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Estimated generic prices for novel treatments for drug-resistant tuberculosis

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Running title: Estimated generic prices of new TB drugs

Synopsis

Background: Estimated annual incidence of MDR-TB is 480,000, representing 5% of TB incidence, but 20% of mortality. Multiple drugs have recently been developed or re-purposed for the treatment of MDR-TB. Currently, treatment for MDR-TB costs thousands of dollars per course.

Objectives: To estimate generic prices for novel TB drugs that would be possible given large-scale competitive manufacture.

Methods: Prices for linezolid, moxifloxacin, and clofazimine were estimated based on per-kilogram prices of active pharmaceutical ingredient (API). Other costs were added, including formulation, packaging and a profit margin. The costs of projection for sutezolid were estimated to be equivalent to those for linezolid, based on chemical similarity. Generic prices for bedaquiline, delamanid, and pretomanid were estimated by assessing routes of synthesis, costs/kg of chemical reagents, routes of synthesis, and per-step yields. Costing algorithms reflected variable regulatory requirements, efficiency of scale based on demand, and were validated by testing predictive ability against widely-available TB medicines.

Results: Estimated generic prices were USD $8-$17/month for bedaquiline, $5-$16/month for delamanid, $11-$34/month for pretomanid, $4-$9/month for linezolid, $4-$9/month for sutezolid, $4-$11/month for clofazimine, and $4-$8/month for moxifloxacin. Estimated generic prices were 87%-94% lower than current lowest available prices for bedaquiline, 95%-98% for delamanid, 94%-97% for linezolid. Estimated generic prices were $168-$395 per course for the STREAM trial modified Bangladesh regimens (current costs $734-$1,799), $53-$276 for pretomanid-based three-drug regimens, and $238-$507 for a delamanid-based four-drug regimen.

Conclusions: Competitive large-scale generic manufacture could allow supplies of treatment for 5-10 times more MDR-TB cases within current procurement budgets.

Introduction

TB is estimated to have caused 9 million new active infections and 1.5 million deaths in 2013.[1] An estimated 480,000 cases of TB annually are resistant to first-line drugs, termed MDR-TB.[2] While global TB prevalence has remained relatively stable over the last two decades, detected cases of drug-resistant TB nearly tripled between 2009 and 2013.[1] MDR-TB represents 5% of global incidence, but nearly 20% of mortality.[1] 9% of MDR-TB cases have further resistance (XDR-TB).[2] Furthermore, the proportion of cases that are drug-resistant may be underestimated due to poor coverage of drug susceptibility testing.[3] Treatment success rates are 86% for drug-sensitive TB (DS-TB), 45% for MDR-TB, and just 22% for XDR-TB.[1]

The WHO categorises TB medicines into Groups 1 (first-line), 2 (injectables), 3 (fluoroquinolones), 4 (bacteriostatics), and 5 (drugs with limited evidence, including newer drugs).[2,4] Group 5 includes several recently developed or repurposed treatments for drug-resistant TB: bedaquiline, delamanid, clofazimine, and linezolid. Delamanid, approved in the EU,[2] and bedaquiline, approved in the EU and the USA,[5,6] have been recently added to the WHO Model Essential Medicines List, along with linezolid.[7]

While many TB medicines have severe side effects, and require at least 20 months of treatment for MDR-TB and 24 months for XDR-TB,[2] several promising new 9- and 6-month combination regimens containing bedaquiline and/or pretomanid are currently under investigation for treating MDR-TB. Current trials investigating these regimens include STREAM, STAND, NC-005, and Nix-TB.[8–11] The MDR-END trial will assess a longer regimen that includes delamanid.[12]

Tuberculosis care regularly incurs high health expenditures in low- and middle-income countries, where 95% of notified TB cases are diagnosed.[1,13] In 2013, more than 39,000 patients diagnosed with MDR-TB were on waiting lists for treatment.[1] Barriers to adequate treatment include low drug-susceptibility testing (DST) coverage, lack of access to laboratory-based diagnosis, lack of treatment monitoring, as well as high drug prices.[14,15] For MDR-TB, where drugs alone cost thousands of dollars per patient,[14] sustainable price reductions could both allow scale-up of treatment and cost savings. The establishment of an effective generics market for novel MDR-TB regimens will require political prioritisation, overcoming of patent barriers, and adequate demand volume. Demand would in turn be driven by improved detection rate, increased evidence on optimal regimens, and demand-side interventions such as pooled procurement by international funders and governments.

