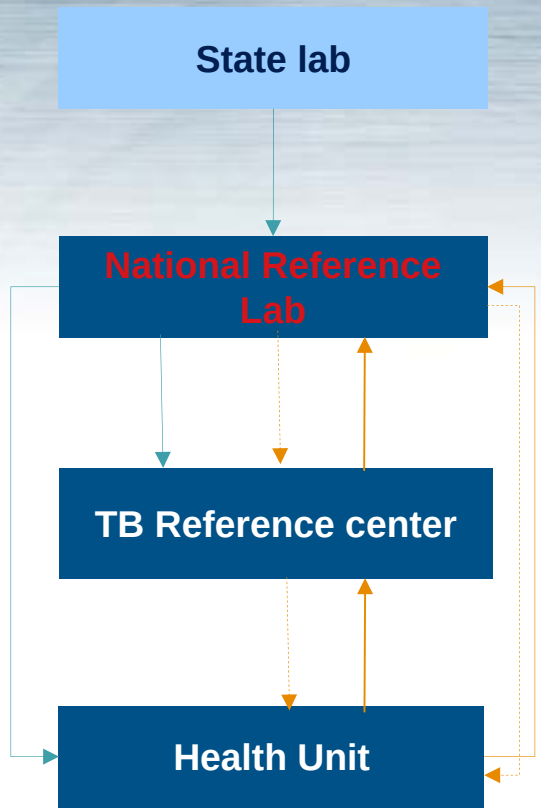
Source: IMS interviews

For MDR-TB, Helio Fraga is the main reference center that stocks and distributes drugs to supervised facilities

Distribution

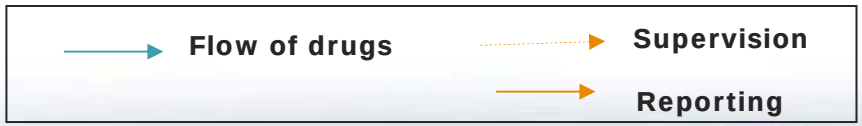
1. Lab distributes directly to National Reference Lab, who stocks all TB MR drugs
2. Upon notification from TB reference center, Helio Fraga directly distributes drug to reference center or to health unit where patient has been identified.

   Drugs are ear-marked for a specific patient.
3. In some instances where a local health unit is authorized to treat the TB MR patient, Helio Fraga will distribute directly to the unit



Flow of Reporting and supervision

3. Reference center reports cases directly to National Reference Lab and remains under their supervision for patient care.
2. In many instances patients are referred to the reference center for further diagnosis and treatment. In instances where a patient will remain at the health unit, in which case, the reference center is responsible for supervising the health unit.
1. If a TB MR case emerges, health unit must report case to reference center.



Source: IMS interviews

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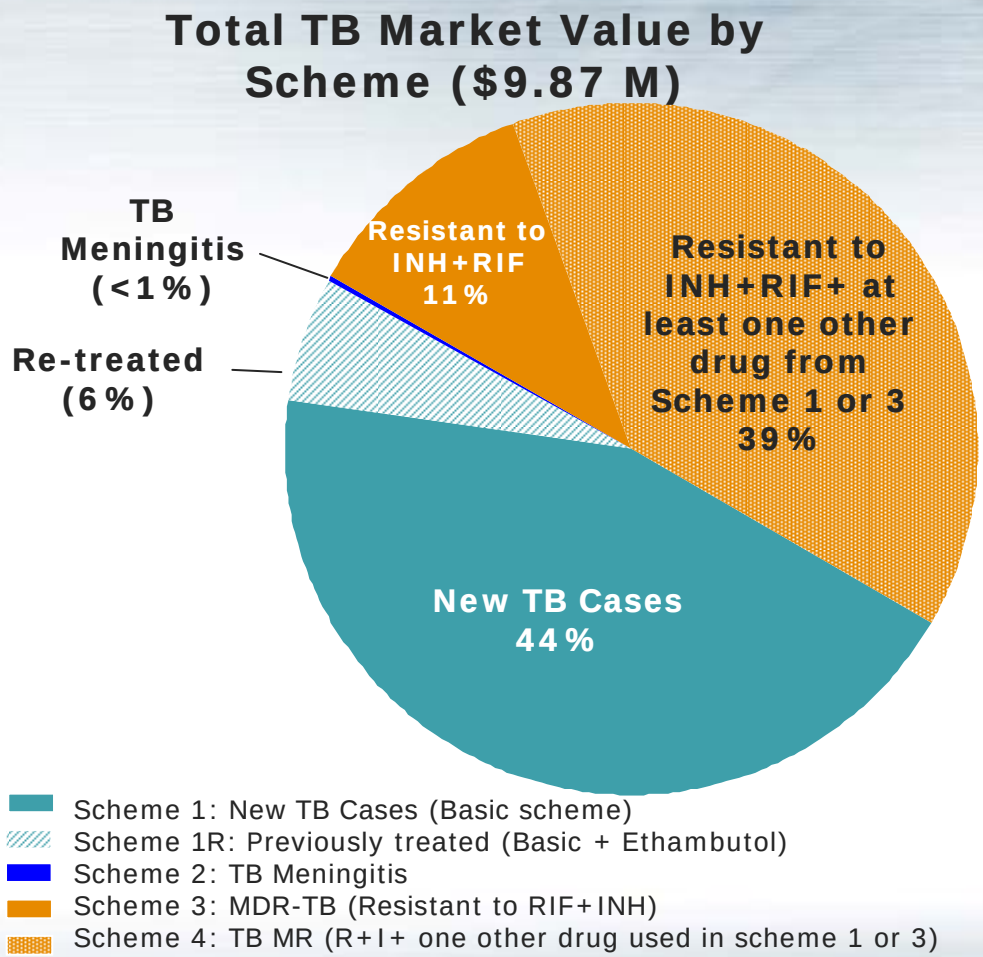
The Brazilian TB market is valued at almost $10 M USD



