Tuberculosis drug issues: prices, fixed-dose combination products and second-line drugs

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SUMMARY

Access to tuberculosis drugs depends on multiple factors. Selection of a standard list of TB drugs to procure is the first step. This paper reviews the advantages and disadvantages of procuring and using fixed-dose combination (FDC) products for both the intensive and continuation phases of treatment. The major advantages are to prevent the emergence of resistance, to simplify logistic management and to reduce costs. The major disadvantage is the need for the manufacturers to assure the quality of these FDCs by bioavailability testing.

The paper reports on the inclusion of second-line TB drugs in the 1999 WHO Essential Drug List (EDL). The need to ensure that these drugs are used within established DOTS-Plus programs is stressed.

The price of TB drugs is determined by many factors, including producer prices, local taxes and duties as well as mark-ups and fees. TB drug prices for both the public and private sectors from industrialized and developing countries are reported. Price trends over time are also reported. The key findings of this study are that TB drug prices have generally declined in developing countries while they have increased in developed countries, both for the public and private sectors. Prices vary between countries, with the US paying as much as 95 times the price paid in a specific developing country. The prices of public sector first-line TB drugs vary little between countries, although differences do exist due to the procurement methods used. The price of tubercul cin, a diagnostic agent, has increased dramatically in the US, with substantial inter-country variations in price.

The paper suggests that further research is necessary to identify the reasons for the price disparities and changes over time, and suggests methods which can be used by National Tuberculosis Programme managers to ensure availability of quality assured TB drugs at low prices.

OVERVIEW OF CURRENT TUBERCULOSIS DRUG ISSUES

Since streptomycin became available in 1948 and other tuberculosis (TB) drugs were discovered in the 1950s and early 1960s, 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 3 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 to or do not take effective treatment for this widespread disease.

The major reasons for lack of access to TB drugs are 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, wide variations exists between countries, and in the United States 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, the World Health Organization (WHO) and the IUATLD (International Union Against Tuberculosis and Lung Disease) have promoted the use of directly observed treatment (DOT) utilizing fixed-dose combination (FDC) treatments.1 Concerns have been raised about quality in the production of these drugs.

A recent troubling development in TB control has been the rapid emergence of multidrug-resistant tuberculosis (MD-RTB) in industrialized, developing and transitional countries. Accurate diagnosis and characterization of drug sensitivity patterns of specific infections are difficult in many countries. Even once the sensitivity patterns are known, ensuring the availability of reserve antibiotics is at present difficult due
to the high cost of these drugs. The reasons for their high cost include market failure, monopoly position or patent protection for a few modern drugs.

This paper addresses all of these issues, and suggests what a National Tuberculosis Program (NTP) manager can 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. In 1992 Chaulet wrote one of the few papers that has addressed issues related to the supply of anti-tuberculosis drugs and national drug policies. At the time, he reported, 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%, and pointed out the importance of integrating anti-tuberculosis drug supplies into national drugs policies.

In a WHO report in 1994, Weil 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, in 1999, Catalani 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 FDC products. In a paper entitled ‘Estimate of the global market for rifampicin containing fixed dose combination tablets’, Norval et al. 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

A major initiative by the WHO and the IUATLD in 1998 and 1999 was aimed at promoting the use of FDC tablets for first-line treatment of TB in all TB programs, including both DOT and standard programs. The justification for promoting FDCs is the simplicity of treatment, with minimized prescription errors and improved compliance. In addition, changing to FDCs would simplify drug management and prevent the misuse of rifampicin for treating other conditions such as chlamydiae. In this era of multi-drug resistance, ensuring that the patient receives all four or two drugs helps to prevent the emergence of resistance due to shortages of particular drugs.

FDC formulations have been used for a number of years 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. FDC formulations have been popular with private practitioners who treat tuberculosis.

The major concern about FDC formulations has been that of quality. Accocella, 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 FDCs. The bioavailability problem appears to be limited to rifampicin, and is related to the crystalline structure of the drug.

To address these problems, the WHO has agreed on standard formulations for FDC products, and have included them 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 patient body weight (Table).

In addition, the WHO has specified a standardized protocol for in vivo assessment of rifampicin bioavailability. This abbreviated protocol allows for six blood samples over 8 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 8-hour urine specimen could be used (G Ellard, Personal communication; Geneva 1999 December).

In addition to establishing the abbreviated protocol, the WHO is moving to recognize a number of laboratories as reference laboratories for assaying these FDC preparations with particular reference to

<table>
<thead>
<tr>
<th>Rifampicin + isoniazid tablet, 60 mg + 30 mg, 150 mg + 75 mg, 300 mg + 150 mg, 60 mg + 60 mg, 150 mg + 150 mg (for intermittent use 3 times weekly)</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Rifampicin + isoniazid + pyrazinamide + ethambutol tablet, 150 mg + 75 mg + 400 mg + 275 mg</td>
</tr>
</tbody>
</table>
bioavailability. Two laboratories have already been recognized, and others are in the process of registration as reference laboratories.

