

Tuberculosis Drug Issues: Prices, Fixed Dose Combination Products and Second Line Drugs

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Overview of Current TB Drug Issues

Since Streptomycin became available in 1948 and other TB drugs were discovered in the 1950's and early 1960's, drug treatment of tuberculosis has become the mainstay of treatment. Where effective drugs are available, cure rates in excess of 90% are common. However, when drugs are not available or compliance rates are lower cure rates fall dramatically. The fact that about three million people die each year from tuberculosis reflects that despite the availability of effective treatment, many people in developing and transitional countries do not have access or do not take effective treatment for this widespread disease.

The major reasons for a lack of access to TB drugs is the cost of these drugs, the failure of delivery systems and a lack of emphasis in programs on ensuring compliance. All of the first line drugs are off patent and their prices should be close to production costs. However great variation exists between countries and in the US TB drug prices have increased rapidly. Many countries with major tuberculosis disease loads have been undergoing political, economic or health sector reform. This has often had an adverse effect on the efficiency of TB drug delivery systems. Finally, compliance remains an issue due to the long duration of therapy and the number of drugs to be taken. To address these issues WHO and IUATLD (International Union Against Tuberculosis and Lung Disease) have promoted the use of Directly Observed Treatment (DOT) utilizing Fixed Dose Combination (FDC) treatments. Quality concerns have been raised about the production of these drugs.

A recent troubling development in TB control has been the rapid emergence of Multiple Drug Resistant Tuberculosis (MDRTB) in developed, developing and

transitional countries. The accurate diagnosis and characterization of the drug sensitivity pattern of specific infections is difficult for many countries to do. Even once the sensitivity patterns are known, ensuring the availability of these reserve antibiotics is at present difficult due to the high cost for these drugs. The reasons for the high cost of these drugs include market failure, monopoly position or patent protection for a few modern drugs.

This paper will address all of these issues and suggest what a National TB program manager could do to ensure the availability of low cost, quality TB drugs.

Literature Review

Standard texts exist which describe the management of drug supplies in developing countries. Drug management includes selection, procurement, distribution, rational use, financing and quality assurance. The standard textbook "Managing Drug Supply" does not refer to the particular issues specific to tuberculosis drugs.

Chaulet in 1992 wrote one of the few papers that addressed issues related to the supply of anti-tuberculosis drugs and national drug policies. At that time, he reported that TB drugs accounted for about 3% of global drug consumption in low-income countries. He also highlighted how additional costs such as taxes and duties, commercial wholesales and retail markups etc increased the cost of the drugs either to the patient or to the health system by between 47% and 95%. Additionally, he pointed out the importance of integrating anti-tuberculosis drug supplies into the national drug policies.

Weil (1994) in a WHO report described the global situation for TB drugs at that time based on a survey of 74 developing countries. The paper highlighted issues such as difficulties in forecasting requirements, dramatic differences in prices on a country to country basis, and problems in quality assurance and distribution. Laing, in his discussion of this paper provided further information on the differences in prices between countries and highlighted the continued increase in TB drug prices in US compared with stable or declining costs internationally. He also pointed out that major differences in prices existed between non-profit suppliers. More recently Catalani (1999) estimated that the Indian market for TB drugs was about \$139 million with most of the drugs being sold through the private sector. Most of these drugs were provided in fixed dose combination products. In a paper titled "Estimate of the global market for rifampicin containing fixed dose combination tablets" by Norval et al (1999) the authors estimated the global market to be 305 million FDC tablets. Clearly this is only one component of the global market for TB drugs.

Fixed Dose Combination Tablets FDC's

A major initiative by WHO and IUATLD in 1998 and 1999 was aimed at promoting the use of Fixed Dose Combination tablets for the first line therapy of

TB in all TB programs, including both DOT and standard programs. The justification for promoting FDC's is the simplicity of treatment, with minimized prescription errors and improved compliance. In addition changing to FDC's would simplify drug management and prevent the misuse of rifampicin for treating other conditions such as chlamydae. In this era of multiple drug resistance, ensuring that the patient receives all four or two drugs helps to prevent the emergence of resistance because of particular drug stock outs.

Fixed Dose Combination formulations have been used for a number of years. These have been in different dosage forms in a single tablet or in "combo" packs in which a number of different drugs are blister packed for easy and standard dose consumption. Fixed Dose Combination formulations have been popular with private practitioners who treat tuberculosis.

The major concern about FDC formulations has been that of quality. Acocella in 1988 and in subsequent papers demonstrated that the bioavailability of rifampicin could be affected by combining the drug with other first line drugs. Simple dissolution and colorimetric assays were not able to predict the bioavailable rifampicin content of the FDC's. The bioavailability problem appears to be limited to rifampicin and is related to the crystalline structure of the drug.