Source: MOH Estimates, 2004

Public market only:

- **All distribution of 1st and 2nd line medicines is through the MOH**
- **Private sector (retail pharmacies) prohibited from selling TB medicines**
- **About half of the market value is for drug resistant patients**

1st line drugs represent half of the total market value today

Total TB Market

1st line market

- **1st line drugs account for ~4.9M USD or 50% of the total market**
- **Public sector only**
- **Drugs traditionally produced internally through state, military or national laboratories**

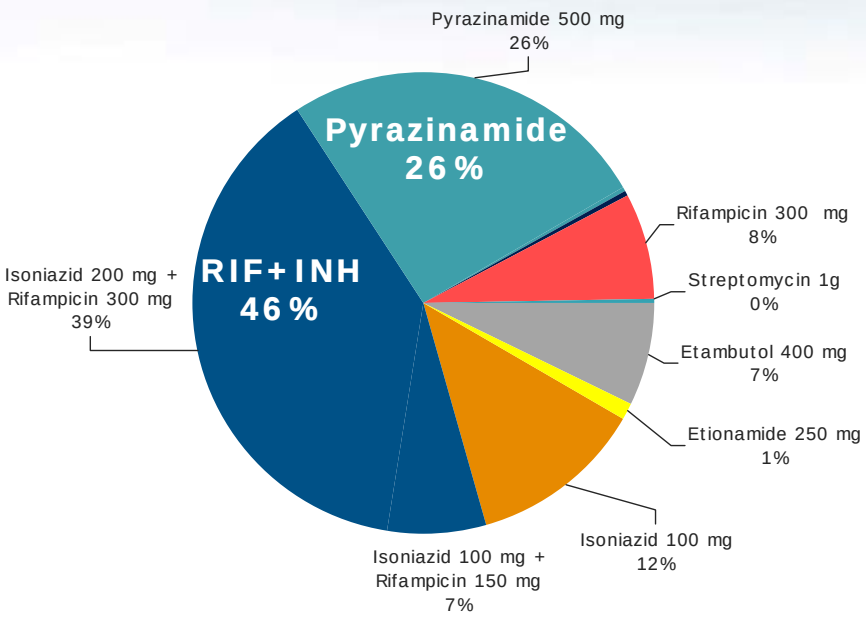
2nd line market

- **2nd line drugs account for ~5M USD or 50% of total market**
- **Some 2nd line drugs procured from international manufacturers through public tender; remainder produced internally**

