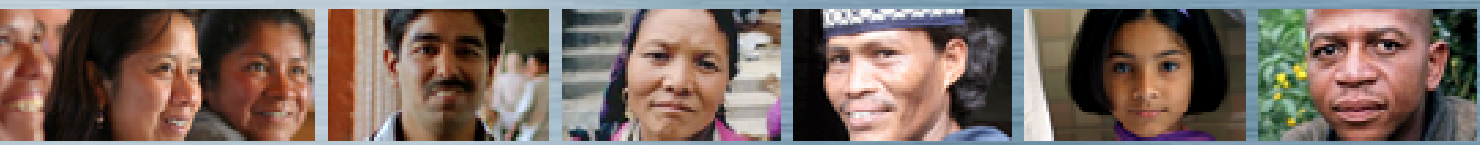
TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

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

France Case Study



Prepared with IMS Consulting

November 2006

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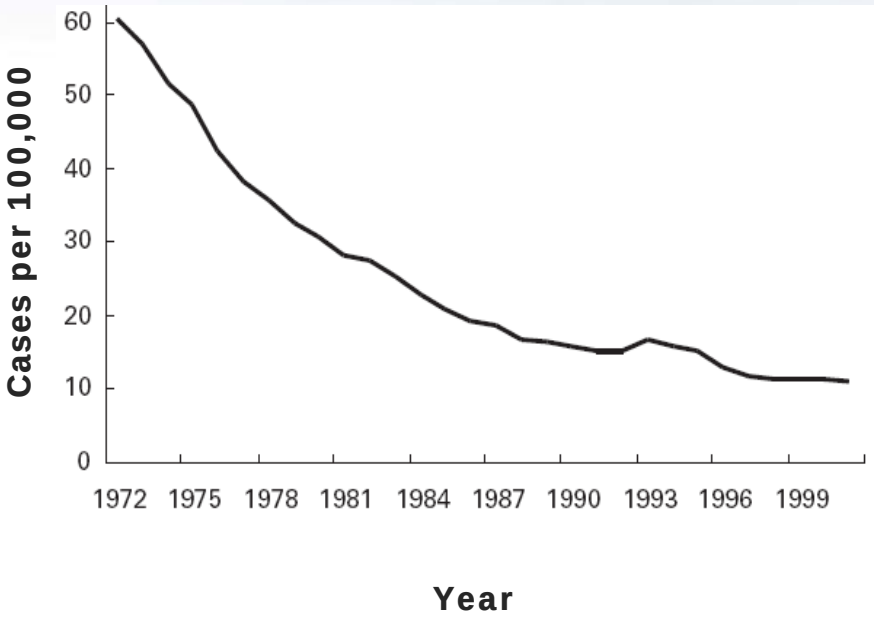
In France, the TB notification rates fell steadily for 20 years



Notification

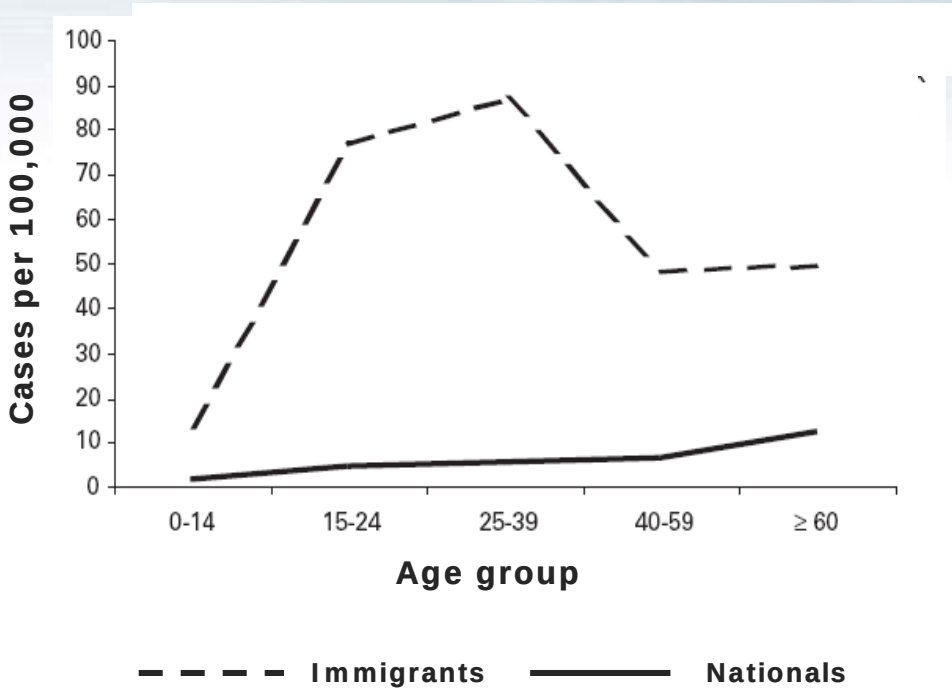
- Between 1972 and 1988 the number of notified cases of TB in France fell by 71%, more recently cases have begun to level off
- In total 6,242 cases were reported in mainland France in 2004

Detection

- Physicians are required to notify the Department of Health and Social Affairs (DDASS) of all suspected cases of TB
- Despite this obligatory declaration it is estimated that only 50% of cases are reported due to physicians failing to notify the DDASS

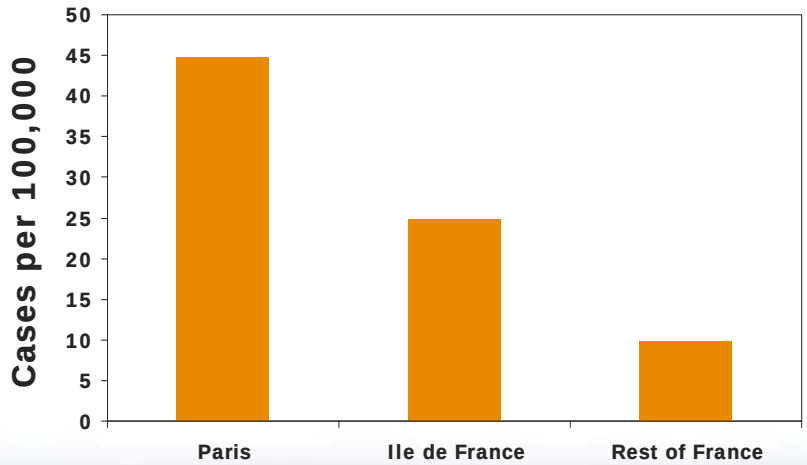
Source: Superior Council for Public Hygiene Guidelines; Bulletin Epidemiologique Hebdomadaire

Prevalence of TB is highest in Paris and, in particular, amongst immigrant populations



Epidemiology

- A majority of cases of TB in France are seen in immigrants
- Prevalence in highest in Paris as a result of the large concentration of high risk groups (i.e. PLWHA and immigrants from endemic countries) and high levels of poverty



Source: Superior Council for Public Hygiene Guidelines; Bulletin Epidemiologique Hebdomadaire

There are three major bodies involved in TB care at a national level

1 Directions Départementales des Affaires Sanitaires et Sociales (DDASS)

Sub-department of the Department of Health and Social Affairs

Responsible for surveillance and monitoring

2 Statutory health insurers

Receive funding from the treasury

Responsible for distributing funding to healthcare providers

3 Superior Council for Public Hygiene

Independent body consulted by the Minister of Health

Responsible for development of treatment guidelines

Source: Superior Council for Public Hygiene Guidelines, PQ Systems, Interviews, DH Website

Directions Départementales des Affaires Sanitaires et Sociales (DDASS) is a national body responsible for TB surveillance and monitoring and acts as the de facto national TB program

Department of Health and Social Affairs

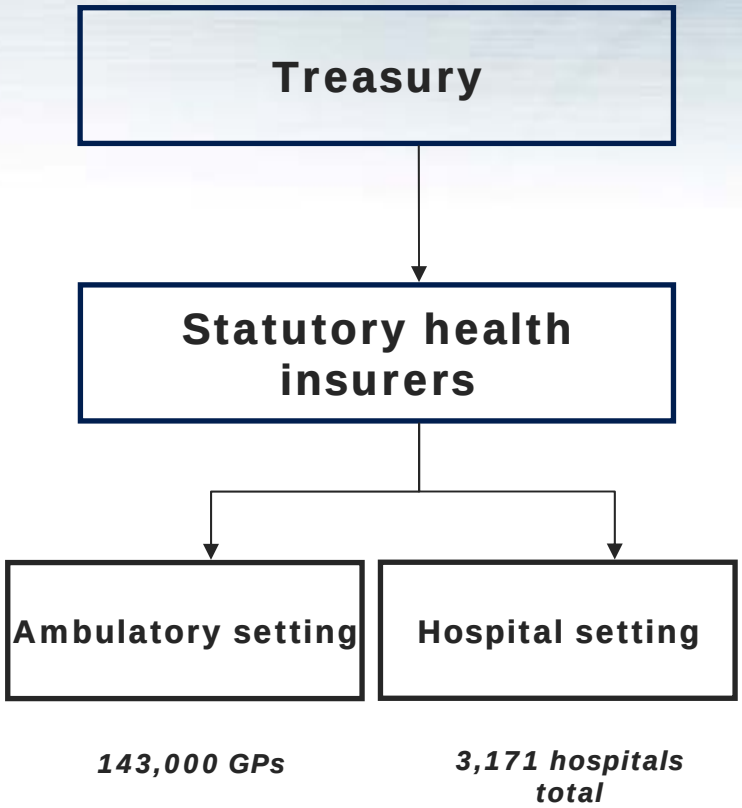
Directions Départementales des Affaires Sanitaires et Sociales