To address these problems, WHO have agreed on standard formulations for FDC products and these have been included in the WHO Essential Drug list 11 Revision undertaken in November 1999. These formulations have been established to assure optimum dosing with a simple schedule related to the weight of individuals.

Table 1 Extract from WHO Drug Information Vol. 13, No. 4, 1999

rifampicin + isoniazid tablet, 60 mg + 30 mg, 150 mg + 75 mg, 300 mg + 150 mg

tablet, 60 mg + 60 mg, 150 mg + 150 mg (for intermittent use 3 times weekly)

rifampicin + isoniazid + pyrazinamide tablet, 60 mg + 30 mg + 150 mg, 150 mg + 75 mg + 400 mg tablet, 150 mg + 150 mg + 500 mg (for intermittent use 3 times weekly)

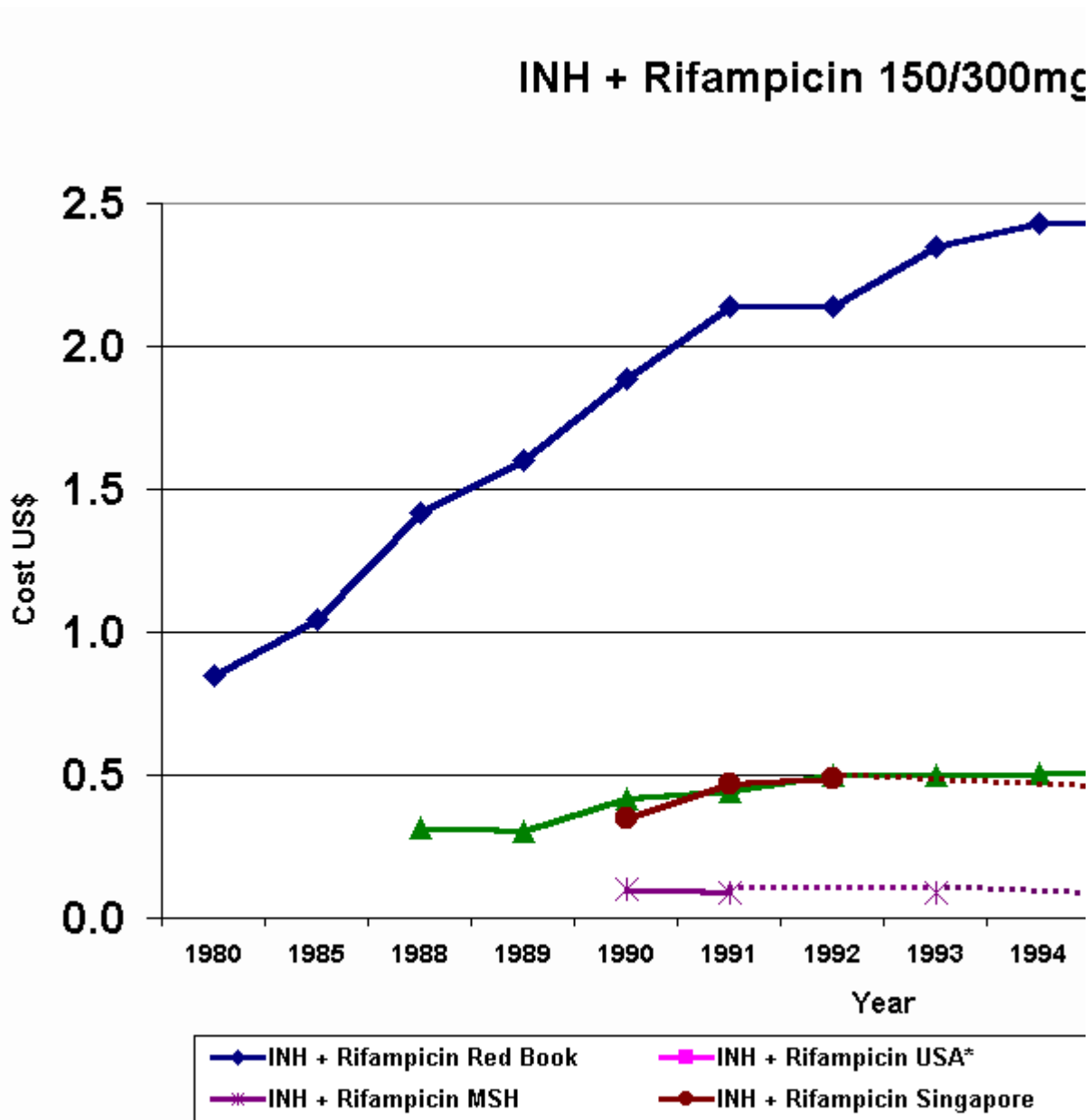
rifampicin + isoniazid + pyrazinamide + ethambutol tablet, 150 mg + 75 mg + 400 mg + 275 mg

