INT J TUBERC LUNG DIS 12(10):1173–1181

Estimating the market for tuberculosis drugs in industrialized and developing nations

N. R. Schwalbe,*† W. A. Wells,* A. P. Geaneotes,‡§ A. Forcellina,‡¶ M. G. Lee,‡ L. DiCola,‡ H. R. Ignatius,* C. L. Walker,‡ T. Raafat,‡ N. Patel‡

*Global Alliance for TB Drug Development, New York, ‡IMS Health Inc, New York, New York, USA; †GAVI Alliance, Geneva, Switzerland; §John F. Kennedy School of Government, Harvard University, Cambridge, Massachusetts, ¶McKinsey & Company, New York, New York, USA

SUMMARY

BACKGROUND: The successful introduction of new drugs into low- and middle-income countries requires an understanding of the existing market size and market dynamics for the therapeutic area of interest. The drug markets in these countries are, however, less well understood than those in high-income countries.

METHODS: The global market for tuberculosis (TB) drugs was estimated by studying in detail six high-burden countries and four high-income countries, followed by extrapolation. Data were derived from existing pharmaceutical audit databases and interviews with government officials, medical staff and suppliers.

RESULTS: The use of qualitative inputs to inform the collection of quantitative information, notably to identify where the major flows of TB drugs are located, allowed a confident estimate of the global market for first-line TB drugs. Final ranges were US$261–316 million or US$310–418 million, depending on whether case notification rates or incidence were used for extrapolations.

CONCLUSIONS: An estimation of the global TB drug market is made more reliable by a qualitative understanding of TB drug distribution pathways, which differ greatly among countries. The understanding of this structure in key high-burden countries provides the basis for a simpler update of the market estimate in the future.

KEY WORDS: market size; tuberculosis drugs; global estimate

THE ACTUAL OR PROJECTED market size for particular pharmaceuticals is a key motivator for future innovation: it determines whether, and how vigorously, a profit-based enterprise will further investigate an area for new, improved drugs. An understanding of market dynamics is also critical to determining how drugs can be distributed efficiently.

Both market size and market dynamics can be tracked by using large databases maintained by organizations such as IMS Health Inc. IMS recruits samples of doctors and pharmacies to report, respectively, their prescription and drug sales information. Although these reporting networks are well established in industrialized countries, and to some extent in emerging market economies, they are largely absent from developing countries. For this reason, information on market size and market dynamics is often both lacking and hard to derive for diseases predominantly found in the developing world.

Some market estimations for neglected disease therapies have taken a simple approach: the estimated number of cases is multiplied by the estimated price of the drug (or drug regimen) to reach a total. For example, this methodology was used by the US Institute of Medicine to estimate the market for artemisinin combination therapy for malaria,[1] and by the World Health Organization (WHO) to estimate the potential global market for rifampicin-containing fixed-dose combinations for tuberculosis (TB).[2] More complicated models have been used to project the markets for new product classes (e.g., an acquired immunedeficiency syndrome vaccine[3]); these projections use a very different set of assumptions and methods than are used for actual, established markets.

A global market estimate for TB drugs will be a valuable tool in attempts to introduce new TB drugs. These drugs are needed to improve a regimen that takes too long and puts too much of a burden on overstretched health care systems. TB is second only to the human immunodeficiency virus as the leading infectious killer of adults worldwide: an estimated one third of the world's population is infected with *Mycobacterium tuberculosis*, which causes TB, and TB killed ~1.6 million people worldwide in 2005.[4]

There have been various cost and cost-effectiveness estimates for TB treatment.[5–15] These studies, however, have generally surveyed costs within a single country and calculated the entire cost to the health system, with

Correspondence to: William Wells, Global Alliance for TB Drug Development, 24th Floor, 40 Wall St, New York, NY 10005, USA. Tel: (+1) 646 616 8628. Fax (+1) 212 227 7541. e-mail: william.wells@tballiance.org

Article submitted 7 December 2007. Final version accepted 13 June 2008.

drug costs being relatively minor compared to staffing and other system costs.

The Global Alliance for TB Drug Development (TB Alliance) made an initial estimate[16] of the global market for TB drugs in 2001, based in part on a survey by the WHO.[17] This estimate did not, however, include a detailed description of the TB drug distribution systems, and the level of confidence in the estimate was therefore limited. In partnership with IMS, the TB Alliance recently undertook a new study that investigated market size and market dynamics for TB drugs using a new, more extensive methodology.

Based on this new study, an overview of the market dynamics and a summary of the market sizing results have been published.[18,19] The current article outlines more extensively the methodology used for this new estimate of the market size for first-line TB drugs, and analyses the factors affecting the accuracy of and confidence in this estimate. The methodology used qualitative information to validate and inform the collection of quantitative information. A similar combination and level of qualitative and quantitative effort may be required to understand other drug markets in developing countries, especially when they rely substantially on public sector distribution.

METHODS

Data sources

Market structure, market dynamics, and the relative roles of the public and private sectors in procurement and distribution were studied to prevent omission of important sectors of the market or false generalizations that could result in estimations that are artificially high.

The current study used both qualitative and quantitative methods for data collection. The qualitative investigations were needed to ensure that the quantitative data, for example from IMS databases, were accounting for the major sources and locations of TB drugs. The qualitative research and IMS data together helped determine market values for the countries studied. These values were then extrapolated to derive a global estimate.

Qualitative information was sought on topics including the selection process for TB drug suppliers, the role of public and private payers in purchasing first- and second-line TB medicines, and the flow of TB medicines from the supplier to the end user. Data from reports and one-on-one interviews were used to answer questions such as:

- What value and volume of TB medications flow through particular channels?
- Are the distribution mechanisms and channels for TB drugs different from those utilized for the bulk of the pharmaceutical marketplace? If so, why?
- Who are the key payers and distributors for TB medications? What roles are played by global groups, the government and public sector, and the private sector?
- How are TB medications reimbursed, at what level and by whom?
- Do payment issues differ in terms of first- and second-line TB medications, and if so, how?
- Are TB drugs priced differently than other pharmaceutical products? If so, why?

Ten countries with diverse geographies, pricing and health system structures were chosen for this study. Six of the 10—Brazil, China, India, Indonesia, the Philippines, and South Africa—are among the 22 countries identified by the WHO as high-burden countries (HBCs). Together, these six countries carry approximately 50% of the world's TB burden.[4] As so-called emerging economies, they are also of interest to the pharmaceutical industry.