In HIV/AIDS, competitive generic production of antiretroviral medicines (ARVs) resulted in rapid price decreases, allowing treatment scale-up:[16] By mid-2014, 15 million people were on treatment.[17] More than 70% of ARVs used in low- and middle-income countries are manufactured by Indian generics companies.[18] In this analysis, we calculated estimated generic prices for new TB medicines, assuming robust competitive generic production.

Methods

We calculated estimated generic prices by combining data on the costs of the active pharmaceutical ingredient (API) with other cost components of manufacturing, using algorithms outlined below. Data on API exported from India were extracted from an online database for 2015.[19] Estimated generic prices were calculated for rifampicin, isoniazid, pyrazinamide, ethambutol, amikacin, kanamycin, levofloxacin, capreomycin, prothionamide, and cycloserine for the purpose of validating our costing algorithms. Per-kilogram pricing data for exported API and algorithms were used to estimate generic prices for moxifloxacin, linezolid, and clofazimine. Where robust export data were not available (bedaquiline, delamanid, sutezolid, pretomanid), we calculated estimated prices based on the processes used for the synthesis of these compounds. All monetary values are expressed as US dollars ($).

Costing algorithms

Previous price-estimation studies have combined API price with dosage information, formulation and packaging costs to estimate the generic price of the finished product.[20-22]

We developed algorithms based on information provided confidentially by multiple large generics companies, and by testing through comparison of algorithm-predicted prices for Group 1-4 drugs (for which robust generic competition already exists) to current prices available through the Global Drug Facility (GDF).[23] These algorithms are described below and shown as a flowchart in figure 1, using the example of moxifloxacin. The 'high-demand' algorithm represents a scenario in which market dynamics are similar to those of existing Group 1-4 medicines, while the 'low-demand' algorithm represents the early stages of global use and/or a limited scope of indications.

India is a major producer of generic medicines, producing more than 70% of HIV treatments used in low- and midle-income countries,[17] and all suppliers in long-term supply agreements with GDF are generic companies manufacturing in India.[24] For generic price calculations, we thus assumed manufacturing in India.

A generics manufacturer quoted a formulation and primary packaging cost of $0.008 per pill, assuming production in a facility approved for export to the European market, and a batch size of 500,000 packaged tablets. We included a conversion cost of $0.01 per pill in the high-demand algorithm and $0.04 in the low-demand algorithm. These assumed conversion costs are greater than, that is, conservative in relation to, those set out in the Indian National Pharmaceutical Pricing Authority's 'Norms for Conversion Cost (CC), Packing Charges (PC) and Process Loss (PL)'.[25]

Excipient contents were gathered from information published by the originator companies (Table S1), and per-kilogram excipients costs were extracted from export data. Addition of excipient costs assumed that the total weight of excipients in a pill is 4 times that of the API, and that the whole excipient weight is made up of the most expensive excipient. A cost of $0.10 per month was included for packaging and package inserts in the high-demand algorithm, and $0.35 in the low-demand algorithm. Finally, a profit margin for manufacturers was added on top of all costs – 10% in the high-demand algorithm, 50% in the low-demand algorithm. These profit margins are in line with typical generic producer margins reported elsewhere.[26]

For injectable drugs, the price per vial was extracted from export data (as API data were unavailable). To this, secondary packaging costs and profit margins were added as for the other groups.

Stringent Regulatory Authorities

The dominant mechanisms for API quality-assurance are approval by a Stringent Regulatory Authority (SRA) or approval by the WHO's prequalification programme (PQP). Countries considered to have SRAs comprise EU member states, the USA, Japan, Canada, Switzerland, Australia, Norway, and Iceland.[27]

Meeting internationally variable regulatory requirements adds costs to API manufacture. For the antiretroviral market, export-import data would suggest that a 35-50% incremental cost increase is common for SRA-approved APIs, which was confirmed in confidential discussion with large generics manufacturers. To recognize this variation in our generic price calculations, we used ranges of API prices to cover the higher API cost when produced at SRA standard, and the lower API cost for a 'non-SRA' standard.