In addition, WHO have specified a standardized protocol for in vivo assessment of rifampicin bioavailability. This abbreviated protocol allows for six blood samples over eight hours to be taken rather than the extended 15 time point collections over 48 hours. This abbreviated protocol will hopefully lead to more manufacturers entering the field and undertaking bioavailability testing to assure quality. For testing batch to batch variation and to check whether changes in manufacturing procedure have affected bioavailability, a single eight-hour urine

specimen could be used.

In addition to establishing the abbreviated protocol, WHO is moving to recognize a number of laboratories as reference laboratories for assaying these FDC preparations with particular reference to bioavailability. Two laboratories have already been recognized and others are in the process of registration as reference laboratories.

The price of FDC's has been a concern. However, the historical trend for the cost of the two-drug combination has been downwards as shown in Chart below:



Historical price of two drug combination tablets of Rifampicin and Isoniazid

One concern that has been expressed is that FDC's will be seen as an alternative

to DOTS. This clearly is not the intention of advocates of FDC's who without exception are strong protagonists of DOTS. The major benefit of FDC's for DOTS programs is the simplicity of procurement, storage and distribution of two drugs rather than the four different tablets. Also, the dosage will be simplified into a three or four or five tablet daily schedule depending on the weight of the individual. As a small proportion of patients will react to the drugs, single dosage forms will also need to be available but these should be kept at a level where a TB specialist would be able to adjust the dosage.

Concerns previously expressed that procuring only FDC preparations would adversely affect small-scale local producers are legitimate. Many of these producers can produce the other first line drugs and do not try to produce rifampicin containing products. However, the primary aim of a National TB control program is to treat TB as effectively as possible, not to promote or encourage the local small-scale pharmaceutical industry. This is the role of the Ministry of Industry, not the Ministry of Health!

In summary, the universal use of FDC preparations are likely to improve the efficiency of TB control programs and prevent the emergence of MDRTB in those environments where it is not yet a problem. Any use of FDC preparations is dependent on an effective quality assurance program and regular rifampicin bioavailability testing of the formulations using the abbreviated WHO protocol.

Drugs for the Treatment of Multiple Drug Resistant Tuberculosis (MDRTB)

As has been well documented by WHO and others, Multiple Drug Resistant Tuberculosis (MDRTB) has emerged as a major public health threat. There are many causes for this epidemic but the major method of response is the treatment of infected individuals with medication appropriate to the resistance pattern of their organism. This poses a major problem in many poor countries where these drugs are either not available or are very expensive. Also, the long duration of treatment, the need to include an injectable preparation and the requirement for sophisticated laboratory monitoring makes the treatment of MDRTB a challenge for most countries.

At present WHO and IUATLD recommends the use of a Category Two treatment regimen for patients who do not convert after a primary course of therapy. This Category Two treatment regimen adds another drug, usually Streptomycin to the four drugs already used. While this regimen was reported to be effective in 1983 and 1986, the rationale for this regimen in an MDRTB environment can be questioned. If the cause of the treatment failure was multiple drug resistance adding a fifth drug to the four already failed drugs is likely to generate resistance to that fifth drug. Thus as MDRTB increases, the need to be able to undertake drug culture and sensitivity testing will increase as will the demand for these second or third line drugs. Providing accurate laboratory results will also be a challenge for many countries. Based on the experience from Peru and field experiences in other countries, it would appear desirable to pair laboratories in

developing countries with counterpart laboratories in developed countries. These developed country laboratories would then be responsible for training exchanges, quality assurance and for providing a reference laboratory function.

The selection of which drugs would be included in the treatment regimens has been the subject of active discussion. Many of the drugs are not very effective, may have toxic side effects and may be very expensive. At a recent meeting of the WHO Expert Committee on Essential Drugs a special category was created for these drugs. The list of drugs appears in the publication but not in the Essential Drug List 11th revision. The following is the draft text, which will appear in the next publication of the WHO Technical Report Series on the Selection of Essential Drugs.

7. Reserve anti-infective agents

The increasing prevalence of strains of common pathogenic bacteria resistant to widely available, relatively cheap antimicrobials included in the model list is, in many cases, dangerously eroding their effectiveness

It is becoming increasingly common for important pathogens to emerge in a country or locality that are shown, on susceptibility testing, to have developed resistance to all normally appropriate essential drugs. In these circumstances a reserve antimicrobial is needed. A reserve antimicrobial is an antimicrobial that is useful for a wide range of infections but, because of the need to reduce the risk of development of resistance and because of its relatively high cost, it would be inappropriate to recommend its unrestricted use.