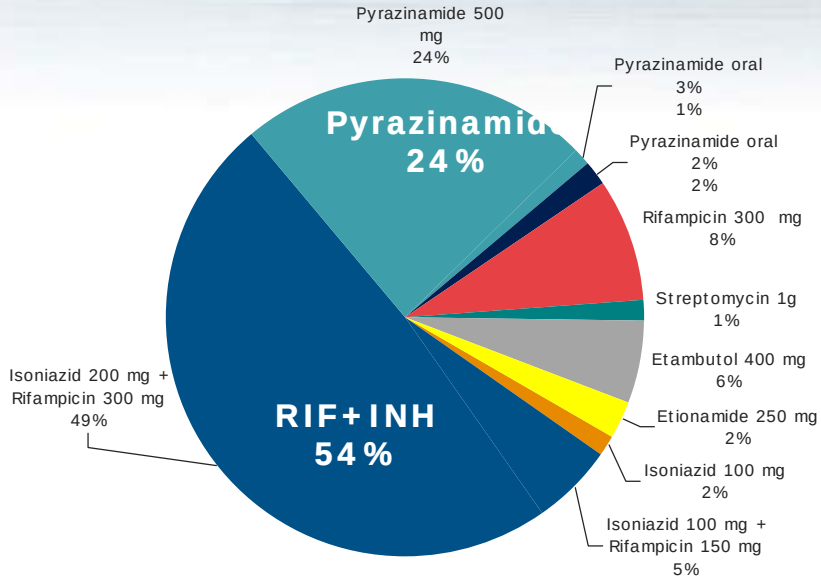
Source: MOH Estimates, 2004

For the 1st line market, about half of the value and volume is for FDCs of isoniazid and rifampicin

Total 1st Line TB Market Value by Drug in 2005 (5 M USD)*



Total 1st Line TB Market Volume by Drug in 2005 (102.8 M units)



**6 Million including buffer stock*

Source: MOH Estimates, 2004

Cost per regimen is significantly higher for 2nd line regimens

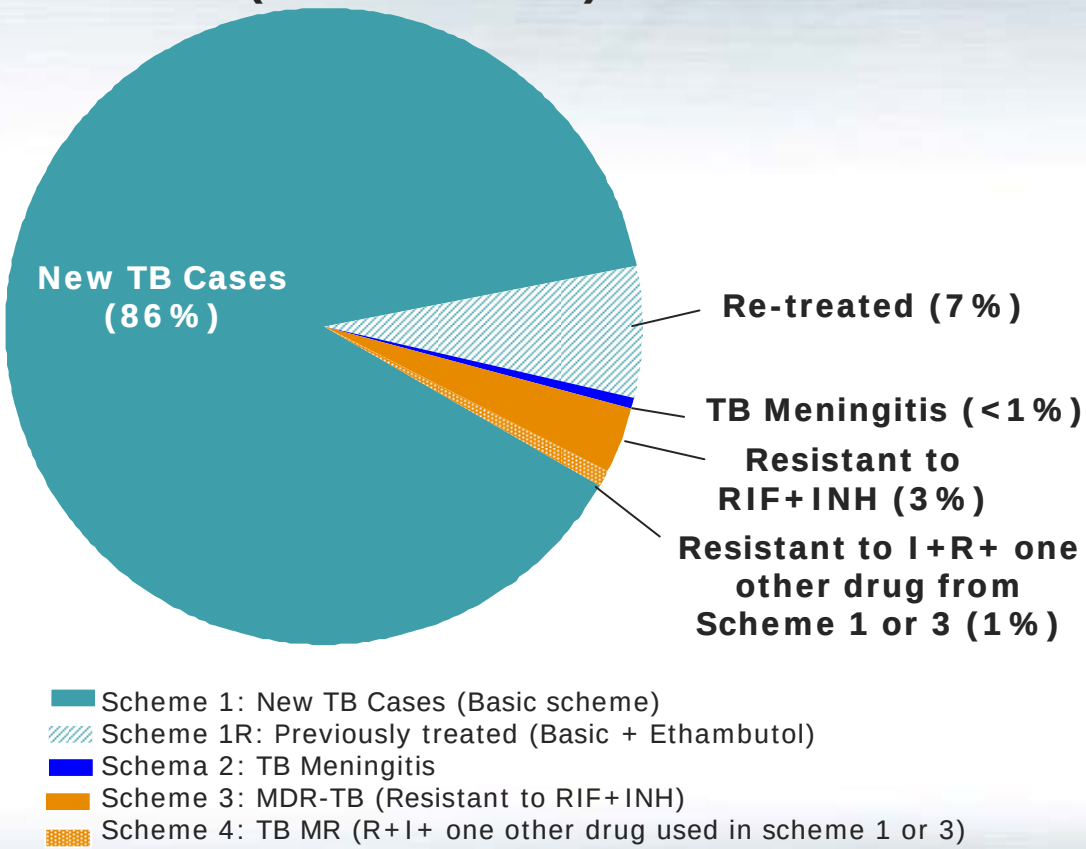
	# of patients	Cost per patient ($)	Total value ($)
Scheme 1* **(New TB Cases)**	107,000	$41	$4,387,000
Scheme 1R **(Re-treated)**	8,186	$69	$567,454
Scheme 2 **(TB Meningitis)**	573	$62	$35,492
Scheme 3 **(Resistant to RIF+INH)**	4,093	$270	$1,105,110
Scheme 4 **(Resistant to RIF+INH + at least one other drug from scheme 1 or 3)**	1,070	$ 3,625	$3,879,007