- Physicians are required by law to report all cases of TB to the DDASS
- The DDASS then traces and screens all contacts of TB patient and records epidemiological data about the patients
- This data is passed to the Institut de Veille Sanitaire (InVS) for collation
- Data on treatment outcomes are not routinely reported, but default rates are estimated at 22%
- Data on HIV infection among TB cases is not routinely reported

Source: Department of Health and Social Affairs, interviews

Statutory health insurers set budgets for all public and semi-private sector GPs and hospitals for all diseases

Flow of funding



Treasury

- Money is collected from taxpayers by the treasury
- The Agence Centrale des Organismes de Securite Sociale (ACOSS) is responsible for distributing funding to the health insurers

Statutory health insurers

- Distribute funding to the hospitals and GPs in both the public and semi-private sector

Healthcare providers

- Responsible for providing care to patients
- Receive block funding from the health insurers which they are able to spend without restriction by the insurers
- Size of patient contributions depend on whether the facility is public or semi-private

Source: PQ Systems

The Superior Council for Public Hygiene makes clinical recommendations, one of which is the use of BCG vaccination in all children under the age of six

Age Group	Recommendation
Children under 6 years old	***Vaccination is obligatory*** Administered at birth to children at medium to high risk and before starting school for all others
Children over 6 years old	***Vaccination is obligatory*** Administered when first entering an educational establishment
Adults	***Vaccination on a case-by-case basis*** Strongly recommended to people in certain occupations, certain ethnic communities and people exposed to infected persons

Source: Superior Council for Public Hygiene Guidelines

The Superior Council for Public Hygiene recommends a four drug regimen for active TB patients

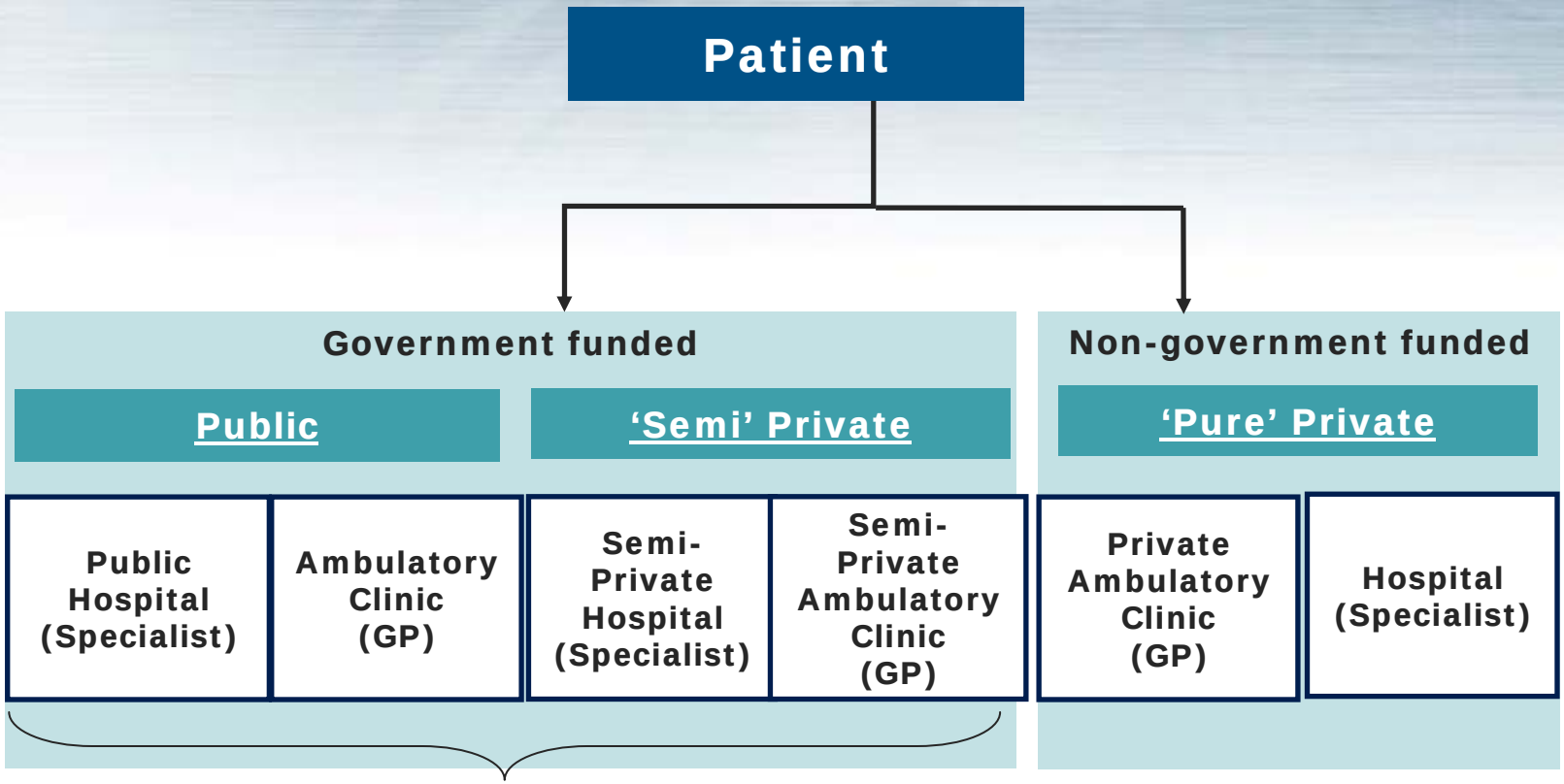
Category	Definition	Initial Phase	Continuation Phase
New patient	Smear positive patient not having previously received care	2HRZE	4HR
Isoniazid resistance	Infected with TB resistant to isoniazid	2RZ	-
		3RE	-
MDR TB	Infected with TB resistant to two or more 1st line drugs	5 drugs the organism is susceptible to (at least 2 of which, preferably 3, should not have been used before) – until sputum negative	At least 3 drugs the organism is susceptible to for a further 9 months (up to 24 months)
Latent	Positive Mantoux test or interferon-gamma immunological test. No symptoms	6-12H	-
		3RH*	-
		4R	-
		2RZ	-

**The most common approach to treating latent TB in France*

As there are not explicit guidelines for the treatment of MDR TB specialists treating a patient with it are able to contact a specified member of the National Reference Laboratory for treatment advice at the beginning of treatment. Those requiring extra assistance are able to contact refer their patient for treatment by this person

Source: Superior Council for Public Hygiene Guidelines

TB patients can be treated in government or non-government funded sectors, although most are treated in the government funded sector

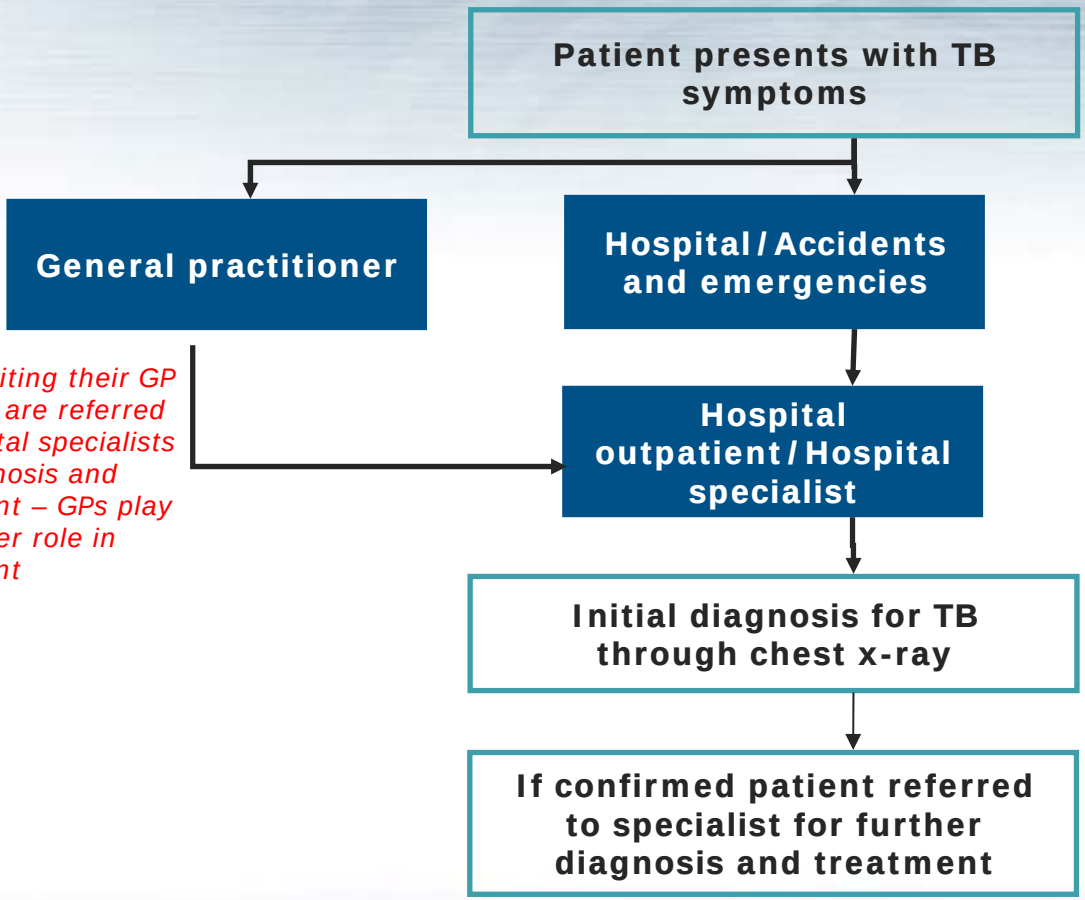


Most patients will receive all treatment in the government funded sector

Source: PQ Systems, interviews

Patients can visit their GP, but most go directly to a hospital Accident and Emergency Department