The concept of reserve antimicrobials is of practical relevance only when information is available on the prevailing susceptibilities of important bacterial pathogens. Many schemes have been initiated for laboratory-based monitoring of resistance to antimicrobials but there is a need for international co-ordination. (32,33) It has already been emphasized that reference laboratories need to be established in developing as well as developed countries in order to monitor the resistance of important bacterial pathogens. Knowledge of prevailing susceptibility patterns is vital to the selection and use of antimicrobials and to the development of appropriate prescribing policies. Without these data the health of seriously ill patients could be jeopardized. Knowledge of susceptibility patterns should come from proper laboratory investigations. Research directed towards improving the link between the results of laboratory testing and prescribing policies is needed. Decisions on drug use should be taken on the basis of standardized therapeutic efficacy testing.

The findings of high level of resistance to isoniazid and rifampicin together, known as multi-drug resistant tuberculosis (MDRTB), in some countries/geographical settings, emphasises the need for the use of second-line anti-tuberculosis drugs in such locations. However, it is strongly recommended by WHO that the prescription and use of such drugs be

restricted to specialised centres with appropriate well trained staff and facilities as defined by WHO-approved DOTS-Plus for MDRTB treatment programmes (34), and under scientifically justified treatment regimens (34, 35). These drugs must not be made available outside of the public sector, and should be under the strict control of governmental DOTS-Plus pilot projects. DOTS-Plus pilot projects should be implemented only in areas with successful DOTS programs for tuberculosis control.

The drug products deemed essential for this use (including some already listed under anti-infectives are:

<i>capreomycin</i>	<i>powder for injection, 1000 mg in vial</i>
<i>cycloserine</i>	<i>capsule or tablet, 250 mg</i>
<i>para-aminosalicylic acid (PAS)</i>	<i>tablet, 500 mg, granules, 4 g in sachet</i>
<i>ethionamide</i>	<i>tablet, 125 mg 250 mg</i>
<i>amikacin</i>	<i>powder for injection, 1000 mg in vial</i>
<i>kanamycin</i>	<i>powder for injection, 1000 mg in vial</i>
<i>ciprofloxacin</i>	<i>tablet, 250 mg, 500 mg</i>
<i>ofloxacin</i>	<i>tablet, 200 mg, 400 mg</i>
<i>levofloxacin</i>	<i>tablet, 250 mg, 500 mg</i>

These are the drugs that should be procured by programs, which aim to treat MDRTB. However, at present due to the cost, duration of use required and the serious side effects of these drugs, they have not been widely used in developing countries. In pilot projects in South Africa and Peru encouraging results have been obtained. In 1999 a series of meetings were held to establish what has become known as DOTS Plus programs. These programs aim to treat MDRTB in developing countries. The key components of a DOTS-Plus program have been described to be:

- Political Will and support of relevant government bodies
- Access to adequate laboratory facilities for smear microscopy, culture and drug susceptibility testing
- Directly observed therapy

- Uninterrupted supply of first and second line drugs
- Use of reliable monitoring system to assess outcomes
- Operational research to identify constraints to implementation

These key elements presuppose that an efficient DOTS program is already in existence and that every effort is being made to prevent the emergence of MDRTB.

One of the unresolved issues in the discussion of DOTS Plus programs is whether standardization of customized treatment regimens should be used. Here, the experiences of South Africa and Peru differ with better results in Peru from customized regimens while in South Africa the standardized regimens were more successful. It appears likely that as more experience is gained, and better sensitivity data becomes available, better standardized regimens will be devised and more opportunity for customized individual regimens will develop. The availability of the South African standard and customized regimens on the World Wide Web is a useful resource, which could be used as a basis for developing national regimens. Addressing the need to reduce the price of these drugs is critical and it is likely that during 2000 pooled procurement activities will occur and non-profit suppliers will start to distribute MDR drugs at considerably lower prices. However, a risk remains that if these drugs are used in poorly managed programs and supervised therapy does not occur, the global TB situation could be made worse. Clearly it is better to have no program than to have a poorly managed DOTS Plus program.

Of concern is the virtual absence of new TB drug development occurring at present. The reason for this is that the research based pharmaceutical companies do not see an adequate return for their investment. A proposal has been made by Percoul and others that an Orphan Drug Act could be developed for European and US governments to support the development of drugs for tropical and other diseases of poverty such as tuberculosis. Such approaches may have promise but are unlikely to solve the problem of not having effective drugs available in the short to medium term.