*Daily regimen used

Source: MOH Estimates, 2004

As such, despite representing about half of the value, the 2nd line regimen represent only about 4% of the volume (Schemes 3 and 4)

Total TB Patient Volume by Scheme (Patient Basis)



- **Out of total of 120,000 patients, 4% (or about 5,163 patients) were either resistant to RIF+INH only or + another drug:**
- **4,093 are resistant to RIF+INH (Scheme 3)**
- **1,070 are resistant to RIF+INH+ one other drug used in Schemes 1 or 3 (Scheme 4)**

Source: MOH Estimates 2004

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Appendix: Interviewed Stakeholders

Individual	Organization	Position
Dr. Joseney dos Santos	National TB Program	National TB Program Mgr
Dr. Waldir Silva	National TB Program	TB Program Advisor, MOH
Dr. Joao Batista Oliveira	Farmanguinhos	MOH consultant to Farmanguinhos
Dr. Miguel Hijjar	National Reference Lab (Helio Fraga)	Director of National Reference Lab
Andrea Sousa De Ataide	MOH/ National TB Program	Pharmacy services
Dr. Joel Keravec	Projeto MSH – Rational Pharmaceutical Management Program – Management Sciences for Health	Director MSH Office- Brazil/ former Anvisa
Dr. Vera Galesi Marilene Vinhas	Sao Paulo State TB Program	State TB Program Manager Pharmacist at warehouse
Dr. Naomi Komatsu	Sao Paulo Municipal TB program	Municipal TB Program Mgr
Dr. Lisia Freitas	Rio de Janeiro State TB Program	State TB Program Manager
Dr Betina Durovsky Dr Solange Cavalacante	Rio de Janeiro Municipal TB Program	Municipal TB Program Manager
Dr. Rosangela	Bahia State TB Program	State TB Program Manager
Dr Edilson	Minas Gerais State TB Program	State TB Program Manager

Appendix: Interviewed Stakeholders (continued)

Individual	Organization	Position
Dr Luis Gustavo Bastos	Project MSH/ RPM Plus - Brazil	MSH consultant/ practicing physician
Dr Jorge Rocha	Project MSH/ RPM Plus - Brazil	MSH consultant/ practicing physician
Dr. Fernando Fiuzza	Instituto Clemente Ferreira TB Reference Center São Paulo TB Reference Center	Physician
Dr. Ana Regina	Centro Municipal de Saúde Píndaro de Carvalho Rodrigues (DOTS)	Physician
Dr. Paulo Alburquerque	Policlinica Amaral Peixoto (Non-DOTS clinic)	Physician
Dr Afranio Kritski	Universidade Federal do Rio de Janeiro	Director of Academic TB Program
Dr German Filho	Fundação Ataulfo de Paiva - RJ	Director and former PNCT program mgr
Dr Marcio Thome	BEMFAM (NGO)	Director of logistics and supply

Appendix: Brazil Dosing Guidelines

PNCT TB Drug Treatment Regimen for Scheme 1

Category	PNCT Regimen (mg/day) for patient over 45 kg	WHO recommended for 45kg	WHO recommended for 70 kg
Rifampicin	600 mg	450 mg	600 mg (because of max)
Isoniazid	400 mg	225 mg	350 mg
Pyrazinamide	2,000 mg*	1125 mg*	1750 mg*
Ethambutol	not used for previously untreated patients	675 mg*	1050 mg*

Details on the 1st line Regimen

Initial phase is 2 month. Continuation phase is 4 months.. Pyrazinamide (and ethambutol) not used in continuation phase.

Source: Brazil MOH; Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC). The Hague: Tuberculosis Coalition for Technical Assistance, 2006. See appendix for full treatment regimens for all schemes.