Patient flow through initial diagnosis



After visiting their GP patients are referred to hospital specialists for diagnosis and treatment – GPs play no further role in treatment

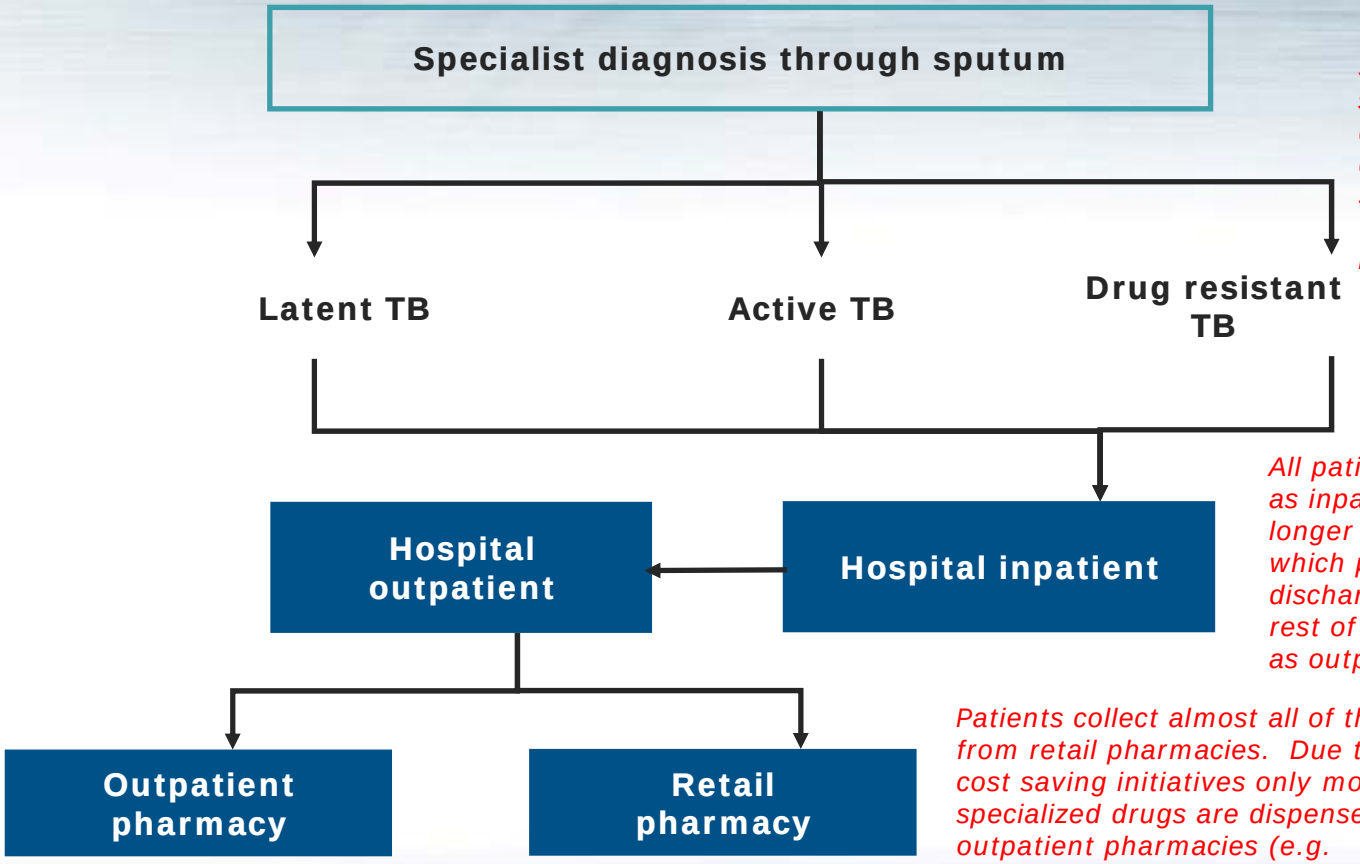
A majority of patients (75%) will go directly to Accident and Emergency. It is cheaper than paying to see a GP. Those identified by Accident and Emergency as potentially having TB are sent straight to the hospital specialist for diagnosis and treatment

Patient suspected of having TB after initial chest x-ray are referred to a hospital specialist for further diagnosis and treatment. Patients may be referred to a public or private hospital specialist

Source: PQ Systems, Interviews

Specialists confirm the initial diagnosis, categorize and treat TB patients

Patient flow through confirmation of diagnosis and treatment



Specialists use sputum samples to confirm diagnosis and check for drug resistance. Samples are sent to a 'Centre National de Référence' Laboratory

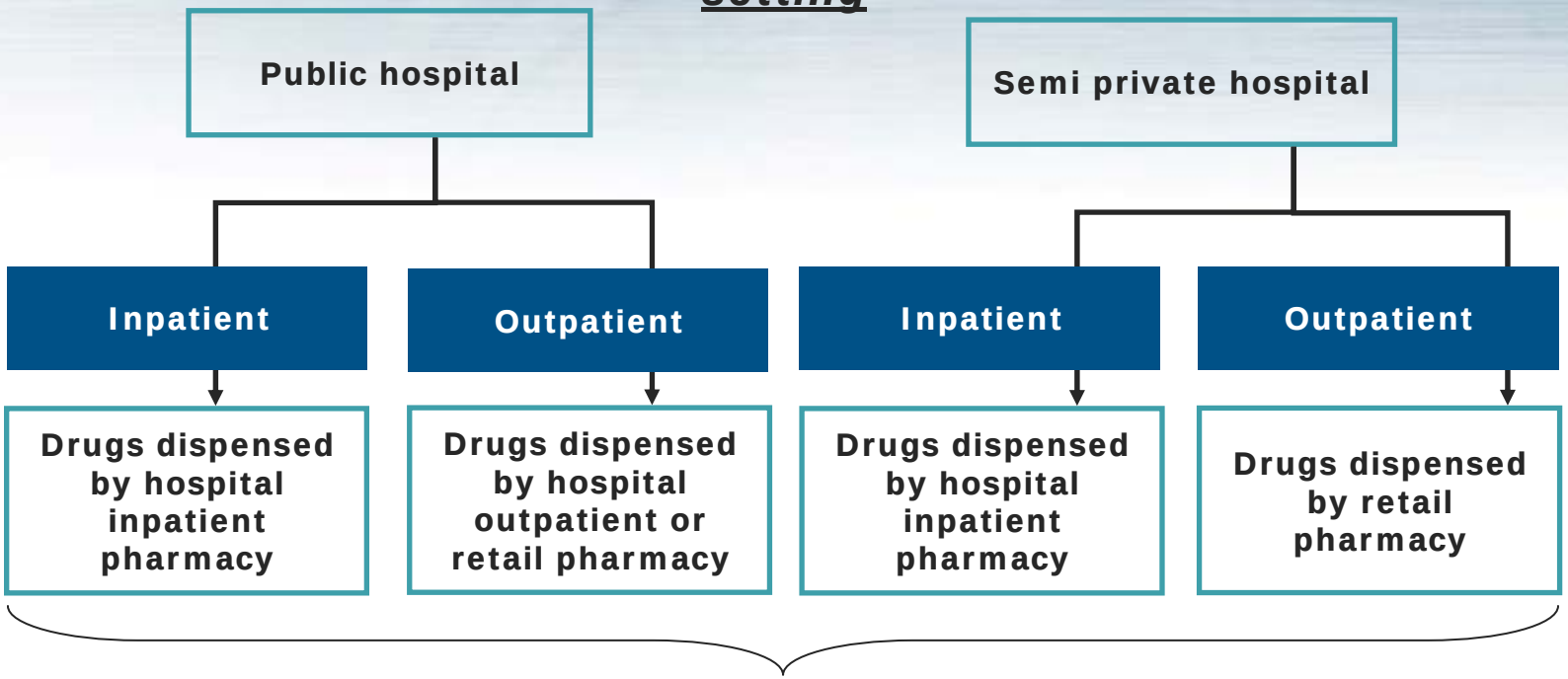
All patients are treated as inpatients until no longer contagious at which point they are discharged. Receive the rest of their treatment as outpatients

Patients collect almost all of their drugs from retail pharmacies. Due to French cost saving initiatives only more specialized drugs are dispensed by outpatient pharmacies (e.g. streptomycin).

Source: Superior Council for Public Hygiene Guidelines, Interviews

TB treatment and drugs have a special listing under the French healthcare system and so are completely free of charge to patients

Charges for TB drugs in each healthcare setting



TB is classified as an Affection de Longue Duree (ALD) and so exempt from all consultation fees, hospital charges and drug co-pays irrespective of sector. All treatment and drugs are always 100% covered by social security and free of charge.