Tuberculosis Drug Prices

Drug prices are determined by many factors. While the price set by the manufacturer is one determinant, there are many other. These include customs duties, registration fees, national and local taxes, wholesaler to retailer and retailer to customer markups. In most countries varied price control mechanisms exist, as the pharmaceutical market is generally perceived not to be a "free" market. In countries such as New Zealand the use of reference pricing and other measures has been effective in reducing drug costs substantially albeit at the risk of reducing the range of drugs available.

Methods

To determine US and international TB drug prices now and how they have changed over time, a number of data sources were consulted. (Appendix 1) For the US private sector prices in 1999 and over time the Red Book was used. The actual prices paid by an institution may be rebated from this price. While this publication does include HCFA prices these were not included, as access to these drugs at these prices is limited. Average prices of all producers for their largest pack sizes were calculated. For US public sector prices the actual prices paid by the Massachusetts Public Health department and New York Public Health department were averaged for current pricing. Massachusetts data was also used for prices paid over time. For international prices over time the average prices quoted in the Management Sciences for Health Drug Price Indicator guide was used. This is a compilation of prices of drugs offered by non-profit suppliers and by a few tender prices from developing countries. Prices from Japan were provided by staff from the Research Institute for tuberculosis in Kiyose Japan. Tender prices for African countries were obtained from the AFRO Essential Drugs price indicator list published in July 1998. Information about Indian drug prices were provided by Dr Urmilla Thatte from Mumbai. The public sector prices are those from the tenders awarded by the Mumbai municipal corporation and the private sector prices are those in the Mumbai city market. Information on South Africa was obtained from the tender award for 1999. Prices for Singapore, Pakistan, Russia and Kazakhstan were provided by colleagues in those countries. Prices for tuberculin were provided by respondents on the TB-Net electronic discussion group, Massachusetts Public Health Department and UNICEF, Copenhagen. The public sector prices were tender prices and the private sector prices were lowest market prices for the largest pack sizes. Obviously prices for private sector drug prices may vary substantially in a country and these prices except for the US should be seen as indicative rather than definitive. The prices quoted over time are in US\$ at the time. They have not been corrected for the effect of inflation.