The project also surveyed four high-income countries—France, Japan, the United Kingdom and the United States—that have a low burden of disease but a higher cost of TB treatment. These four countries account for ~1% of global TB incidence but 61% of the total global market for all pharmaceuticals.*

For each of the countries, the TB Alliance and the IMS developed extensive maps describing the health care system, the financing of the TB program (including TB drug purchases specifically), and the flow of patients and drugs within the system.[19]

IMS databases were a key source for quantitative information. These databases are compiled from IMS pharmaceutical audits, which are continuous national market surveys, with results compiled periodically, based on statistically representative samples of sales, prescriptions and prescribing patterns. All audits are conducted so that they capture the value of drug sales when sold by the manufacturer (not the value of sales to the end user).

Audits varied according to local requirements and, when the data were available, covered both private and public sectors and both out-patients and in-patients (see supplemental material for country-specific details).† The private retail market was covered by IMS databases in all countries researched in this study. The private hospital market was covered by IMS databases in all researched countries except for the UK, where these data were not available but considered not relevant, as TB is treated almost exclusively in the public sector. The public sector (i.e., government payers) was covered by IMS databases in France, Japan, South Africa, the UK and the US; alternative sources of data on the public sector for other researched

* IMS Knowledgelink. http://www.imshealth.com

† Supplemental material is available in the online version of this article at http://www.ingentaconnect.com/content/iuatld/ijtld/2008/00000012/00000010/

countries are described below. In Brazil, private retail and private hospital data were available but not relevant to TB sales.

Of note, it is the location of the dispensing, not the location of the prescribing, that matters in determining a market estimate. In a number of high-income countries, such as the UK, most of the drug prescribing takes place in the public sector, through the National Health Service, but those drugs are usually dispensed and therefore paid for in the private sector. In other countries, however, government programs may directly purchase and dispense the necessary TB drugs.

Global procurement service agencies (PSAs) were also surveyed for the value and quantity of the drugs distributed. These agencies included the Stop TB Partnership's Global Drug Facility (GDF) for first-line drugs and the Green Light Committee (GLC) for second-line drugs. Other agents, such as the Royal Crown Agents, the Pan American Health Organization (PAHO), Inter-Agency Procurement Services Organization (IAPSO), United Nations Children's Fund (UNICEF), and the Netherlands-based International Dispensary Association (IDA), were surveyed, but their contribution to the TB market was found to be negligible or otherwise accounted for.

To supplement the IMS databases, some suppliers provided data on costs and sales of TB drugs in certain countries, and some National TB Programs (NTPs) provided data on the number of patients treated in the public sector, spending on drug procurement, and costs per product and regimen in the public sector. Using these multiple data sources, market estimates could often be cross-checked. See the Supplemental Material and detailed country reports[19] for country-specific methodologies.

Data collection strategy

Initial detailed analysis was followed by extrapolations. For the detailed analysis, the global TB market was divided according to three types of TB drug payers: global PSAs, selected high-income countries and selected HBCs. A description of the methodology used to quantify the market in each of these groups appears below.

Global analysis

Electronic searches were conducted in February 2006 to find existing information on TB drug markets and identify any major procurement service agencies. Directed searches of websites (WHO, international aid agencies, and the Global Fund to Fight AIDS, TB and Malaria [GFATM]) were used to understand if and how donor aid is used to fund the purchase of TB drugs. The GDF and GLC websites were reviewed for information on procedures and pricing. These searches were supplemented by interviews with key staff from multilateral organizations, funders, PSAs, manufacturers, technical assistance agencies and non-governmental organizations (NGOs). Interviews were conducted according to a structured interview guide and interviewees were asked to provide additional written materials and to name additional people to interview both for questions related to the global market and for information on the countries in the scope of the study.

High-income countries studied

In high-income countries, TB statistics and diagnostic and treatment guidelines were sourced from government websites. A total of 15 interviews were conducted with stakeholders in these countries, including government payers, hospital administrators and pharmacists, prescribers and staff from government TB programs. The IMS databases were used to estimate the value and volume of the first- and second-line markets. No additional data (e.g., government- or supplier-provided data) were used. Key assumptions included the following:

- IMS databases were assumed to capture 100% of the first- and second-line TB markets in the high-income countries studied.
- In the UK, it is assumed that there are no sales in the private hospital sector for TB.
- In HBCs, first-line drugs and their fixed-dose combinations were assumed to be used exclusively for first-line TB.
- Second-line treatments in all countries and first-line treatments in high-income countries were assumed to have substantial use in indications other than TB. Therefore, all these data were factored by indication (usually based on the International Classification of Diseases [ICD-10] codes, where available from IMS databases, or from qualitative insights), and estimates incorporate TB use only.

HBCs studied

Information in IMS databases was generally less complete for the public sector in HBCs than for the overall market in high-income countries, or there was more uncertainty about the location of major TB drug expenditures in HBCs. There was therefore a greater emphasis on the HBCs on qualitative investigations to map the TB and health care environment. During visits to five of the six HBCs in the study, we conducted a total of 106 interviews with stakeholders. For Indonesia, interviews took place by phone only.

The stakeholders who were interviewed included TB program administrators (national, regional and local), prescribers, manufacturers, pharmacists and staff in government procurement and purchasing departments, regional WHO offices, NGOs, relevant international organizations and pharmacy chains. Interviewees supplied additional reports. As with the high-income country surveys, these interviews were structured and aimed to elicit an understanding of who was procuring TB drugs, how they were distributing them, what entity was paying for the TB drugs, how the payment

system worked, and the role of the private and public sectors in the provision of TB drugs.

Some NTP administrators also provided quantitative information on case notification figures and incidence, allocations and actual spending for TB drugs in the public sector, the number of patients in each treatment category, and costs paid by the public sector per regimen and per product.

Market size estimates for the HBCs studied were based on actual dollar amounts provided by government sources (for the public sector) and IMS databases (for the private sector, in countries where it was significant, and the public sector, where the data were available). Qualitative corroboration of these figures came from a number of different sources, including interviews with some major suppliers of TB drugs.

In both HBCs and high-income countries, the estimated market value for each country was cross-checked by multiplying incidence figures (from government sources) for each patient category (active, latent, retreated and resistant patients) by the average cost per regimen, assuming that each patient receives a full regimen.