The price of FDCs has been a concern. However, the historical trend for the cost of the two-drug combination has been downwards, as shown in Figure 1.

One concern that has been expressed is that FDCs will be seen as an alternative to DOTS. This clearly is not the intention of advocates of FDCs, who without exception are strong protagonists of DOTS. The major benefit of FDCs for DOTS programs is the simplicity of procurement, storage and distribution of two rather than four different tablets. Also, the dosage will be simplified into a three, four or five tablet daily schedule depending on the weight of the individual. As a small proportion of patients will experience reactions to the drugs, single-drug forms will also need to be available, but are to be kept at a level where only a TB specialist can adjust the dosage.

Previously expressed concerns 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 an NTP is to treat TB as effectively as possible, and 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 NTPs and prevent the emergence of MDR-TB 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 MULTIDRUG-RESISTANT TUBERCULOSIS**

As has been well documented by WHO and others, MDR-TB has emerged as a major public health threat. There are many causes of this epidemic, but the main 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 MDR-TB a challenge for most countries.

At present the WHO and the IUATLD recommend the use of a Category II treatment regimen for patients who do not convert after a primary course of therapy. This Category II 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 its use in an MDR-TB environment can be questioned. If the cause of the treatment failure was multidrug resistance, adding a fifth drug to the four already failed drugs is likely to generate resistance to that fifth drug. Thus as MDR-TB 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

![Figure 1](image-url)  
*Figure 1* Price history of two-drug RMP + INH combination tablets. RMP = rifampicin; INH = isoniazid; MSH = Management Sciences for Health.
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 industrialised countries, which 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 11th revision of the Essential Drug List.17 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 coordination [. . . ]. 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 multidrug-resistant tuberculosis (MDR-TB), 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 MDR-TB treatment programmes [. . . ], and under scientifically justified treatment regimens [. . . ]. 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:

- Capreomycin Powder for injection, 1000 mg in vial
- Cycloserine Capsule or tablet, 250 mg
- Para-aminosalicylic acid (PAS) Tablet, 500 mg, granules, 4 g in sachet
- Ethionamide Tablet, 125 mg 250 mg
- Amikacin Powder for injection, 1000 mg in vial
- Karamycin Powder for injection, 1000 mg in vial
- Ciprofloxacin Tablet, 250 mg, 500 mg
- Ofloxacine Tablet, 200 mg, 400 mg
- Levofloxacin Tablet, 250 mg, 500 m

These are the drugs that should be procured by programs aiming to treat MDR-TB. 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.13 In 1999, a series of meetings was held to establish what has become known as DOTS-Plus programs. These programs aim to treat MDR-TB 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 MDR-TB.

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,

* Quoted from Draft provided by Dr M Couper WHO.
Tuberculosis drug issues: prices, FDCs and second-line drugs

S199

while in South Africa the standardized regimens were more successful. It appears likely that as more experience is gained, and better sensitivity data become available, better standardized regimens will be devised and more opportunity for customized individual regimens will develop. The availability of the South African standard customized regimens on the World Wide Web is a useful resource which could be used as a basis for developing national regimens.18 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 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 et al. 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.19,20 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 others. These include customs duties, registration fees, national and local taxes, and 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.21

METHODS

To determine current US and international TB drug prices and how they have changed over time, a number of data sources were consulted (Appendix). 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 Health Care Financing Administration (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 were 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 Re-
search Institute for Tuberculosis in Kiyose, Japan; tender prices for African countries were obtained from the WHO AFRO Region Essential Drugs price indicator list published in July 1998; and 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 except for the US these prices 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 first-line drugs increased by an average of 10.66% per year, Massachusetts public sector prices increased by 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 in Figure 2.

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%/year in the private sector and 2%/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 in Figure 3.

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 100 mg in the US private sector and the tender price in Zimbabwe. The lowest ratio of maximum/minimum price is 27 for rifampicin and isoniazid (150/100 mg combination tablets) between the public sector in South Africa and in India. For all drugs except isoniazid, US prices are the highest in the world; Japan has the highest isoniazid prices.

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 in Figure 4.

Tuberculin
While tuberculin is strictly a diagnostic agent it is produced and procured as a drug. The prices of these agents have risen dramatically in the US over the past few years; the reasons for this price increase are not clear.

DISCUSSION

At this stage, the reasons for these dramatically different drug prices have not been investigated. However, to summarize, it appears that for first-line drugs the ‘free market’ appears to be functioning effectively and that prices are similar between most countries tendering for these drugs. These prices are also close to the MSH Drug Price Indicator guide and the WHO AFRO price guide. Thus it is possible for procurement officers to budget and procure these drugs using these prices as stable indicators of the likely costs for drugs. For the US, both public and private TB drug prices are far higher than the international prices. But US authorities are not permitted to import products from other countries unless they are registered with the US Food and Drug Administration (FDA). A number of international TB drug manufacturers have been inspected by the FDA and found to be acceptable (S Solomon, Director Medical Products Quality assurance staff, following a Freedom of Information request, 16 February 2000). Barriers do exist to these companies marketing their finished products in the US. While the US does not charge a fee to register generic drugs, other countries such as Russia charge a registration fee of $12 000.