Source: PQ Systems, interviews

Social security also funds the treatment of TB for immigrants living in France

Immigrant entitlement to healthcare within the government funded sector

Status	GPs	Hospitals
Immigrants who have lived in France for <3 months	100% healthcare coverage "for urgent treatments whose absence could lead to death or a serious deterioration in health of that person or their unborn child"	
Immigrants who have lived in France for >3 months earning less than €597.16 per month Asylum seekers	Covered by AME (Aide médicale de l'Etat) and so patients are entitled to receive treatments covered by the CMU (Couverture Maladie Universalle) free of charge	

- CMU is a statutory health insurance provided to people who do not qualify for any other statutory insurance
- As they are covered by CMU, immigrants are entitled to free access to the French healthcare system as they do not have complementary insurance they must usually pay co-pays
- However, as TB is an *Affection de Longue Durée* there are no co-pays associated with it and so immigrants receive treatment for TB free of charge

Source: www.cyes.info

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In the France, TB drug procurement mechanisms vary according to the setting in which drugs are dispensed

Procurement mechanisms

Hospital buying groups

- ***Public hospitals located within cities with buying groups***

Direct negotiations

- ***Public hospitals not located within cities with buying groups***
- ***Semi-private hospitals***
- ***Retail pharmacy***

NB: GPs do not treat TB patients and so are not included here

Source: PQ Systems, Interviews

A number of public hospitals within the large cities have formed buying groups which procure drugs on their behalf

Procurement mechanisms

Hospital buying group

Direct negotiations

Public Hospitals

- Public hospitals within the cities of Paris, Lyon and Marseilles operate buying groups, which negotiate directly with manufacturers on behalf of all group members

- These groups must use a bid and tender system for all purchases of £100,000 or more (mandatory under EU law for public hospitals)

Source: PQ Systems, interviews

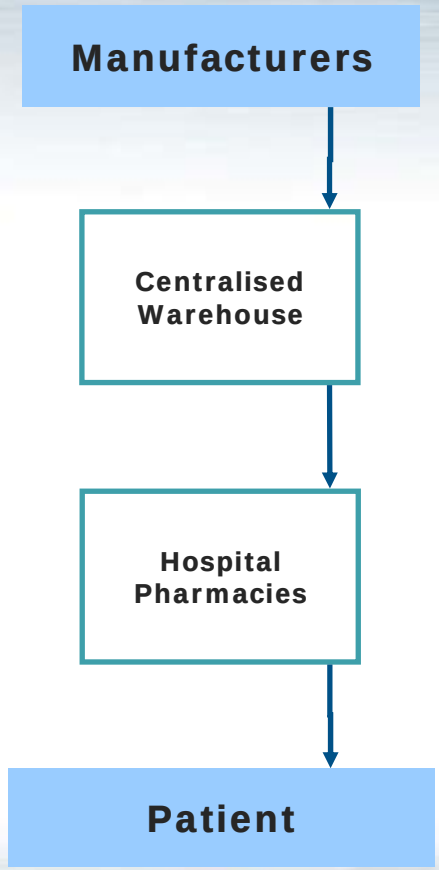
These drugs are distributed by manufacturers to a centralized group warehouse from which each hospital pharmacy sources its drugs

Drug Flow: Public Hospitals (buying group)

***1st point of sale*: Manufacturers holding the contract with the buying group supply drugs direct to a centralized warehouse at the agreed price**

***2nd point of sale*: Drugs are purchased by the buying group and held in the warehouse until required by a hospital within the group. The hospital receiving the drugs issues a payment to the buying group**

***Hospital sale*: Hospitals distribute drugs to the patient. The patient, or their complementary insurer, will pay a certain level of co-pay and the remainder is paid by social security**



Source: PQ Systems, interviews

All other public and semi-private hospitals must negotiate directly with suppliers to procure drugs

Procurement mechanisms

Hospital buying group

Direct negotiations

Public and Semi-Private Sector Hospitals

- Public hospitals that do not belong to buying groups and semi-private hospitals negotiate individually with manufacturers
- Must also operate a bid and tender system for all purchases of £100,000 or more (mandatory under EU law)

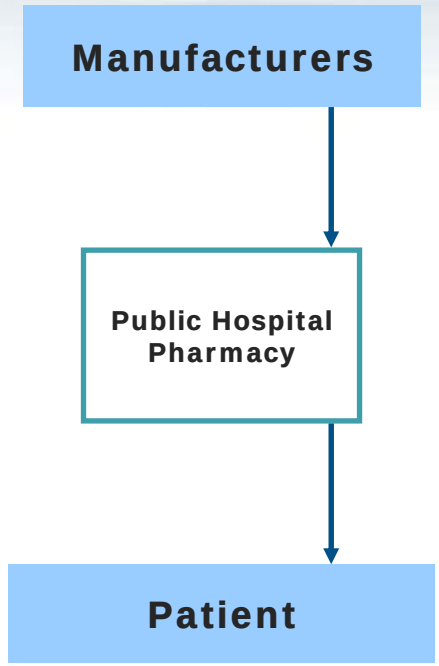
Source: PQ Systems, interviews

Suppliers then distribute drugs directly to the hospital pharmacies

1st point of sale: Manufacturers holding the contract supply drugs at the agreed price direct to hospitals or, if they lack a distribution network, via a wholesaler

Hospital sale: Hospitals then distribute drugs to the patient. The patient, or their complementary insurer, will pay a certain level of co-pay and the remainder is paid by social security

Drug Flow: Public (non-purchasing group) / Semi-private Hospitals



Source: PQ Systems, interviews

Retail pharmacies are not entitled to form chains and so negotiate individually

Procurement mechanisms

Hospital buying group

Direct negotiations

Retail Pharmacies

- **Retail pharmacies are not permitted to form pharmacy chains in France**
- **Instead, each pharmacy individually negotiates prices with wholesalers or manufacturers (in rare cases)**
  - **Suppliers may only offer authorised margins and discounts to pharmacists, in turn, pharmacists are only permitted to use specified mark-ups, thus profitability is limited**

Source: PQ Systems, interviews

Wholesalers and manufacturers then distribute drugs directly to the purchasing retail pharmacy

Drug Flow: Retail Pharmacy Sector

1st point of sale: **Manufacturers supply drugs to wholesalers or direct to the purchasing pharmacies**

2nd point of sale: **Wholesalers sell drugs to pharmacies. Margins are limited for most generic (covers most TB drugs) and all branded products to roughly 10% of ex-manufacturers price**

Pharmacy sale: **Drugs are always reimbursed at the list price so the larger the discount the pharmacist can obtain the greater the profit**

Source: PQ Systems, interviews

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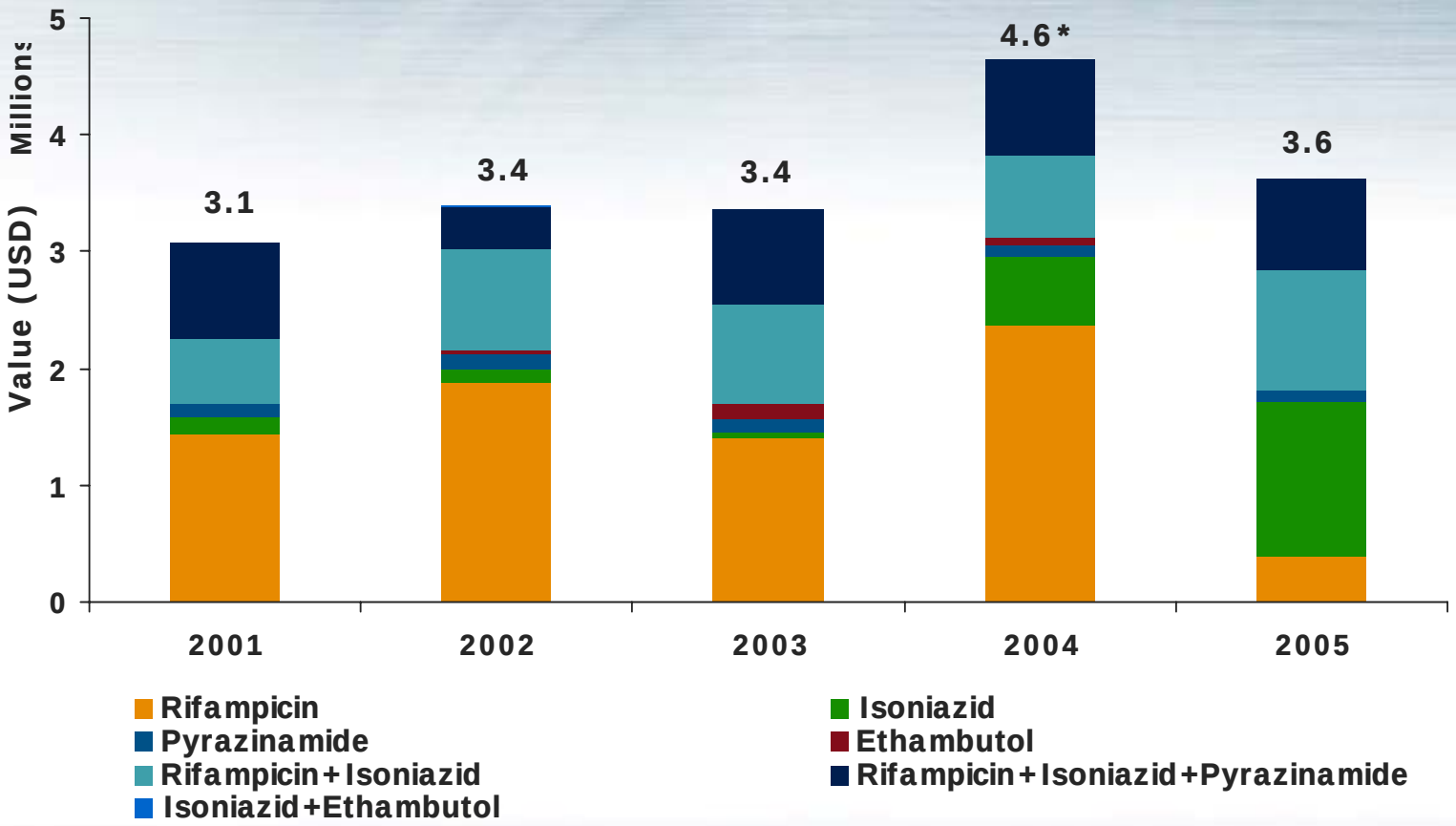
The 1st line TB drug market has been relatively stable over the past five years and is currently valued at 3.6M USD