Deriving an estimate for the global first-line TB treatment market

The estimate of the global TB drug market was derived by extrapolating the data gathered from the 10 study countries to cover all countries in the world. To maximize the accuracy of this process, countries were categorized into three groups based on burden of disease, economic status, and anticipated cost per patient. The groups (see the Supplemental Materials for a list of countries in each group) included:

- *High-income countries*. The 20 countries in this group include high-income countries in Western Europe plus Australia, Canada, Japan, New Zealand and the US.
- *HBCs*. These countries are the top 22 countries in terms of absolute TB burden, as defined by the WHO.
- *Rest of the world*. This includes the 168 countries and territories listed in the WHO 2006 Global TB Control Report[20] that were not counted in either the high-burden or high-income country segments.

Quantitative data about DOTS notification figures and incidence in these countries came from the WHO.[20,21] GDF staff provided data on the value and volume of GDF drugs supplied to each country for the period 2003–2005. GLC provided data on the number of patients approved for each program in each country and costs per unit for each drug on the GLC-approved list.

High-income countries

Market sizes for the four high-income countries under study were derived directly (primarily based on the IMS databases). For extrapolations to the other 16 countries in this group, three price points for a full first-line TB regimen—US$250, $350 and $450 per patient (based on the range of costs found in the four countries studied)—were used. The three costs were multiplied by the case notification figures for each country (from the WHO TB database)[21] to give a market range. Because TB is a reportable disease and the surveillance systems are considered reasonable in these countries, the case notification figures are assumed to represent the actual numbers of patients treated for TB.

High-burden countries

Market size figures for the six HBCs under study were derived directly from the IMS databases and government sources, as described above. The access to IMS databases was possible because all six of these HBCs are emerging economies with coverage by IMS; the same is not true of many other HBCs. For the remaining HBCs, the number of TB cases was multiplied by an estimated cost per regimen.

A low-end estimate of patient numbers was based on the number of TB cases reported in the WHO TB database for 2004[21] as having been treated by DOTS programs. The high-end estimate came from TB incidence figures.[21] This latter figure accounts for all cases, including those untreated or treated by private providers, and is a truer measure of market potential, as it assumes that every incident TB case receives a full course of treatment for TB.

For the cost per patient, three different price points were used: US$20, $30 and $40 per year. This was based on GDF prices at the low end and public market prices in the researched countries at the high end.

For the 11 HBCs that received TB medicines from the GDF in the form of direct procurement or grants, extrapolated figures were checked against GDF-reported values for 2005. In the two of 11 cases where the GDF value exceeded the low end of the extrapolated range (based on the US$20 scenario), GDF values were used to represent the total market for that country.

Rest of the world

For the 'rest of the world' segment, the market value estimation used the same prices and procedures as for the non-researched HBCs. GDF values were used for the 18 territories and countries in which the GDF value was greater than the lower end of the country's estimated range.

Deriving an estimate for the second-line TB treatment market

To evaluate the size of the second-line TB treatment market in the 10 study countries, the actual expenditures on TB drugs were sourced directly from the government and GLC (for public sector programs) and from IMS databases (for the private sector).

Table 1 Estimates of the global first-line drug market using the low-end approach (calculated on the basis of case notification in HBCs and 'rest of the world'), in million $US

Price ranges	HBCs	Rest of the world	High-income countries	Total
Low	199.7	19.9	41.8	261.4
Medium	210	28.6	49.1	287.7
High	221.5	38.1	56.4	316

HBC = high-burden countries.

Table 2 Estimates of the global first-line drug market using the high-end approach (calculated on the basis of incidence in HBCs and 'rest of the world'), in million $US

Price ranges	HBCs	Rest of the world	High-income countries	Total
Low	228.3	39.9	41.8	310
Medium	254.8	59.9	49.1	363.8
High	281.4	79.8	56.4	417.6

HBC = high-burden countries.

RESULTS

Overall market estimate for first-line drugs

Adding together the estimates of the TB drug market for high-income countries, HBCs and the rest of the world yielded a low-end range (based on case notification, see Table 1) of US$261–316 million and a high-end range (based on incidence, see Table 2) of US$310–418 million. Note that for high-income countries, there was no difference in the figures for the low- and high-end ranges, as case notification was used as the basis for both ranges.

Determining the accuracy of the first-line treatment estimate

For the public sector, figures were checked by comparing the top-down calculations (from IMS in high-income countries, or government sources or wholesalers in HBCs) and bottom-up calculations (from patient numbers multiplied by drug costs, which is reliable only if adherence rates are high). Results are shown in Table 3. In the six countries where the comparison was possible, there was close agreement between the two figures.

A similar analysis was not possible for the private sector, as values for both variables were poorly defined. Reporting of patient numbers in private markets in HBCs is uneven, and the regimens used in the private sector could only be established by a large census of providers in each country, which was out of the scope of this investigation.

Data were available to factor by indication in high-income countries but not in all HBCs. Any resulting errors should, however, be minimal. The substantial public sector HBC numbers were supplied either by TB programs that use drugs only for TB or, in South Africa, by suppliers who sell only fixed-dose combinations that are used only for TB. In the private HBC markets, the first-line drug that is most commonly used for other indications—rifampicin—was used for other indications in only 0.7% (Indonesia), 1.2% (Philippines) or 19.1% (South Africa) of cases. Adjusting the total across all six HBCs based on these figures would result in a change of between US$94 000 (using 0.7%) and $1.8 million (using 19.1%).

We also investigated the robustness of the extrapolations used to figure the 'rest of the world' and 'non-

Table 3 Value of first-line drugs by top-down and bottom-up methods, public sector only, in million $US

Country	Top down	Bottom up	Comments
Brazil	NA	4.9	No comparison was made, as the only source of drugs (the public sector) supplied information suitable for a bottom-up calculation
China	8.3	9.0	These figures apply only for drugs purchased through the National Center for Tuberculosis Control and Prevention (NCTB); an additional $11.3 million of public sector drugs flow through local tenders
France	3.6	3.2	
India	24.3	23.9	Includes allowance for buffer stock
Indonesia	NA	5.8	Only a bottom-up calculation was done for the public market due to lack of in-country work; it was based on stock records and not patient numbers
Japan	11.3	NA	Insufficient in-country work for bottom-up calculation
Philippines	2.2	2.5	
South Africa	18.3	NA	No bottom-up calculation was performed, as record keeping and adherence numbers were not considered reliable enough
UK	4.0	4.3	
USA	16	12	The bottom-up calculation was probably lower because the average weight of patients was assumed to be only 55–60 kg. In addition, the prices may have differed from the two states in which they were sampled.