For second-line drugs the situation is more complex. There are a limited number of suppliers, large-scale tenders have not yet been announced and the true international price is not clear. At present the ‘free market’ is not yet functioning efficiently. However, as demand increases and as more DOTS-Plus programs are established, it is likely that the prices of these drugs will decrease and stabilize at lower levels.

Further research is needed to identify the reasons for the considerable price variations that exist between countries and between the public and private sectors within the same countries. As tuberculosis is a disease of such public health significance it may be reasonable, in countries where the private sector provides a substantial portion of the TB care, to allow the private sector to purchase FDC drugs at national tender prices. This would substantially reduce the price to patients and would likely boost the use of FDC preparations.
Figure 3  Drug prices: comparison between countries. a) ethambutol 400 mg; b) isoniazid 100 mg; c) rifampicin 150 mg; d) ciprofloxacin 500 mg; e) streptomycin 1 g; f) ethionamide 250 mg; g) cycloserine 250 mg; h) kanamycin 1 g. MA = Massachusetts; Pub = public; Pvt = private; MSH Intl = Management Sciences for Health International.
c  
Rifampicin 150mg

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d  
Ciprofloxacin 500mg

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Figure 3  Continued
Tuberculosis drug issues: prices, FDCs and second-line drugs

Figure 3

**Streptomycin 1g**

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**Ethionamide 250mg**

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Figure 3  Continued
Figure 3  Continued
Managing TB drug supply
Pharmaceuticals are a critical component of any tuberculosis program. Selecting a limited list of drugs, particularly using FDCs as the basis for the initial treatment of TB cases, simplifies management substantially. When procuring drugs, it should be remembered that the assured quality of the drug and the reliability of the supplier are more important than the price. For this reason, restricted tender with pre-qualification of bidders combined with performance monitoring is the procurement method of choice. An alternative is to procure from non-profit suppliers such as UNICEF or IDA. Pooled procurement of second-line drugs may be an option to consider. This can be difficult to organize, but may offer an alternative to the present, very expensive direct procurement. The storage and distribution of TB drugs may be contracted out to private organizations or managed by the NTP. In gen-

Figure 4  Cost of tuberculin—comparisons between countries (a) and over time (b). MA = Massachusetts.
eral, large central medical stores are inherently inefficient, although central procurement units may be very effective, particularly if they tender on an ‘as needed’ basis rather than for a fixed quantity. Pharmacies may play a role in storage, distribution and supervision of DOTS in countries where pharmacies are widely available. Ensuring the correct use of these TB drugs is very important and is the basis of the DOT component in National DOTS Programs. Preventing the misuse of TB drugs such as for the treatment of chlamydiae infections with rifampicin is important to prevent the emergence of rifampicin resistance.

CONCLUSION

Ensuring the reliable supply of assured quality TB drugs at the best possible price is the aim of any TB program. With the changes occurring in FDCs becoming available and strongly advocated and the emergence of MDR-TB, program managers will need to become more competent in drug management. However the outlook is promising. FDCs will simplify drug management and should, when incorporated into a DOTS program, prevent the emergence of MDR-TB. International prices for TB drugs have fallen and stabilized at a level where it should be possible for most countries to purchase their needed drugs. The situation for second-line MDR drugs is more complex. However, during 2000, it is likely that non-profit suppliers and pooled procurement activities will reduce the prices substantially. The duration of therapy, the laboratory support needed and the cost of the drugs will make DOTS-Plus programs expensive and they are thus likely to need international financial and technical support.

References


Appendix Tuberculosis drug price reference list

- USA Public Data—Massachusetts State Department of Health, Division of Tuberculosis Prevention and Control, 1990–2000
- Singapore—Shyamala Narayanaswamy, Singapore General Hospital: gpashy@sgh.gov.sg
- South Africa—Dr Wilbert Bannenberg, SADAP coordinator: bannewa@httsa.pwv.gov.za
- Ukraine, Kazakhstan—Andrei Zagorski: Azagorski@msh.org
- Russia Public—Russian Ministry of Health tender, May 1999, George Oswald: goswald@online.ru
- Russia Public—Russian Ministry of Health tender, May 1999, George Oswald: goswald@online.ru
- India Public, India Private—prices from the private sector and the public sector, KEM Hospital: mthatte@boms5.usln.net.in
- International Dispensary Association (IDA)—Strichting IDA sales department 1999 tuberculosis prices: ida—sale@euronet.nl
- Pakistan—market prices of tuberculosis drugs 2 February 2000, John Walley: hssjd@lucs-01.novell.leeds.ac.uk
- Cameroon—Ndi Ndi Joseph, Assistant TB Program Manager, Tuberculosis Control Unit, Ministry of Public Health, Cameroon