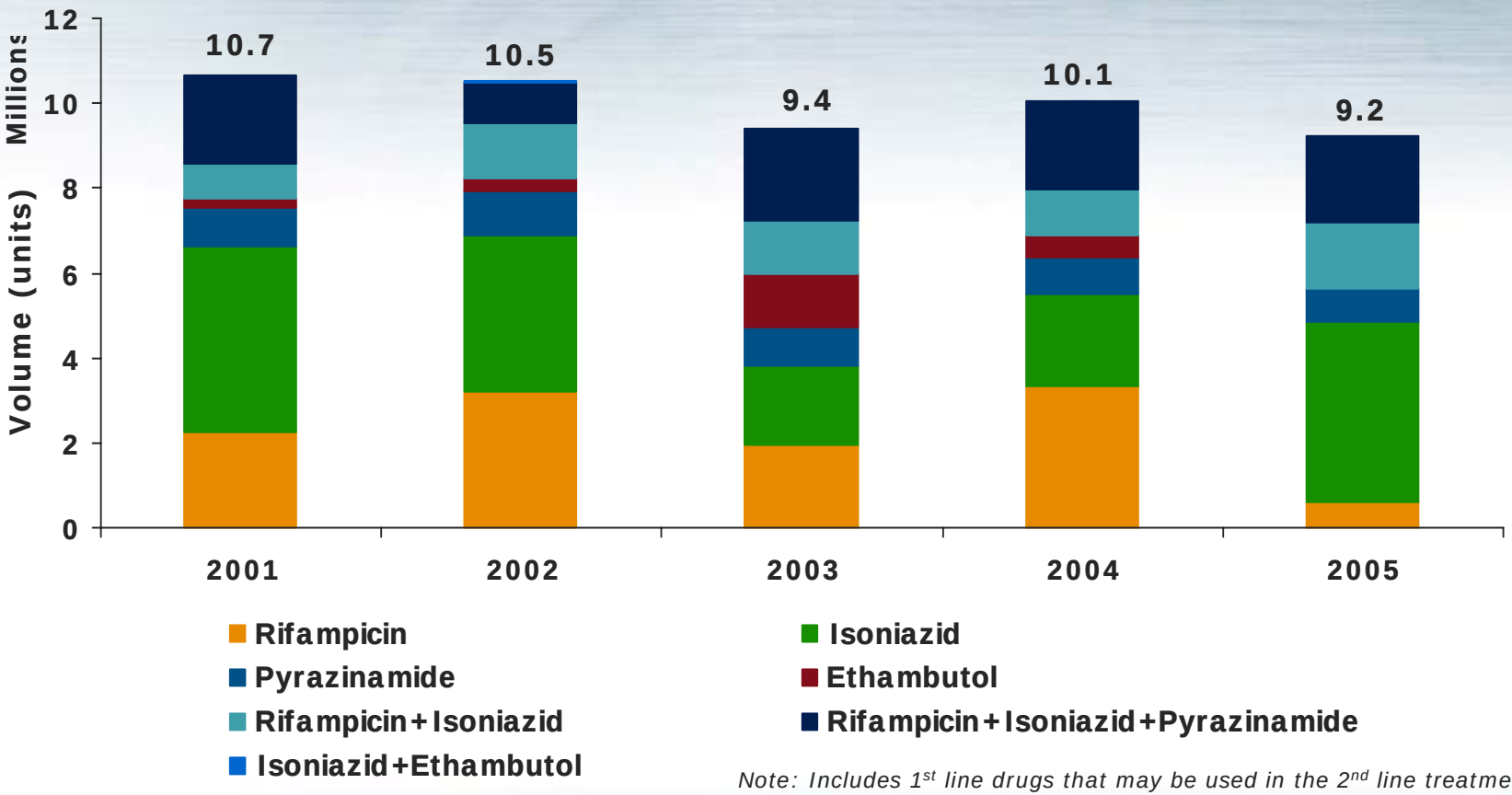


Note: Includes 1st line drugs that may be used in the 2nd line treatment

Source: IMS MIDAS data

*Fluctuations were interpreted around limitations of IMS data base around percent sales of use for TB

The volume of the 1st line market has also been stable—9.2M units were dispensed in 2005



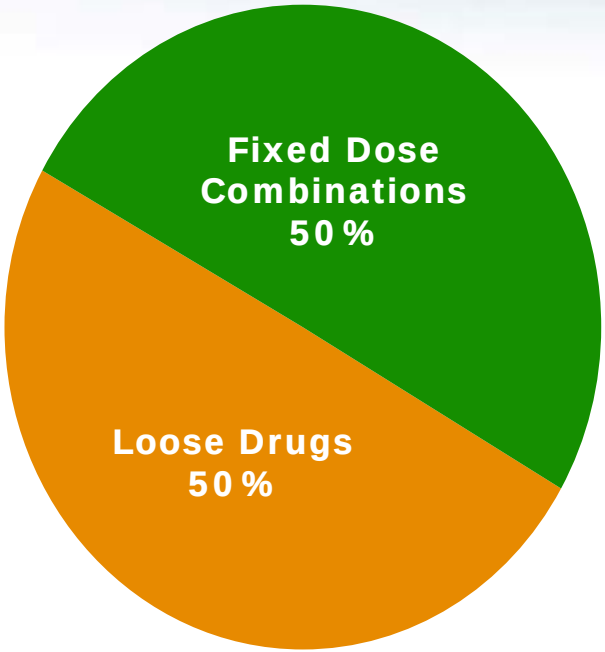
Note: Includes 1st line drugs that may be used in the 2nd line treatment

Volume refers to the number of units (e.g. tablets) dispensed

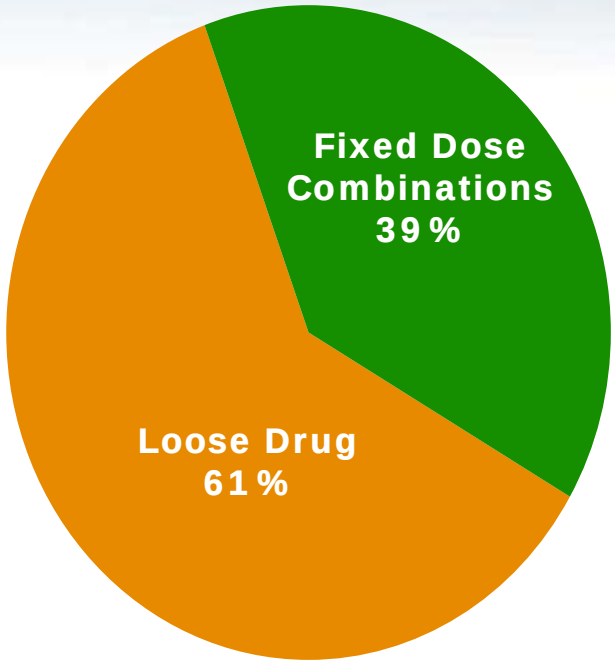
Source: IMS MIDAS data

FDCs currently account for 50% (1.8M USD) of the French market value and 39% (3.6M units) of the volume

Total 1st Line TB Market Value by Formulation in 2005 (3.6M USD)



Total 1st Line TB Market Volume by Formulation in 2005 (9.2M USD)



Note: Includes 1st line drugs that may be used in the 2nd line treatment

Volume refers to the number of units (e.g. tablets) dispensed

Source: IMS MIDAS data

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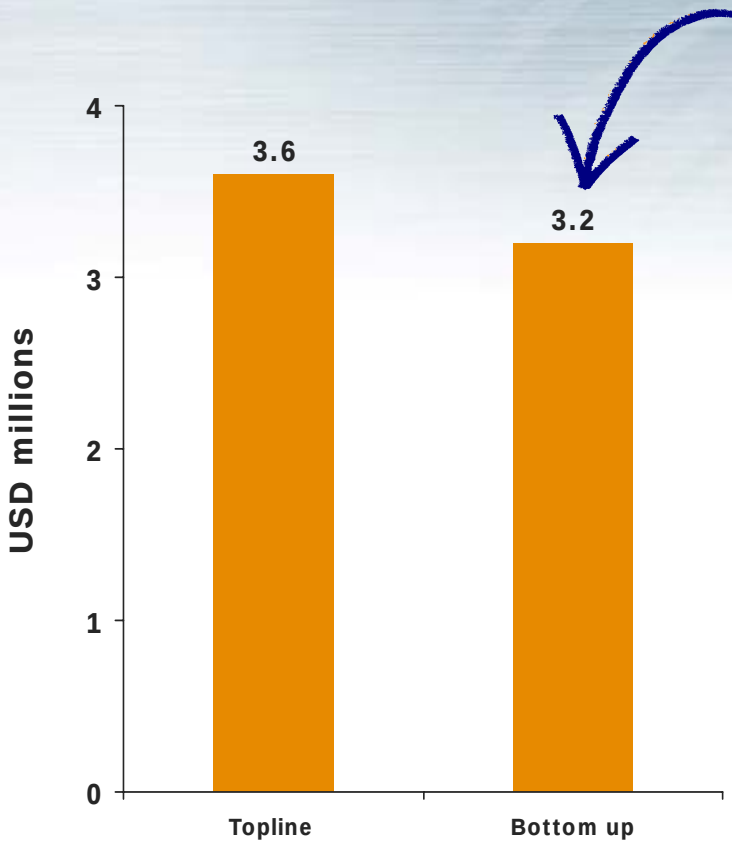
Bottoms up estimates confirm the top line value data and give a 1st line market estimate of between 3.2-3.6M USD