Where sufficient export data were available, we derived the API price range by calculating a volume-weighted mean price for all exports to countries without SRAs ('non-SRA price'), and a volume-weighted mean price of exports to countries with SRAs ('SRA price'). For prothionamide, where data were available only for non-SRA exports, we multiplied the weighted mean 'non-SRA price' by 1.5 to derive a likely 'SRA price'.

For medicines where export data showed artificially large non-SRA to SRA price differences, presumed due to patent protection and other market barriers, we used a representative API price for the 'non-SRA price' based on substantial volumes sold at this price, and multiplied by 1.5 to derive an 'SRA price'. This was the case for moxifloxacin and linezolid, and graphs showing the wide distributions of prices for these APIs, and the representative prices chosen, are available as Figures S1 and S2.

For novel drugs where export data were not available, we estimated API costs based on the synthetic processes described in originator patents, assuming significant volume demand, process optimization work, and price competition in the market.

Current prices

Current prices were gathered from the price catalogues of the GDF and Médecins Sans Frontières (MSF), national drug price databases, and online price comparison websites (Table S2). Exchange rates of the 16th of June 2015 were used.

Total regimen costs

In calculations of total regiment costs for novel regimens currently under investigation, estimated generic prices were used for all group 5 drugs and moxifloxacin, and current GDF prices were used for all other drugs.

Volume demand

Where Indian export data were available, we calculated the total volume exported in kilograms or number of vials, as applicable. For bedaquiline, delamanid, pretomanid, and sutezolid, potential export volumes were calculated as the amount of API needed to produce sufficient treatments for 108,000 patients annually. This patient number derives from assuming treatment with drug in question of 50% of those diagnosed with MDR-TB, unchanged epidemiology, and a 60% improvement in MDR-TB detection rates among those diagnosed with TB (from the current 45% to 72%).[1] This assumed improvement in detection rates would be in line with the trend in detection rates 2009-2013.[1]

Results

Global overviews of lowest currently available prices are shown in figure 2. Current and calculated generic prices, patent expiry dates, and export volumes are shown in table 1 and figure 3. Current lowest and estimated generic prices of novel TB regimens are shown in table 2.

Group 1-4 drugs

Calculated generic price ranges for Group 1-4 drugs all overestimated or included current GDF prices, with the exception of moxifloxacin (figure 3).

Moxifloxacin

Export data showed a segmented market and rapid per-kilogram API price reductions over 2010-2016 (Figure S1). In this period, 27 tonnes of moxifloxacin API were exported in the price range $160-$200/kg (18% of total exported volume). We therefore estimated a non-SRA API price of $180, and an SRA price of $270/kg. This yielded an estimated generic price of $3.49-$7.91 per patient per month (figure 1).

Bedaquiline

Based on current prices for raw materials and yields similar to those reported in the patent literature, it is clear that the advanced intermediates for making bedaquiline API are not expensive - they are rapidly synthesized in good yield from very inexpensive starting materials. However, the bond-making step that forms the chiral centre is difficult to execute in high yield, and the subsequent separation of enantiomers through classic resolution is

reported to provide only modest yields of chirally-pure API. We estimated the API price to be $1,600-2,600/kg in the early years of production, depending on the overall recovery of chiral resolution, and assuming production in 100kg batches (equivalent to about 5,300 six-month treatments). Indian import data showed 181kg of bedaquiline exported from Belgium to Bangalore in 2015, priced between $2,288/kg and $3,077/kg. On the basis of synthesis analysis and observed exports, we estimate bedaquiline API to cost $2,300/kg for 'non-SRA' and $3,450/kg for 'SRA' standards. Following the high- and low-demand algorithms, this yielded estimated generic prices for bedaquiline of $7.83-$17.22 per patient per month.

Delamanid and pretomanid

The route of synthesis for delamanid is short, consisting of three steps. Based on raw material costs and yields, the estimated API cost of production is between $230 and $350 per kg. Additional costs of processing bring the API costs up to $320-$490/kg. Multiplying the upper bound by 1.5x gives an 'SRA price' estimate of $735/kg. An API cost of $320-$735/kg given an estimated generic price of $4.89-$15.57 per person per month.