NA = not available.

researched HBC' segments. For example, it is possible that some prices for TB drugs may diverge from the range of $US20–40, especially in middle-income countries. This would raise the value of this segment.

For the 'rest of the world' segment, the impact of this should not be significant, given that these countries combined represent ~12% of worldwide incidence.[20] For example, using the high-income prices (US$250, $350 and $450) rather than the HBC prices (US$20, $30 and $40) for all 'rest of the world' countries that are classified as high-income by the World Bank[22] resulted in an increase of the estimates of between US$7 and $30 million.

Similarly, the use of the lower prices should not be a problem for most of the non-researched HBCs. The 16 non-researched HBCs fall into three income classifications. Fourteen are classified as low-income by the World Bank, and one (Thailand) is classified as low middle-income.[22] It is unlikely that TB drug prices in these countries significantly exceed the values in the researched HBCs, which include one low-income country, three low middle-income countries and two upper middle-income countries.

Russia—the one remaining non-researched HBC—is, however, an upper middle-income country. The total estimated market for first-line drugs in Russia was US$6.6 million using the $40 per course estimate as in other HBCs. Subsequently, the actual price for a course of first-line treatment in Russia was found to be significantly higher (see case study)[19] and follow-up research led to a revised estimate of US$38–47 million for the total cost of first-line TB drugs in Russia.

Finally, our confidence in the extrapolation is increased by applying the same extrapolation technique to the researched HBCs. The total number for first-line drugs from all sources derived using our detailed in-country research was US$175 million for the six researched HBCs. This falls at the upper end of the extrapolation range calculated using standardized pricing for the same six HBCs (US$52–175 million). This is consistent with our existing discussion, i.e., the researched HBCs are on average in higher World Bank income categories than the typical HBC, and so we would expect their actual prices to be at the upper end of the standardized range.

Deriving an estimate for the second-line market in the countries studied

The overall market estimate for second-line drugs in the 10 countries studied was ~US$54 million. These countries represent an estimated 57% of the global burden of multidrug-resistant (MDR) TB[23] and were responsible for 37% of the MDR-TB cases notified in the 27 global priority countries in 2006.[24]

It was not possible to make an estimate for the global second-line market because there were too many factors that varied in unknown ways within and between countries (see Discussion). Moreover, in some countries, IMS data were insufficient to factor use of potential second-line drugs for TB as opposed to other indications.

DISCUSSION

The commercial importance of pharmaceuticals in the industrialized world has led to the creation of databases that track pharmaceutical purchases. In most developing countries these systems are not present or not as extensive, making it challenging to derive market estimates for drugs for diseases primarily affecting these countries. It is however, possible to do so.

The results of such an estimate for TB drugs are summarized in Table 1 and Table 2, and are presented in more detail in our earlier report[18] and country reports.[19] This study provides unique insight into the size and complexity of today's global TB market.

Although the total market estimate is not inconsiderable, the TB marketplace is highly fragmented because it is shared by more than four drugs and a multiplicity of suppliers. Drug development is expensive and drug companies require a large potential market to encourage them to initiate a project. It may be that the fragmented TB drug market is not large enough to provide such incentives for innovation, at least for commercial companies acting alone. For example, the domestic spending of France, Japan, the UK and the US combined on TB drugs is less than US$50 million per year, representing less than 0.008% of the value of the global pharmaceutical market, although their spending on all drugs accounts for 61% of that total global pharmaceutical market. The low cost of the current regimen also raises the problem of a potentially low profit margin for new drugs.

In this article, we have outlined the method used to derive these market estimates for TB drugs, and the factors affecting the accuracy and confidence in these estimates. For the qualitative investigations, a primary focus was to determine the major distribution channels for TB drugs. TB treatment in France, for example, was found to be mainly based in hospitals, whereas in the US it was out-patient-based. The site and method of treatment helped determine where the major sales of TB drugs were to be found and which data were most appropriate for determining the size of the market.

Understanding the distribution points is critical to understanding the market, and this is especially true for TB drugs. Because TB is considered a public health threat, most countries have a national disease control program for TB within the public sector. In Brazil, for example, IMS data were not relevant, as all TB drugs were administered by governmental systems that are not captured in the IMS databases. IMS data were, however, instrumental for investigating several of the emerging market economies in which the private market for drugs and the surveillance of that private market are well established.

A previous market estimate for TB drugs made in 2001 placed the global market value in 2000 at US$400–458 million for first-line drugs.[16] The ranges reported here are similar, although the top of our top-end range (US$418 million) only just overlaps the range suggested for 2000. It is difficult to estimate the direction in which the market size would have moved from 2000 to 2005. Drug prices have dropped, but the TB burden has increased slightly from 8.3 million new TB cases in 2000[25] to 8.8 million in 2005,[4] and DOTS coverage has increased.

There is some uncertainty surrounding the 2000 estimate. This estimate used the best data available at the time, but for the public sector this consisted of an incomplete WHO survey conducted via mail or internet, not in person.[17] Determining the value of the TB drug market was not the primary objective of this survey, and no additional primary research was conducted in HBCs, making it difficult to interpret much of the data. In the current study, however, data were collected directly in these countries and were supported by a clear picture of the health care system.

Moreover, double-counting may have been possible in the earlier study. In countries such as South Africa and the UK, sales originating with public sector tenders (captured by public sector inquiries) may also be captured downstream in IMS data (e.g., at provincial depots in South Africa). The qualitative side of the current study captured this complexity.

The confidence about the market estimate varies for different segments of the estimate. IMS databases were used for the private sector in all 10 countries studied and for the public sector in the high-income countries studied. For these markets, the IMS databases provide a unique access point to direct sales data and are considered a gold standard by pharmaceutical companies worldwide seeking to track sales of their products. In HBCs, IMS data are often the only data available on the private sector except for individual company records, which may not be accessible to researchers. Confidence in IMS and other figures was increased by the multiple in-person interviews, agreement with bottom-up calculations, comparison with GDF figures, sensitivity analysis with the 'rest of the world' segment and consistency of the researched and extrapolated figures for the researched HBCs. A major lesson from our study is that, despite gaps and uncertainties in individual data sources, a robust figure can be obtained by combining data from different sources.