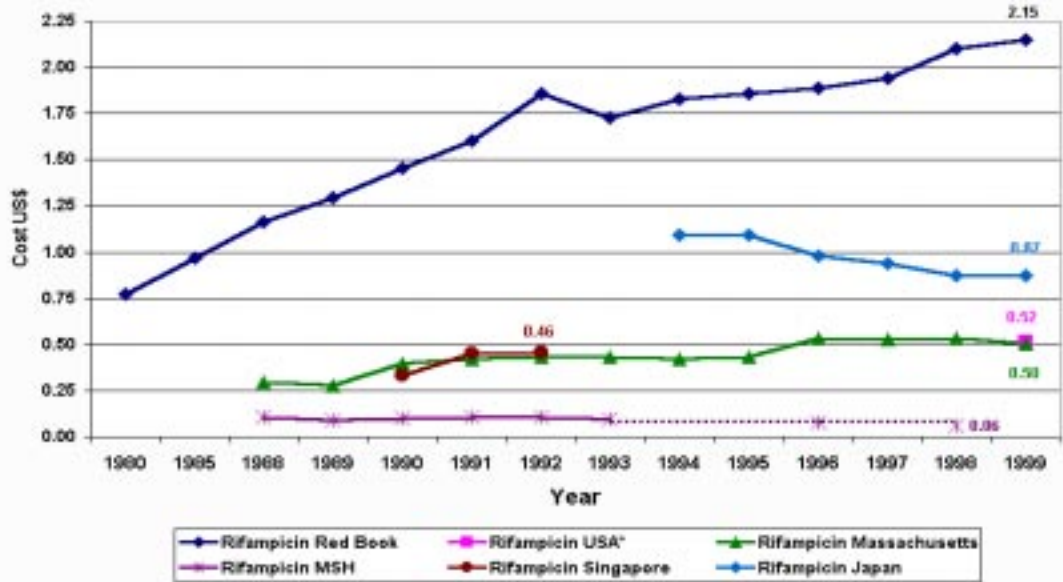
Results

Drug Prices over Time

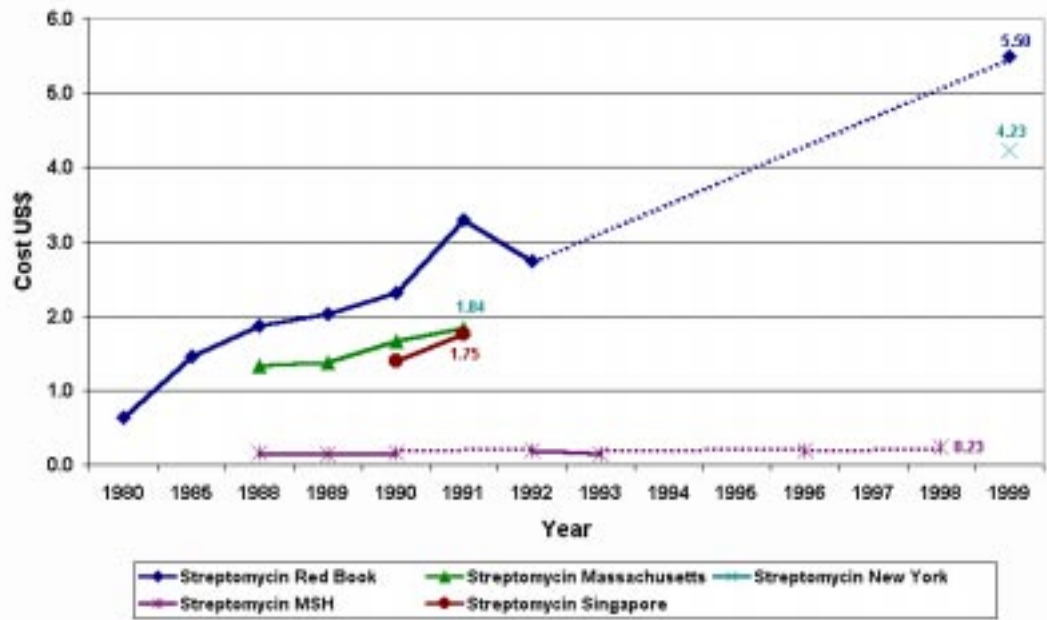
First line drugs (Isoniazid, Rifampicin, Pyrazinamide and Ethambutol) have generally increased in price over the past 20 years while international prices have remained stable or have decreased slightly. US private prices for the first line drugs increased on average 10.66% per year,

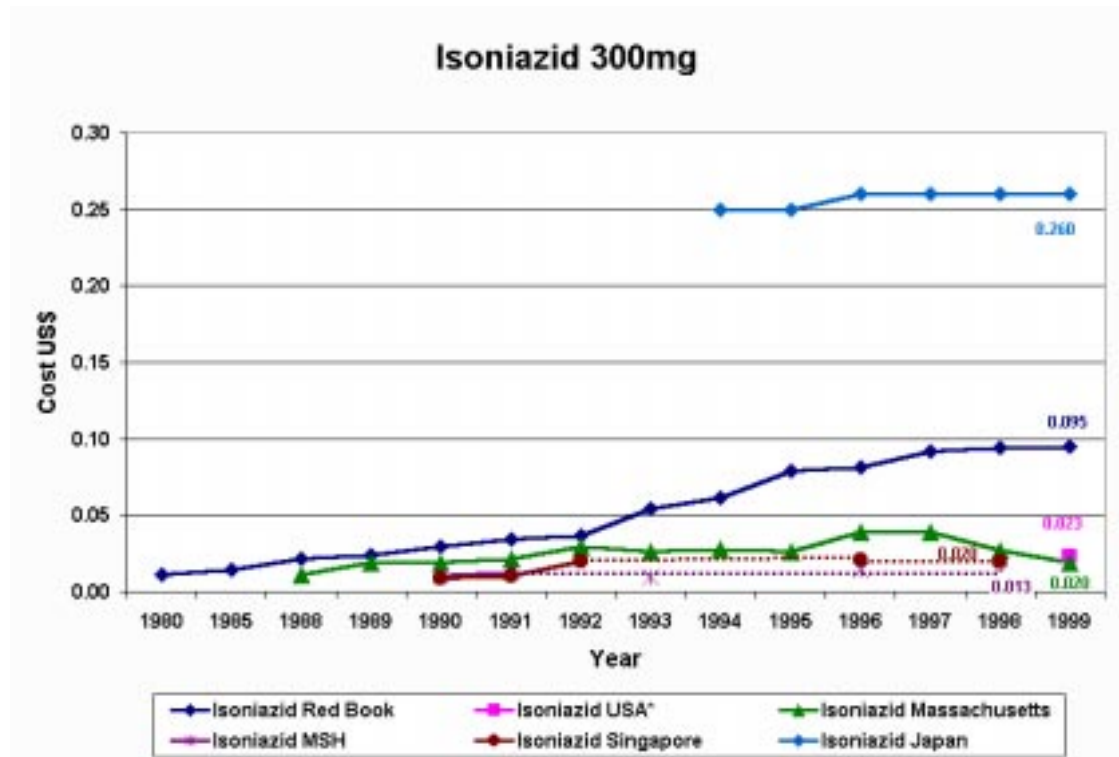
Massachusetts public sector prices increased 4.1% per year while international prices decreased by an average of 2% per year. Data from these sources and from Japan and Singapore are provided graphically below.