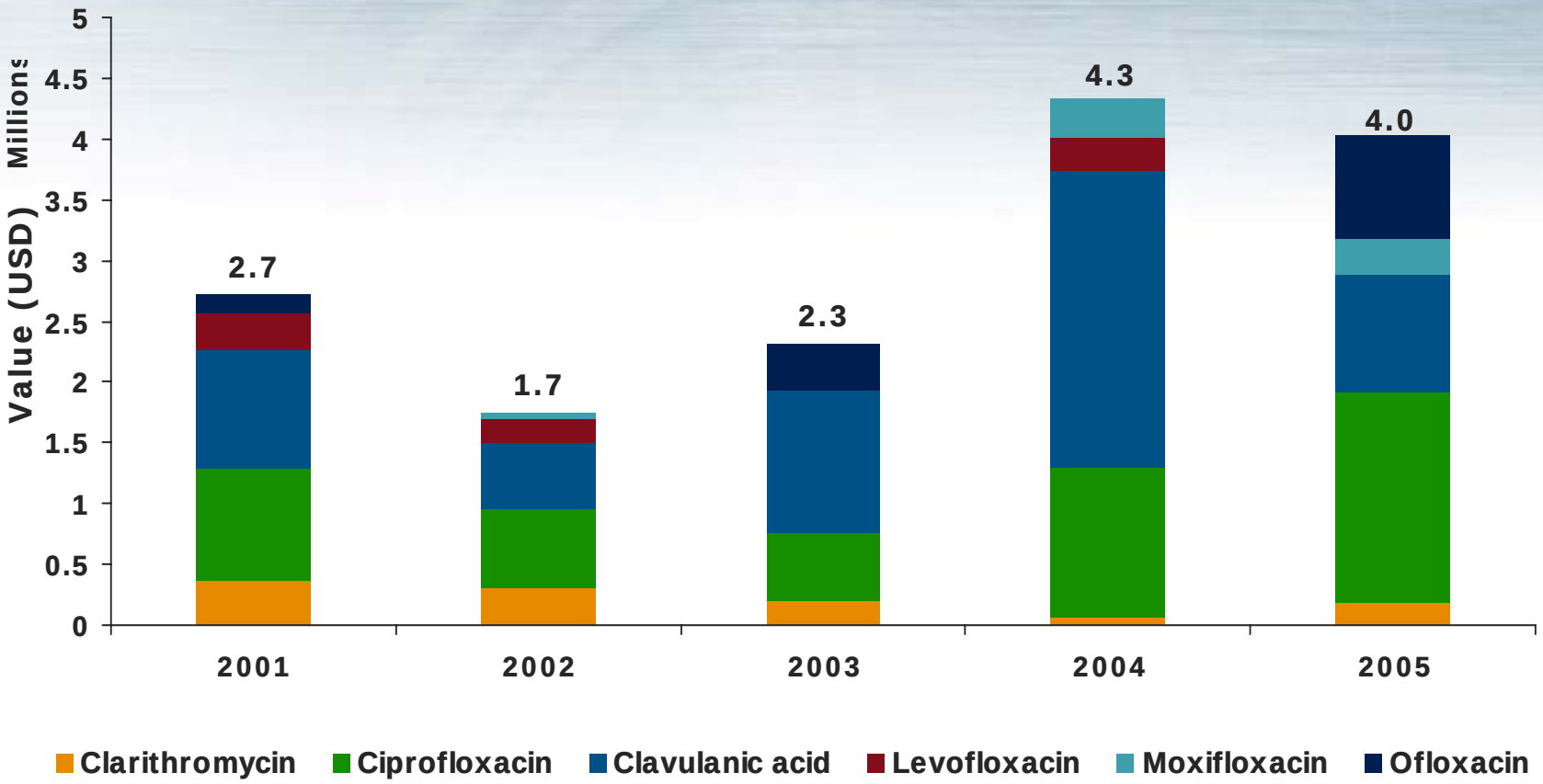
	Active	Resistant	Latent	Retreated
Total patients	6,216			
Patients per category*	5,252	236	452	276
Average cost per patient	270.92	349.05	69.27	270.92
Total cost per category	1,422,862	82,375	31,310	74,774
1st line estimate	1,611,320			
1st line adjusted estimate**	**3,222,640**			

*** A number of studies have suggested that only 50% of cases are reported in France – hence we can increase the estimate by a factor of 2*

Note: Does not 1st line drugs that may also be used in the 2nd line treatment

Source: EuroTB, IMS MIDAS data, IMS analysis, BNF. See appendix for details of calculation

The market value of all 2nd line TB drugs is growing overall and is currently valued at 4M USD

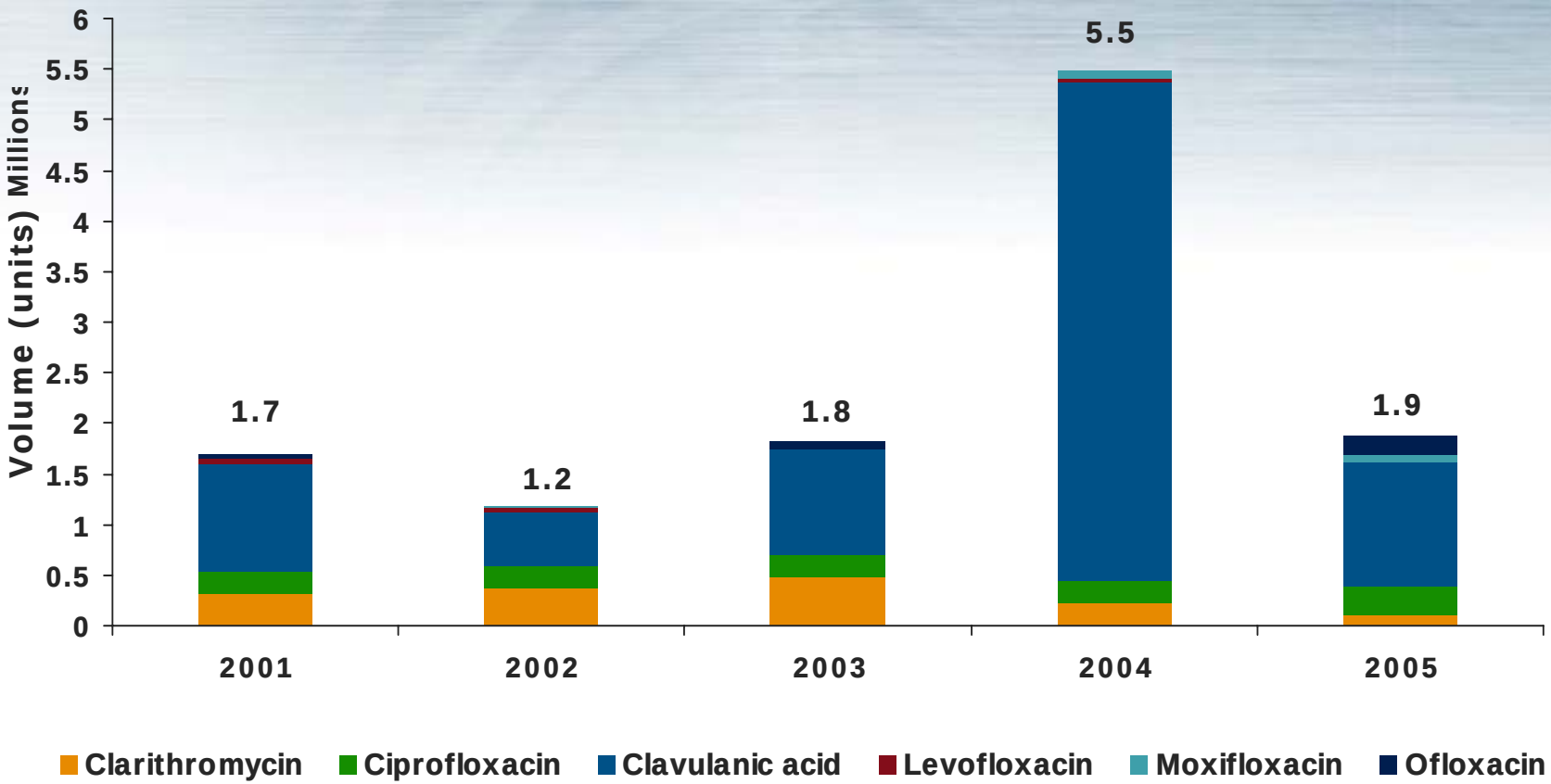


Source: IMS MIDAS data

Note: Includes 1st line drugs that may be used in the 2nd line treatment

*Data was not available for all 2nd line drugs used in this country. Drugs listed do not comprise full 2nd line treatment regimen in this country.