The global second-line TB drug market is, however, difficult to estimate with any confidence. Public sector data are scarce because public financing of second-line treatment is limited. Most patients are therefore found in the private sector, where there is uncertainty and variability in regimens, adherence and length of treatment. There is thus no real 'average cost' for a second-line patient. In addition, most countries do not report case detection or treatment of second-line patients, particularly if they are not treated in the public sector. All these factors make it difficult to estimate the second-line market accurately without conducting extensive primary research in each country.

The original aim was to estimate not just market value but also patient volume for both the public and private sectors. Public sector volume is available via case reporting, but it was not possible to derive an accurate estimate for patient volume for the private sector in any category of countries. Such an estimate would have been based on converting the number of private-sector sales into a number of patients, using assumptions about standard regimens. However, those assumptions were deemed invalid because of the documented variability in first- and second-line prescribing patterns.[26–29] This would introduce a major error when considering the significant private markets that the current study revealed in India, Indonesia and the Philippines.

Despite these challenges, the major part of this market estimate is based on a robust methodology. This methodology includes an analysis of market information from both the public and private sectors and a process for checking that information through interviews and an extensive mapping of global and national procurement and distribution systems. The estimate for TB could be revised in 5 or 10 years with far less effort, as the basic structure of the health systems, and the identity of outlets covered and not covered by IMS data, would already be known. Similar estimates for other diseases could be modeled on the current study, although differences would emerge due to the unique organizing role of NTPs. In any case, such efforts would likely require, as described here, a substantial initial mapping effort.

In addition, the knowledge gained from this study could help in revising IMS data collection methods so that their databases will in the future contain more robust information about drug markets in developing countries, particularly those markets based on drugs that are primarily purchased and distributed by the public sector. When new drugs become available, such information will be critical for understanding how best to introduce the new drugs into developing country markets.

The critical qualitative finding of this study was that the TB drug supply chain showed extensive variation between countries. This variation introduces another level of uncertainty into predictions of supply and demand, and increases the risks that suppliers and procurement agents will make costly errors as they attempt to make decisions based on limited information. Better information on supply and demand could improve forecasting accuracy and certainty. Based on this logic, there has been a recent call for a global 'infomediary' to gather and organize market data for various disease areas in low- and middle-income countries.[30] This organization would act as an intermediary

between those who supply the information, such as NTPs, and those who want the information to assist suppliers with demand forecasting, reduce delays and ensure consistent supply. The current research suggests that a global infomediary that provides information sharing about the drug supply chain, market size and payer systems could be extremely helpful to the development and roll-out of new TB regimens.

Acknowledgements

The authors are very grateful to their project advisors: M Ashiya, S Ewart, J Lewis, M Korsten, R Matiru, J Rankin and D Rouse. TB Alliance officers M Freire, M Spigelman, A Hinman and B Jensen and TB Alliance staff members D Ambrosino, A Barve, A Ginsberg, Z Ma, C Mayer, K Mdluli, S Seidel, C van Niekerk and K Wright provided review, writing and publication support.

Supporting data and review were provided by K Castro, L S Chauhan, D Chin, G Churchyard, K Floyd, P Heitkampp, M Hela, J Hoover, M Howley, H Inoue, F Jouberton, J Keravec, H Kettler, A Kritski, E Molari, S Munsiff, L Mvusi, P-Y Norval, A Ruffino Netto, I Onozaki, N Patel, S Sahu, V S Salhotra, T Tupasi, R G Vianzon, J Vosken, D Weil, F Wares, W Xiaomei and C Yu.

Financial support for this study came from The Netherlands Ministry of Foreign Affairs' Department of Development Cooperation (DGIS) and the Bill & Melinda Gates Foundation.

Author contributions: NRS, APG, AF, MGL and TR contributed to the conception and design of the study; NRS, APG, AF, MGL, LD, HRI, CLW and TR to the acquisition of the data; all authors to analysis and interpretation of the data; NRS, WAW, AF, MGL and LD to drafting of the manuscript; NRS, WAW, AF and HRI to critical revision of the manuscript; and all authors contributed to the final draft of the manuscript.

Conflict of interest statement: APG, AF, MGL, CLW, TR, LD and NP were or are employed by IMS Health Inc, which markets the databases described in this study. NRS, WAW and HRI were or are employed by the Global Alliance for TB Drug Development, whose activities are aimed at developing and making available new therapies for TB.

Role of the funding source: The sponsors of the study, other than those directly employing the authors, had no role in study design, data collection, data analysis, data interpretation or writing of this report. The corresponding author had access to all data in the study and had final responsibility for the decision to submit for publication.