Based on chemical comparison and review of routes of synthesis, we conservatively estimated the cost of synthesis for pretomanid to be quadruple that of delamanid. Given this estimated API cost of $1,280-$2,940, the estimated generic price of pretomanid is $10.80-$34.09 per patient per month.

Linezolid and sutezolid

Export data showed a segmented market and rapid per-kilogram API price reductions over 2010-2016 (Figure S2). In 2010-2016, 7.1 tonnes of exported linezolid API were priced in the

range $130-$150/kg (16% of total exported volume). We thus estimate current linezolid prices to be $140/kg for non-SRA, and $210/kg for SRA API.

Based on the chemical similarity of sutezolid to linezolid, costs of synthesis are likely to be the same if sutezolid reaches similar volumes of production.

These API costs yielded estimated generic prices of $4.29-$9.25 per patient per month for linezolid or sutezolid.

Clofazimine

In 2015, 4.9 tonnes of exported clofazimine API were priced in the range $200-$230/kg (99.8% of all exports), volume-weighted mean $214/kg. 99.0% of exported clofazimine API was to Germany, likely due to a standing agreement.[14] We thus conclude that a price of $214/kg represents SRA-quality API, yielding an estimated generic price of $3.89-$10.72 per patient per month.

Discussion

Novel drugs for MDR-TB could be mass-produced at prices far below current levels. Bedaquiline could be produced for $8-17/month (current lowest price $136/month), delamanid could be produced for $5-16/month (current lowest price $283/month), and linezolid could be produced for $4-9/month (current lowest price $193/month). While current lowest global prices for a full treatment course with MDR-TB combination regimens are in the range of $1,800-$4,600 for 'preferred' regimens not containing novel drugs,[14] novel regimens combined, competitive manufacture, and widespread generic availability could allow around 5-10 times more MDR-TB cases to be treated within the current budgets.

The nine-month STREAM arm B regimen, a slight modification of the Bangladesh regimen that demonstrated a treatment success rate of 88%,[28] could be made available for less than $300 per treatment course – as much as one year of generic second-line HIV treatment.[29] In 2014, $173 million was spent on purchasing second-line drugs through the GDF, for 35,000 treatments, or enough to treat only 26% of estimated detected MDR-TB cases.[1,30] At the highest estimated price for the STREAM B regimen, medicines to treat all 136,000 cases of MDR-TB detected annually would cost only $54 million.[1]

The bedaquiline-containing STREAM arm C and D regimens could be produced for as little as $231 and $168 per patient per course, respectively (C – 80%-87% below current lowest prices; D – 80%-87% below current lowest prices). Pretomanid-based regimens could further reduce prices to $53-$276 per full treatment course. The MDR-END regimen, which includes delamanid and linezolid, could still cost less than $500 per patient despite its longer duration.

Our algorithms were validated as accurate and conservative by comparison to current prices for Group 1-4 medicines, where they either accurately predicted or overestimated current prices (figure 3). An exception to this trend is moxifloxacin – this is unsurprising, as it is the only Group 1-4 drug included in this analysis that is currently patented in some markets.

While currently WHO guidelines recommend the use of newer medicines only if older drugs are likely to be ineffective,[2] affordable access may facilitate a change in the principles of regimen design. For example, Brigden *et al* have proposed "principles for designing future regimens", of which the first principle is that any new regimen "should contain at least one new class of drug".[3] These principles could be adopted more readily if price is removed as a barrier to access.

As of March 2015, fewer than 1000 patients had been treated with bedaquiline, though it has been available for more than 2 years.[31] In a new donation programme, the originator company (Janssen) has agreed to donate 30,000 treatment courses over 4 years,[32] but this amount is sufficient to treat less than 3.5% of MDR-TB cases detected over this period.[1] If demand for bedaquiline rises above this level, generic competition may provide a more effective mechanism for providing sustainable access.

Outside of the donation programme, Janssen uses a tiered pricing scheme for bedaquiline (figure 2). In upper-middle-income countries, which make up 26% of notified TB cases, estimated generic prices would represent a 97% price decrease from current levels.[1] In lower-middle- and low-income countries (69% of notified TB cases), the decrease would be 91%.[1]

Access to delamanid, for which patents are held by the Japanese company Otsuka, has been even more limited.[15,33] It was recently announced that delamanid will be available to Global Fund-eligible countries for purchase via the GDF, priced at $1,700 for the six-month

treatment course,[34] putting it above, for example, the average Indian annual income, and drawing criticism from MSF.[33,35] Our estimated generic price would represent a 96% decrease.