Other than a steep increase in 2004, the volume of 2nd line TB drugs dispensed has remained stable and currently stands at 1.9M units



Source: IMS MIDAS data

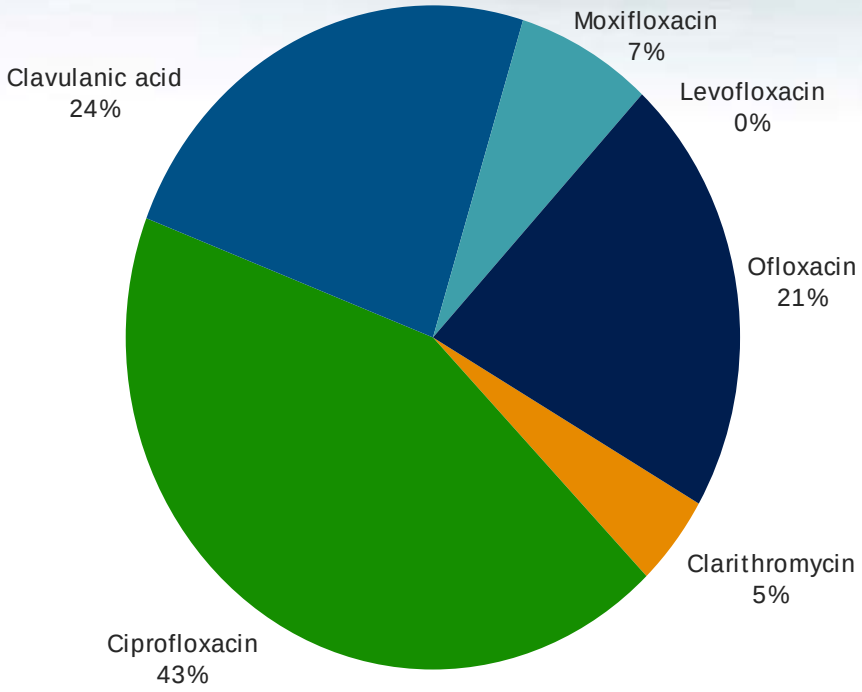
Note: Includes 1st line drugs that may be used in the 2nd line treatment

Volume refers to the number of units (e.g. tablets) dispensed

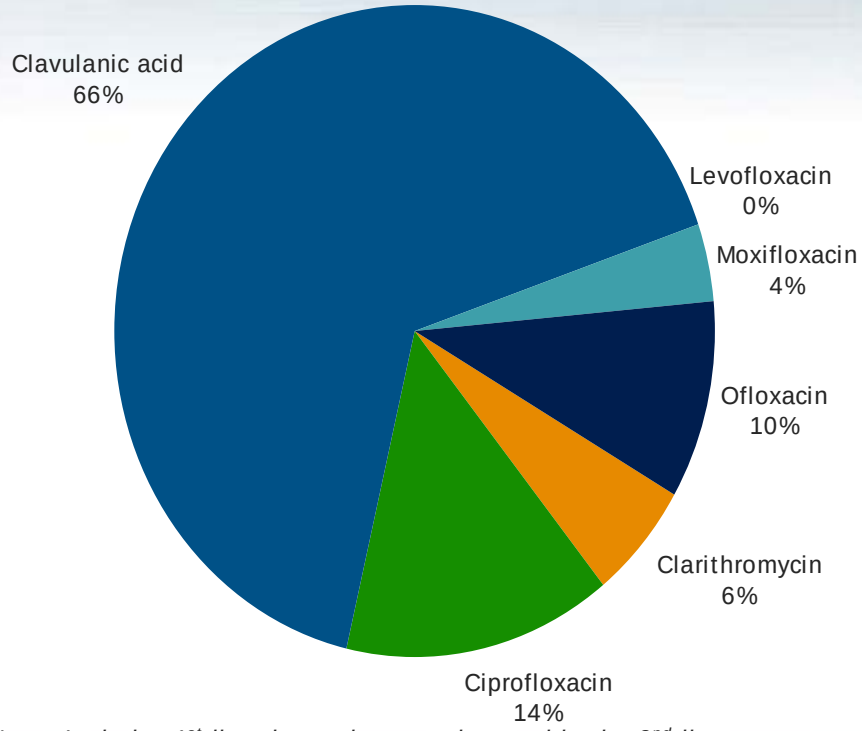
*Data was not available for all 2nd line drugs used in this country. Drugs listed do not comprise full 2nd line treatment regimen in this country.

Ciprofloxacin dominates the 2nd line market value with sales of 1.8M USD, whereas clavulanic acid has the greatest volume of sales with 1.2M units in 2005

Total 2nd Line TB Market Value by Drug in 2005 (4M USD)



Total 2nd Line TB Market Volume by Drug in 2005 (1.8M units)



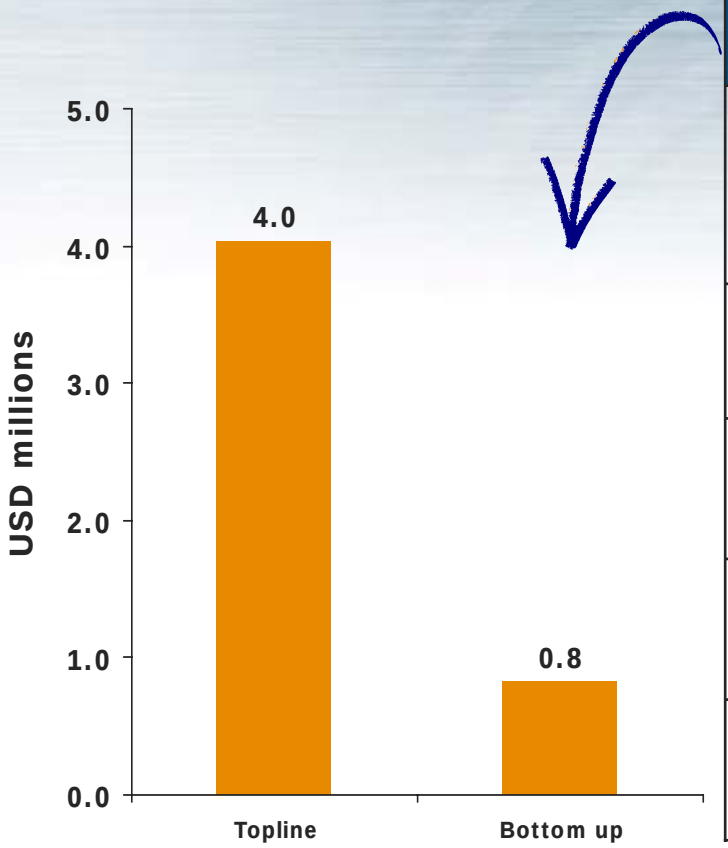
Source: IMS MIDAS data

Note: Includes 1st line drugs that may be used in the 2nd line treatment

Volume refers to the number of units (e.g. tablets) dispensed

*Data was not available for all 2nd line drugs used in this country. Drugs listed do not comprise full 2nd line treatment regimen in this country.

Top line value figures and bottom up calculations suggest the 2nd line market value is 0.8M to 4M USD



	Diagnosed in 2003	Diagnosed in 2004
Total patients receiving treatment in 2004	51	
Patients per category*	25	26
Average cost of treatment	5635	9049
2nd line estimate	376,131	
Adjusted 2nd line estimate**	752,263	

*Note: Does not include 1st line drugs that may also be used in the 2nd line treatment. **A number of studies have suggested that only 50% of cases are reported in France – hence we increase the estimate by a factor of 2*

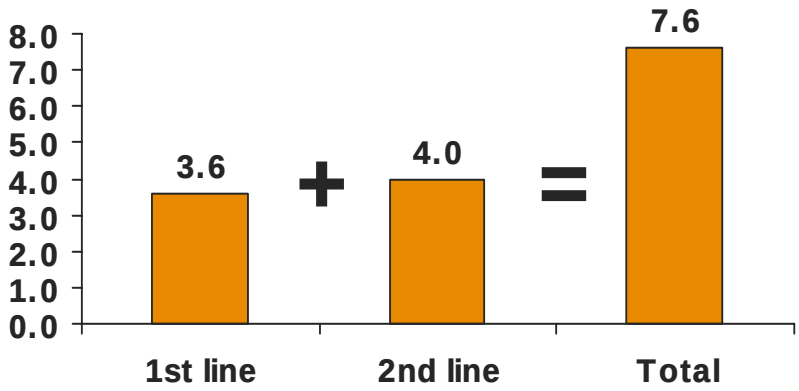
Source: EuroTB, IMS MIDAS data, IMS analysis, WHO, interviews. See appendix for details of calculation

However, it is impossible to perform an accurate bottom up calculation for 2nd line drugs due to large numbers of uncertainties, hence, value is estimated to be 4M USD

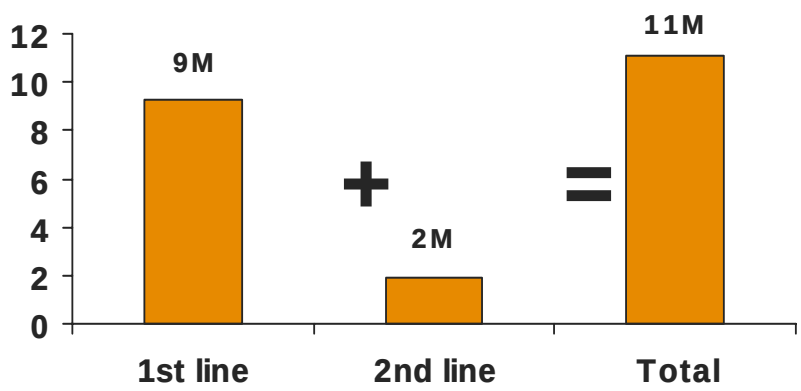
- A bottom up calculation involves assumptions about which drugs are administered to 2nd line patients, the dose at which they are given and the duration of treatment, all of which vary widely between patients
- Additionally, in 1st line patients suffering from side effects the 1st line drug responsible for those side effects is often substituted for a 2nd line drug
- Physicians estimated the incidence of side effects to be between 5-30%, however it is impossible to be certain how many 1st line drugs are substituted in these cases and which 2nd line drugs they are substituted for
- Hence, there are too many uncertainties for an accurate bottoms-up calculation and value is estimated to be $4M USD (based on IMS MIDAS figures)