References

1 Arrow K, Panosian C, Gelband H, Committee on the Economics of Antimalarial Drugs, eds. Saving lives, buying time: economics of malaria drugs in an age of resistance. Washington DC, USA: Institute of Medicine/National Academies Press, 2004.
2 Norval P Y, Blomberg B, Kitler M E, Dye C, Spinaci S. Estimate of the global market for rifampicin-containing fixed-dose combination tablets. Int J Tuberc Lung Dis 1999; 3 (Suppl 3): S292–S300; discussion S17–S21.
3 International AIDS Vaccine Initiative. Forecasting demand for preventive HIV vaccines in India. New York, NY, USA: IAVI, 2007.
4 World Health Organization. Global tuberculosis control: surveillance, planning, financing. WHO report 2007. WHO/HTM/TB/2007.376. Geneva, Switzerland: WHO, 2007.
5 Wilkinson D, Floyd K, Gilks C F. Costs and cost-effectiveness of alternative tuberculosis management strategies in South Africa—implications for policy. S Afr Med J 1997; 87: 451–455.
6 Floyd K, Wilkinson D, Gilks C. Comparison of cost-effectiveness of directly observed treatment (DOT) and conventionally delivered treatment for tuberculosis: experience from rural South Africa. BMJ 1997; 315: 1407–1411.
7 Brown R E, Miller B, Taylor W R, et al. Health care expenditures for tuberculosis in the United States. Arch Intern Med 1995; 155: 1595–1600.
8 Taylor Z, Marks S M, Rios Burrows N M, Weis S E, Stricof R L, Miller B. Causes and costs of hospitalization of tuberculosis patients in the United States. Int J Tuberc Lung Dis 2000; 4: 931–939.
9 Palmer C S, Miller B, Halpern M T, Geiter L J. A model of the cost-effectiveness of directly observed therapy for treatment of tuberculosis. J Public Health Manag Pract 1998; 4: 1–13.
10 Stop TB Partnership/World Health Organization. Global plan to stop TB, 2006–2015. Annex 1: methods used to estimate costs, funding and funding gaps. WHO/HTM/STB/2006.38. Geneva, Switzerland: WHO, 2006.
11 Floyd K, Skeva J, Nyirenda T, Gausi F, Salaniponi F. Cost and cost-effectiveness of increased community and primary care facility involvement in tuberculosis care in Lilongwe District, Malawi. Int J Tuberc Lung Dis 2003; 7 (Suppl 1): S29–S37.
12 Kemp J R, Mann G, Simwaka B N, Salaniponi F M, Squire S B. Can Malawi's poor afford free tuberculosis services? Patient and household costs associated with a tuberculosis diagnosis in Lilongwe. Bull World Health Organ 2007; 85: 580–585.
13 Vassall A, Compernolle P. Estimating the resource needs of scaling-up HIV/AIDS and tuberculosis interventions in sub-Saharan Africa: a systematic review for national policy makers and planners. Health Policy (Amsterdam, Netherlands) 2006; 79: 1–15.
14 Mohan C I, Bishai D, Cavalcante S, Chaisson R E. The cost-effectiveness of DOTS in urban Brazil. Int J Tuberc Lung Dis 2007; 11: 27–32.
15 Resch S C, Salomon J A, Murray M, Weinstein M C. Cost-effectiveness of treating multidrug-resistant tuberculosis. PLoS Med 2006; 3: e241.
16 Global Alliance for TB Drug Development. The economics of TB drug development. New York, NY, USA: Global Alliance for TB Drug Development, 2001.
17 World Health Organization. Global TB drug facility: prospectus. Annex D: WHO survey on TB drug supply experiences in WHO member states. WHO/CDS/STB/2001.10a. Geneva, Switzerland: WHO, 2001.
18 Global Alliance for TB Drug Development. Pathway to patients: charting the dynamics of the global TB drug market. New York, NY, USA: Global Alliance for TB Drug Development, 2007.
19 Global Alliance for TB Drug Development. Pathway to patients: country reports. New York, NY, USA: Global Alliance for TB Drug Development, 2007. http://www.tballiance.org/aaa/groundwork.php Accessed November 2007.
20 World Health Organization. Global tuberculosis control: surveillance, planning, financing. WHO/HTM/TB/2006.362. Geneva, Switzerland: WHO, 2006.
21 World Health Organization. Global health atlas. Geneva, Switzerland: WHO, 2005. www.who.int/globalatlas/dataQuery/default.asp Accessed July 2008.
22 World Bank. Country groups. Washington DC, USA: World Bank, 2007. http://web.worldbank.org/WBSITE/EXTERNAL/DATASTATISTICS/0,,contentMDK:20421402~pagePK:64133150~piPK:64133175~theSitePK:239419,00.html Accessed November 2007.
23 World Health Organization. Anti-tuberculosis drug resistance in the world. Report no. 4. WHO/HTM/TB/2008.394. Geneva, Switzerland: WHO, 2008.
24 World Health Organization. Global tuberculosis control: surveillance, planning, financing. WHO report 2008. WHO/HTM/TB/2008.393. Geneva, Switzerland: WHO, 2008.
25 Corbett E L, Watt C J, Walker N, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med. 2003; 163: 1009–1021.

26 Prasad R, Nautiyal R G, Mukherji P K, Jain A, Singh K, Ahuja R C. Treatment of new pulmonary tuberculosis patients: what do allopathic doctors do in India? Int J Tuberc Lung Dis 2002; 6: 895–902.
27 Rajeswari R, Balasubramanian R, Bose M S, Sekar L, Rahman F. Private pharmacies in tuberculosis control—a neglected link. Int J Tuberc Lung Dis 2002; 6: 171–173.
28 Olle-Goig J E, Cullity J E, Vargas R. A survey of prescribing patterns for tuberculosis treatment amongst doctors in a Bolivian city. Int J Tuberc Lung Dis 1999; 3: 74–78.
29 Sumartojo E M, Geiter L J, Miller B, Hale B E. Can physicians treat tuberculosis? Report on a national survey of physician practices. Am J Public Health 1997; 87: 2008–2011.
30 Center for Global Development. Consultation report of the Global Health Forecasting Working Group. Washington DC, USA: Center for Global Development, 2007.

RÉSUMÉ

CONTEXTE : Le succès de l'introduction de nouveaux médicaments dans les pays à revenus faibles ou moyens exige une connaissance de la taille du marché existante et des dynamiques de marché dans la zone thérapeutique concernée. Les marchés de médicaments dans ces pays sont toutefois moins bien connus que ceux des pays à revenus élevés.

MÉTHODES : On a estimé le marché mondial des médicaments antituberculeux en étudiant en détail six pays à fardeau élevé et six pays à revenus élevés et en extrapolant les résultats. Les données ont été dérivées de bases de données existantes dans les audits pharmaceutiques et par des interviews avec les autorités gouvernementales, les personnel médicaux et les fournisseurs.

RÉSULTATS : L'utilisation d'apports qualitatifs pour éclairer la collecte d'informations quantitatives, notamment pour identifier où se situent les flux majeurs de médicaments antituberculeux, a permis d'arriver à une estimation fiable du marché mondial des médicaments antituberculeux de première ligne. Les écarts finaux ont été de 261 à 316 millions d'US$ quand on se base sur les taux de déclaration des cas et de 310 à 418 millions d'US$ si l'on se base sur les incidences.

CONCLUSIONS : Une estimation du marché mondial des médicaments antituberculeux est rendue plus fiable par une compréhension qualitative des voies de distribution des médicaments antituberculeux qui diffèrent considérablement d'un pays à l'autre. La connaissance de cette structure dans les pays-clé à fardeau élevé pourra servir de base à l'avenir à une mise à jour plus simple des estimations du marché à l'avenir.

RESUMEN

MARCO DE REFERENCIA : La exitosa introducción de nuevos medicamentos antituberculosos en países de escasos y medianos ingresos exige el conocimiento de la dimensión y de las dinámicas del mercado existente en la zona de interés. Sin embargo, los mercados de los medicamentos en estos países se conocen menos bien que los mercados de países de altos ingresos.