Rifampicin 300mg



Streptomycin 1gm





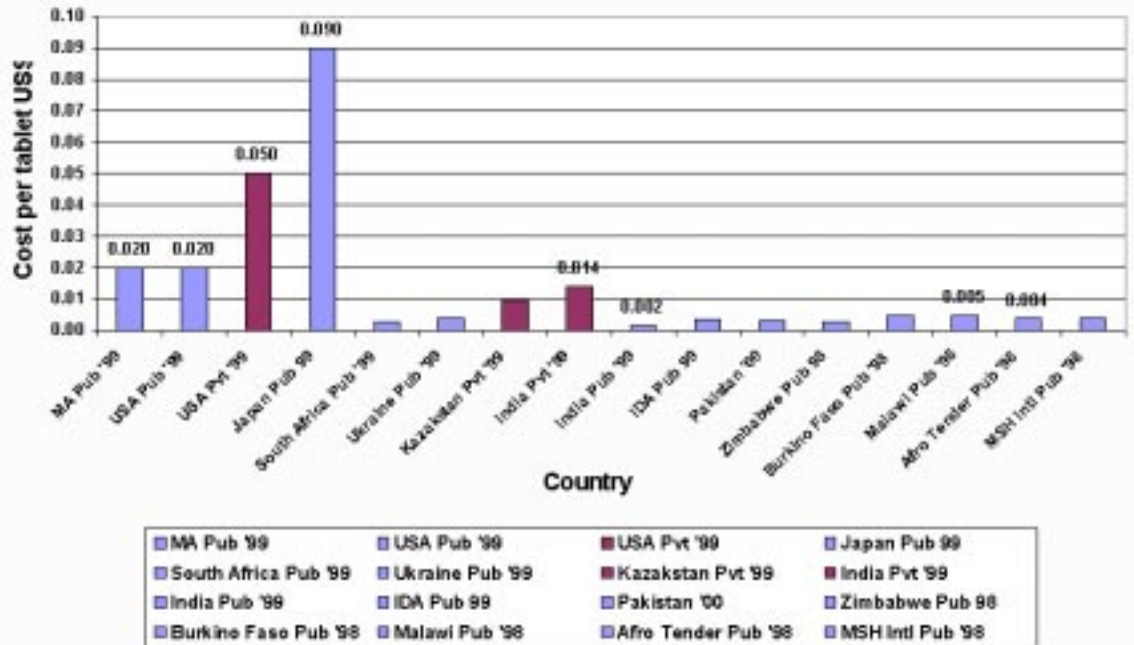
For second line drugs international prices are not available as these drugs were not usually used in these countries during this time. The average rate of price increase for these second line drugs in the US was 6.5%yr in the private sector and 2% per year in the public sector. The exception in this group was Kanamycin, which declined in price in the private sector. These prices and those from Singapore are displayed below.

These charts do demonstrate the absolute differences in prices over time but current prices will be described in more detail below. Other time series charts are available on request.