If we combine the value and volume of 1st and 2nd line drugs we have a market value of 7.6M USD and volume of 11M units

Total French TB drug market value (7.6M USD)



Total French TB drug market volume (11M units)



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Total market value and volume figures for all 1st line drugs in 2005*

1st line drug	Volume (units)	Value (USD)
Rifampicin	599,613	395,006
Isoniazid	4,250,000	1,313,542
Pyrazinamide	794,490	99,189
Rifampicin/isoniazid combinations	1,555,396	1,032,207
Rifampicin/isoniazid/ pyrazinamide combinations	2,046,442	789,165

Source: IMS MIDAS

*Figures for ethambutol and isoniazid/ethambutol combinations were not available for 2005, thus data from earlier years were used

Total market value and volume figures for all 2nd line drugs in 2005*

2nd line drug	Volume (units)	Value (USD)
Clavulanic acid	1,239,410	962,702
Clarithromycin	111,343	181,662
Ofloxacin	184,270	856,686
Ciprofloxacin	268,896	1,735,659
Moxifloxacin	70,056	294,753

Source: IMS MIDAS

*Figures for levofoxacin were not available for 2005, thus data from earlier years were used

Manufacturers of 1st line drugs in France

1st line drug	Manufacturer
Rifampicin	Sandoz; Sanofi Aventis
Isoniazid	Laphal
Pyrazinamide	Sanofi Aventis
Ethambutol	GenoPharm; SERP; GSK
Rifampicin + Isoniazid	Sanofi Aventis
Rifampicin + Isoniazid + Pyrazinamide	Sanofi Aventis

Source: IMS MIDAS

Manufacturers of 2nd line drugs in France

2nd line drug	Manufacturer
Levofloxacin	Sanofi Aventis
Ofloxacin	Sanofi Aventis, Sandoz
Ciprofloxacin	Sandoz
Clavulanic acid	Sandoz

Source: IMS MIDAS

Method of calculating cost of treating 1st line TB patients

- Patient numbers were sourced from the EuroTB website
- Cost of the regimen (for a 70kg patient) was calculated using prices of the most popular brand and pack size (by units sold) for each of the 1st line drugs
- Patient population was split into active, drug resistant, latent and retreated
- The size of each subpopulation of TB patients was then multiplied by the cost of the regimen they receive
- These figures were then summed to give a top-line value
- The low end estimate was derived by summing the lowest cost regimen to treat each of these subpopulations of patients
- The high end estimate was derived by summing the highest cost regimen to treat each of these subpopulations of patients

Method of calculating cost of treating 1st line TB patients (USD)

	Active	Latent	Retreated	Resistant
Total patients receiving treatment in 2004	6,216			
Patients per category*	5,252	236	452	276
Average cost of treatment	270.92	69.27	270.92	349.05
First Line estimate	1,611,320			
Adjusted Second Line estimate*	3,222,640			

**A number of studies have suggested that only 50% of cases are reported in France – hence we can increase the estimate by a factor of 2*

Source: IMS MIDAS, IMS Expertise

Method of calculating cost of treating 2nd line TB patients

Hospital

	Drug	Price per day	Price for one year
Initial Phase	Cipro	3.65	1335.17
	Ofx	4.04	1476.04
	Moxi	3.26	1189.87
	Clav	6.72	2453.89
	Clarith	1.67	611.01
Cont. Phase	Clav	6.72	2453.89
	Clarith	1.67	611.01
	Cicpro	3.66	1335.17
Total cost of treatment - Euros			11,466
Total cost of treatment - USD			14,683
Cost of initial phase			9049
Cost of continuation phase			5635

Retail

	Drug	Price per day	Price for one year
Initial Phase	Cipro	3.26	1189.90
	Ofx	3.30	1205.11
	Moxi	1.67	611.01
	Clav	3.80	1387.00
	Clarith	5.23	1909.41
Cont. Phase	Clav	3.80	1387.00
	Clarith	5.23	1909.41
	Cicpro	3.26	1189.90
Total cost of treatment - Euros			10,789
Total cost of treatment - USD			13,816
Cost of initial phase			8070
Cost of continuation phase			5745

Source: IMS MIDAS, IMS Expertise

MIDAS data in France is collected in government funded hospitals and retail pharmacies

- MIDAS data in France is collected for government funded hospitals and retail pharmacies – drugs dispensed by private hospitals are not included
  - All prescriptions dispensed by pharmacies in public and semi-private hospitals and retail pharmacies are captured in the data
  - Hospital data includes prescriptions dispensed by both hospital inpatient and outpatient pharmacies
- The value data we have used is collected at an ex-manufacturer price and so represents the value of drug sales when sold by the manufacturer (not the value of sales to the end user)
- The volume data we have used collects units sold. The figure given covers the number of individual units sold. In most cases a unit is a single tablet. For injectables it is a single pre-filled syringe

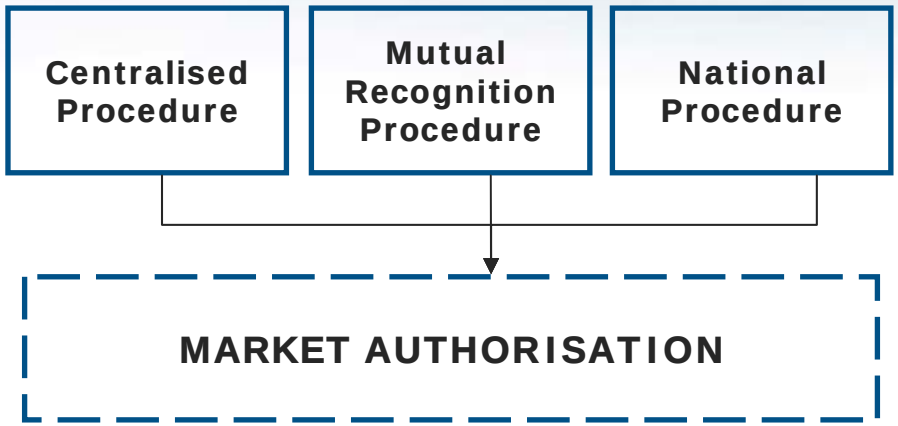
Source: IMS MIDAS

PharmaQuery Systems is IMS's unique online database of Pricing and Reimbursement regulations in 22 key world markets

- PQ Systems provides detailed coverage, on a country by country basis, of 22 key pharmaceutical markets
  - Argentina, Australia, Belgium, Brazil, Canada, Chile, China, Denmark, France, Germany, Hungary, Italy, Japan, Mexico, Netherlands, South Korea, Spain, Sweden, Switzerland, UK and the USA
- It contains detailed information about pricing and reimbursement regulations in each country
  - This information is divided into 4 areas; facts and figures, healthcare system, pharmaceutical market and useful information
- Information is updated daily by a network of multilingual pricing analysts

Source: www.imshealth.com

Manufacturers with new drugs are able to obtain market authorisation through one of three routes



In order to obtain permission to sell a drug in France (marketing authorisation) the manufacturer may apply through one of three routes:

Centralised procedure

- The European Medicines Agency (EMEA) reviews applications and then is able to grant access throughout all EU member states

National procedure

- AFFSAPS is responsible for granting marketing authorisation for drugs in France only
- This would result in access also being granted in all EU member states via mutual recognition

Mutual recognition procedure

- Certain countries within the EU have an agreement in which when a drug is authorised through one of their national schemes it is automatically approved in all EU member states

Once access is granted the manufacturer is immediately free to market their drug in France

Source: PQ Systems

Following marketing authorisation, products are assessed for clinical value by the Transparency Commission (CT)

CT issues an ASMR rating… → **… that corresponds to a reimbursement recommendation** → **In additon, CT decides whether to issue a hospital authorisation**

CLINICAL VALUE ADDED

ASMR RATING CRITERIA	
1	Major therapeutic advance
2	Important improvement
3	Moderate improvement
4	Minor improvements
5	No improvement, but may be reimbursed
6	No improvement, should not be reimbursed

BENEFIT	SEVERITY	
	SERIOUS	NOT
Major	65%	35%
Moderate	35%	35%
Modest but reimbursed	35%	35%
Insufficient	0%	0%
Hospital products	100%	100%
Affections de longue durée	100%	100%

- The CT also grants *Agrément aux Collectivités Publiques* (hospital supply authorizations)
- Obtaining this entitles manufacturers to market their drugs to hospitals

Source: PQ Systems

Finally the actual price and level of reimbursement are determined by CEPs and UNCAM

TRANSPARENCY COMMISSION (CT)

COMITE ECONOMIQUE DES PRODUITS DE SANTE (CEPS)

- A *rapporteur* (external expert) cites the price decided by the manufacturer and the arguments developed to support this proposition
- CEPS compares the price to price in other countries' prices
- If CEPS is not happy with the price then it uses price volume agreements to limit the sales in France
- Manufacturers exceeding the agreed sales are forced to pay back part of their profits

UNION NATIONALE DES CASSIES D'ASSURANCE MALADIE (UNCAM)

- UNCAM use the CT's advice, in particular the SMR rating, to determine the exact rate of reimbursement
- UNCAM is free to place the reimbursement rate anywhere within the range defined by the SMR however to date they have only used 35% or 65%
- The reimbursement rate is published in the *Journal Officiel*

Source: PQ Systems