MÉTODOS : Se evaluó el mercado mundial de los medicamentos antituberculosos mediante el estudio meticuloso de seis países con alta carga de morbilidad y cuatro países de altos ingresos, seguido de extrapolación. Los datos se obtuvieron a partir de las bases de datos de auditorías farmacéuticas y entrevistas con funcionarios, personal médico y proveedores.

RESULTADOS : Se utilizaron entradas cualitativas con el fin de documentar la recopilación de información cuantitativa, sobre todo en cuanto a la localización de los principales flujos de medicamentos antituberculosos, lo cual permitió un cálculo acertado del mercado mundial de los medicamentos de primera línea. Se obtuvieron los siguientes márgenes finales : de 261 millones a 316 millones de dólares y de 310 millones a 418 millones de dólares, según se utilizaran en las extrapolaciones los índices de notificación o la incidencia.

CONCLUSIÓN : El cálculo del mercado mundial de los medicamentos antituberculosos se puede hacer más preciso gracias a una comprensión cualitativa de las vías de distribución, las cuales difieren considerablemente de un país a otro. El conocimiento de esta estructura en países clave con una alta carga de morbilidad aporta las bases que harán más sencilla la actualización de las estimaciones del mercado en el futuro.

APPENDIX 1
Country-Specific Methodology for Market Estimates

HIGH-INCOME COUNTRIES

France methodology

For France, all sales data were obtained from the IMS Multinational Integrated Data Analysis System (MIDAS) database, which covers 943 public hospitals, private hospitals and clinics, and 11 000 retail pharmacies.

Japan methodology

For Japan, all sales data were collected from the IMS MIDAS database, which is based on a sampling of 76 wholesalers (to cover the retail sector), and 6500 hospitals. International classification of diseases (ICD-10) codes were used to identify drugs associated with the treatment of TB, and associated diagnosis codes identified what percent of the drug was used for TB versus all other indications.

United Kingdom methodology

For the United Kingdom, all sales data were derived from the IMS MIDAS database, which covers public hospitals and retail pharmacies (private hospitals comprise a small segment of the drug market). This included data from virtually all recognized wholesalers, including all major wholesaling groups, on all their distribution to retail and doctor outlets, and by the Boots organization on the distribution of dispensing medicines to their retail outlets. The UK hospital data include all pharmaceutical products dispensed within National Health Service hospitals irrespective of their source of supply.

United States methodology

For the United States, where more robust database alternatives exist, three databases were used to cover both the private and public sectors. The National Prescription Audit (NPA PLUS) measures dispensing of prescriptions by a panel of 22 000 retail pharmacies in the US. The IMS National Sales Perspective (NSP) measures sales volume of pharmaceutical products purchased by retail stores (including independent and chain pharmacies) and non-retail channels (including hospitals, clinics and HMOs) from wholesalers and suppliers. The National Disease and Therapeutic Index (NDTI) uses reports from 1381 physicians per month to report diagnoses and prescriptions.

In calculating the size of the US market, the NSP data provided a total value for both first- and second-line products in retail and non-retail sectors. The NPA data provided total volume for retail sectors only. Although the NSP and NPA data sources capture overlapping sectors of the total market, they use different methodologies to collect data and thus help to validate each other.

All drugs falling under the TB ICD-10 codes were pulled by product. The NDTI data were then used to account for the use of each product outside of the TB indication to arrive at a more exact and accurate total value and volume.

HIGH-BURDEN COUNTRIES

Brazil methodology

TB drugs in Brazil are not sold in retail pharmacies and therefore do not appear in the IMS databases. All TB drugs are procured by the central government and are provided for free at the hospital level. The Brazilian Ministry of Health therefore provided data for the annual cost, the number of patients treated in 2004, and the total market value for each of four categories of TB, including naïve TB, previously treated TB, TB meningitis, and drug-resistant TB. Cost per unit and the identity of suppliers for each product were also provided.

China methodology

For the public market in China, the number of units sold and cost per unit was provided by the central government, the Japan International Cooperation Agency (JICA) and the World Bank. The total was corroborated by the National TB Control Program (CDC-NCTB); a slight discrepancy arose probably because the CDC estimate represents a budget allocation for each year rather than an actual expense.

Information on private sector sales came from the IMS MIDAS database. The percentage use of a drug for TB versus other indications is not available as part of this survey, so this information came

from interviews with providers and NCTB staff. Based on this information, 100% of the use of first-line products was assumed to be for TB. Estimates for percent usage of second-line products for TB represent a range only, and are less accurate.

Some funding for TB drugs in China comes directly from provincial governments. The amount of this funding was researched for Guangdong and Shanghai, and these figures were extrapolated to cover the six other provinces that the central government identified as having independent provincial funding for TB drugs.

India methodology

Discussions were held with the Central TB Division and their contracted procurement agency. Together with the latest tender for public sector procurement, these discussions yielded value estimates for the public sector, which in India covers only first-line TB drugs. Added to this were figures for GDF-funded drugs. The GDF figures were not available directly, as GDF money comes from various funding sources in various and overlapping funding rounds. GDF figures were therefore derived indirectly. The UK Department for International Development (DFID) funding figures indicated how much funding was used to cover a certain population with GDF-sourced drugs. This figure was then multiplied to account for all of the population estimated to be covered by GDF-sourced drugs funded by all sources.

The private sector estimate was based on the ORG-IMS Secondary Stockist Audit, which is extrapolated from the sales of approximately 13 000 secondary stockists throughout India. An IMS Prescription Audit Database also records the percentage of prescriptions for any given product that were written for TB; these numbers were used to adjust the second-line sales figures.

Philippines methodology

The NTP in the Philippines purchases all of its TB drugs (first-line drugs only) through GDF. Value and patient volume figures were provided by the NTP per patient category.

Local government units in the Philippines may procure additional TB medicines from local manufacturers. These drugs are, however, distributed through commercial channels and are therefore included in the private market estimates captured by the IMS MIDAS database. This database draws on data from distributors, direct manufacturers, and a sample of 230 drugstores nationwide. MIDAS in the Philippines does not, however, include data on diagnosis by ICD code, so first-line sales figures were left unadjusted and second-line figures were adjusted based on an IMS survey of prescribing patterns. This survey is conducted every 6 months with 565 physicians in the Philippines.