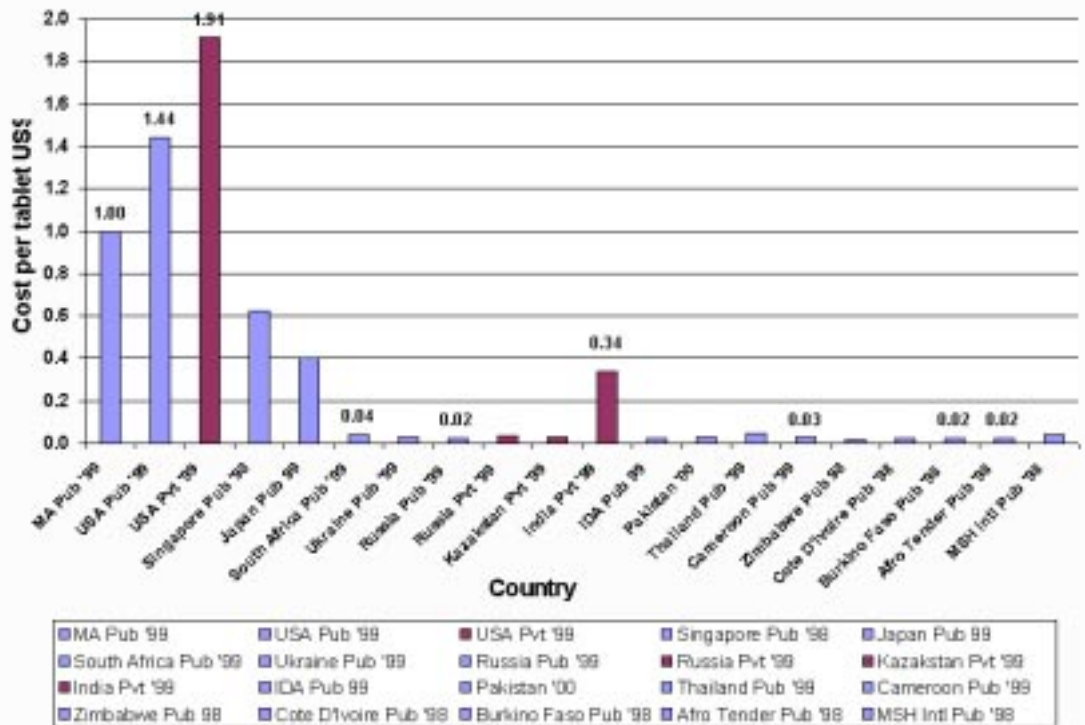
Drug Prices between Countries

Prices vary dramatically between countries with a high ratio of 95 times difference between the price of Ethambutol 100mg in US private sector and the tender price in Zimbabwe. The lowest ratio of maximum minimum price is 27 for Rifampicin and Isoniazid (150/100mg combination tablets) between the public sector in South Africa and in India. For all drugs except Isoniazid, the US prices are the highest in the world. Japan has the highest isoniazid prices.

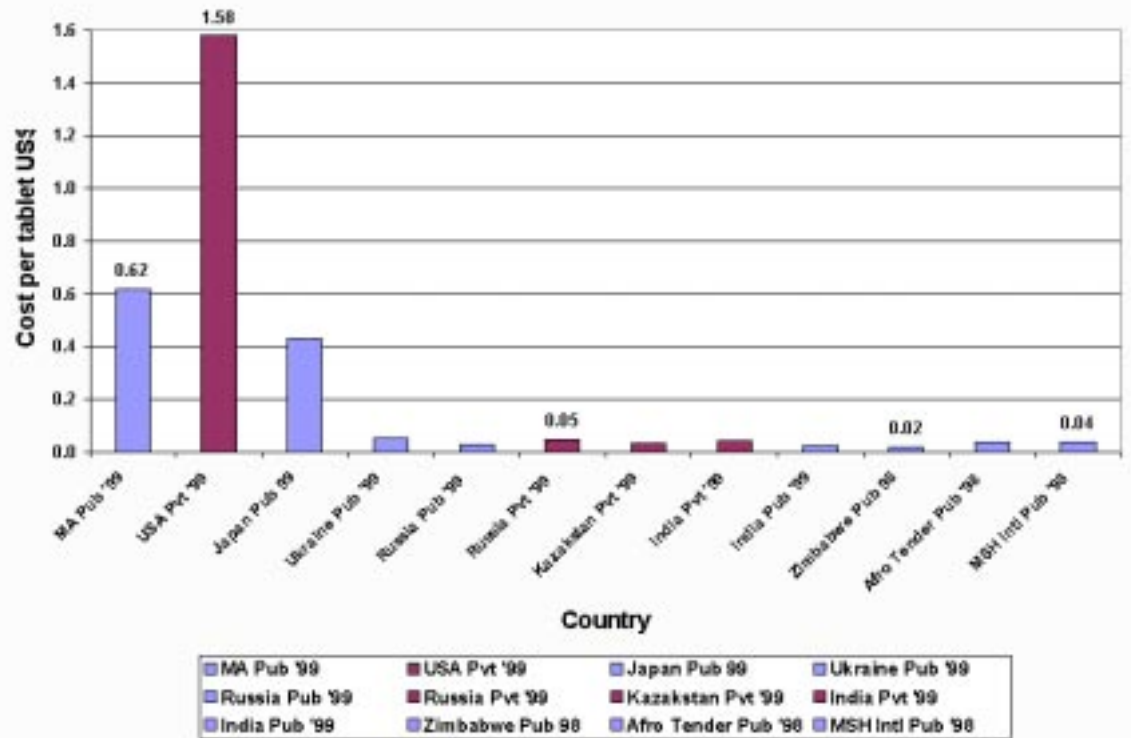
Isoniazid 100mg



Ethambutol 400mg



Rifampicin 150mg



For second line drugs the Max Min ratios are far lower ranging from 2.2 to 6.5 times for the various drugs. The charts of these drug prices are shown below.

Ciprofloxacin 500mg