Indonesia methodology

The public sector in Indonesia provides only first-line drugs, which are procured from GDF and local manufacturers. Deriving estimates of total TB drug expenditures from these sources was not possible because of the lack of in-country research. Therefore, and in contrast to the other countries, public sector calculations were based on a bottom-up calculation. The number of units (from Management Sciences for Health, which provides technical assistance to the central government) was multiplied by price (from stakeholder discussions and the GDF website).

Private-sector data were sourced from the IMS MIDAS database, with adjustment of second-line figures according to prescription data.

South Africa methodology

The public sector is the primary distributor of both first- and second-line TB drugs in South Africa. Sales figures were obtained from discussions with the two key suppliers of first-line drugs for the South African national tender (Sandoz and Sanofi Aventis). These figures were corroborated by discussions with other TB drug suppliers and discussions with national government officials.

Sales figures were not available from the wider variety of suppliers of second-line drugs. Instead, the IMS MIDAS database was queried for TB-related drugs flowing through the provincial depots on behalf of the public sector. The database also yielded a private sector estimate based on sales to pharmacies, dispensing physicians, private hospitals and clinics, buying groups, mail order/courier medicine distributors and other private outlets. The second-line drug sales were adjusted with IMS prescription data to screen out non-TB indication use.

APPENDIX 2
Country Classification

HIGH-INCOME COUNTRIES

Australia
Canada
Denmark
Finland
France*
Germany
Greece
Ireland
Italy
Japan*
Luxembourg
Netherlands (including Netherlands Antilles)
New Zealand
Norway
Portugal
Spain
Sweden
Switzerland
United Kingdom*
United States* (including US Virgin Islands)

* These countries were included in in-depth case studies; market estimates were based on research.

HIGH-BURDEN COUNTRIES

Afghanistan
Bangladesh†
Brazil*
Cambodia
China*
Congo, The Democratic Republic of†
Ethiopia†
India*
Indonesia*
Kenya†
Mozambique†
Myanmar‡
Nigeria‡
Pakistan†
Philippines*
Russia
South Africa*
Tanzania
Thailand
Uganda†
Vietnam
Zimbabwe

* These countries were included in in-depth case studies and therefore market estimates were derived from primary and secondary data sources and analyses.
† These countries were not included in in-depth case studies but are GDF countries. GDF data were compared to ranges developed according to the extrapolation methodology. GDF data were below extrapolated estimates and thus extrapolated estimates were used.
‡ Nigeria and Myanmar were not included in in-depth case studies but are GDF countries. GDF data were compared to ranges developed based on extrapolation methodology. GDF data were above the lower end of the extrapolated estimates (at the lowest price point of $20 using the case notification rate). Therefore, GDF values were used in place of the lower end of the estimates for these countries.
GDF = Global Drug Fund.

REST OF THE WORLD

Albania‡
Algeria
American Samoa
Andorra
Angola‡
Anguilla
Antigua & Barbuda
Argentina
Armenia†
Austria
Azerbaijan‡
Bahamas
Bahrain
Barbados
Belarus
Belgium
Belize
Benin‡
Bermuda
Bhutan
Bolivia
Bosnia-Herzegovina‡
Botswana
British Virgin Islands
Brunei Darussalam
Bulgaria
Burkina Faso‡
Burundi†
Cameroon‡
Cape Verde‡
Central African Republic‡
Chad †
Chile
China, Hong Kong SAR
China, Macao SAR
Colombia
Comoros
Congo†
Cook Islands
Costa Rica
Cote d'Ivoire ‡
Croatia
Cuba
Cyprus
Czech Republic
Djibouti†
Dominica
Dominican Republic†
Ecuador
Egypt†
El Salvador
Equatorial Guinea†
Eritrea†
Estonia
Fiji
French Polynesia
Gabon
Gambia†
Georgia
Ghana
Grenada
Guam
Guatemala
Guinea
Guinea-Bissau
Guyana
Haiti†
Honduras
Hungary
Iceland
Iran
Iraq‡
Israel
Jamaica
Jordan
Kazakhstan
Kiribati
Kosovo* §
Kuwait
Kyrgyzstan
Lao PDR
Latvia
Lebanon
Lesotho
Liberia†
Libyan Arab Jamahiriya
Lithuania
TFYR Macedonia¶
Madagascar†
Malawi
Malaysia
Maldives‡
Mali†
Malta
Marshall Islands
Mauritania†
Mauritius
Mexico
Micronesia
Micronesia‡
Moldova†
Monaco
Montserrat
Morocco
Namibia †
Nauru
Nepal‡
New Caledonia
Nicaragua
Niger†
Niue
North Korea†
Northern Mariana Is
Oman
Palau
Panama
Papua New Guinea†
Paraguay
Peru
Poland
Puerto Rico
Qatar
Rep. Korea
Republic of Moldova
Romania
Rwanda†
Saint Kitts & Nevis
Saint Lucia
Samoa
San Marino
São Tomé and Principe‡
Saudi Arabia
Senegal
Serbia and Montenegro†
Seychelles
Sierra Leone‡
Singapore
Slovakia
Slovenia
Solomon Islands
Somalia†
Sri Lanka†
St Vincent & Grenadines
Sudan†
Suriname
Swaziland
Syria†
Tajikistan‡
Timor-Leste†
Togo‡
Tokelau
Tonga
Trinidad & Tobago
Tunisia
Turkey
Turkmenistan‡
Turks & Caicos Islands
Tuvalu
Ukraine
United Arab Emirates
Uruguay
Uzbekistan†
Vanuatu
Venezuela
Wallis & Futuna Is
West Bank and Gaza Strip
Yemen
Zambia†

* The United Nations Mission of Kosovo.

† These countries were not included in in-depth case studies but are GDF countries. GDF data were compared to ranges developed based on extrapolation methodology. GDF data were below extrapolated estimates and thus extrapolated estimates were used.

‡ These countries were not included in in-depth case studies but are GDF countries. GDF data were compared to ranges developed based on extrapolation methodology. GDF data were above the lower end of the extrapolated estimates (at the lowest price point of $20 using the case notification rate for most countries; at all three price points ($20, $30, $40) when using the case notification rate for Cape Verde and Central African Republic; and at lower price points ($20 and $30) when using the case notification rate and incidence for the Maldives). Therefore, GDF values were used in place of the lower end of the estimates for these countries.

§ No case notification or incidence data available through the WHO database so GDF data used instead.

¶ No case notification or incidence data available through the WHO database or GDF data so not included in estimates.

GDF = Global Drug Fund; WHO = World Health Organization.