The patent on pretomanid is owned by the TB Alliance – a partnership comprising public and private collaborators. Given this, we would not expect pretomanid to be priced with a large mark-up. Early engagement of multiple generic manufacturers will nevertheless be necessary to achieve affordable prices.

Linezolid, moxifloxacin, and clofazimine, integral to novel regimens, can all be sustainably produced at significantly lower prices than are currently available through the GDF. Versions of clofazimine that are not SRA-approved are already available in India at prices below our calculated potential prices.

India and China dominate the ARV market.[26] While our analysis assumed manufacture in India, we believe overall costs of production would not be significantly different if manufacture took place in China. India and China are similar across tax, labour, and infrastructure costs, with India assessed as having lower operating costs in some market reports but not others.[36,37] We are not aware of a data source for the price of exported Chinese API with which a comparative analysis could be undertaken. While API is generally cheaper when bought in China, compared to India,[26] this comparison is difficult to make in a 'like-for-like' manner. China has tended to have stricter patent protection, and therefore, historically, the entrance of Chinese producers into API markets is substantially delayed versus Indian suppliers. In addition, significantly more Indian companies are GMP (Good Manufacturing Practice) certified for the production of ARVs than Chinese; the World Health Organization's prequalification programme currently lists 161 products with manufacturing sites in India, compared to 3 in China.[37,38] The Indian industry has tended to produce more

complicated, more expensive APIs than China. Lastly, Indian manufacturers are also more experienced in manufacturing finished products, and in collaborating with large international agencies.[37,39]

Considering China's lower API costs but greater investments needed in quality approval, as well as the greater experience between international agencies and Indian producers, we believe that in the context of novel TB medicines, there is not likely to be a significant difference in costs of production. We expect that demand volume will play a larger role in determining the cost of APIs and finished pharmaceutical products (FPPs) for MDR-TB in the next few years than will any geographical differences between production sites.

Our analysis estimated the potential prices that could be achieved in the absence of barriers to competitive manufacture and pricing, such as intellectual property. Historically, overcoming these barriers has required significant political efforts.[40]

Of these estimated generic prices, the highest level of uncertainty is associated with bedaquiline, due to the length of the synthetic process. Price reductions would rely on sufficient demand. It is likely that reaching sufficient volume demand to spur a competitive market will be more difficult in MDR-TB than in HIV/AIDS, due to the smaller number of people affected. However, in 2002, when global number of people on HIV/AIDS treatment was still below half a million,[18] prices had already dropped 98% within two years and with only 2 WHO-prequalified manufacturers, to prices that allowed significant scale-up of global treatment scale-up.[16] In this period, the number of patients receiving antiretroviral treatment was similar to the number of patients that currently need MDR-TB treatment, per year (between 100,000 and 200,000).[18]

Sufficient demand will require rapid adoption of new regimens, and improved diagnosis to identify eligible cases. If current trials find toxicity levels that are unacceptable for large-scale programmes, this will limit demand and thus slow price reductions. Funds saved through price reductions can be invested in diagnostics, case detection, and improved surveillance – measures that will in turn contribute to maintaining robust demand for newer medicines.

Lastly, a fragmented market of many simultaneous treatment options may keep prices high. Such market fragmentation has indeed been a historic hallmark of global MDR-TB treatment. Treatment standardisation could counteract this by allowing larger orders for a restricted range of novel medicines, thus encouraging price decreases.

Numerous actors bear responsibility for enabling robust, competitive generic manufacture of newer MDR-TB medicines. Commitment to scale-up MDR-TB treatment programmes by governments of high-burden countries and international funders, including improvement of DST coverage, and the endorsement of a single novel MDR-TB regimen by the WHO would contribute to securing adequate demand volume for newer drugs. Much-needed clinical trials are taking place, but are run by non-profit initatives such as the TB Alliance and continued work will depend on continued philanthropic or international aid funding. Licensing by the originator to the Medicines Patent Pool would likely be the quickest mechanism by which to remove patent barriers to competitive generic production of novel MDR-TB drugs. The Pool has recently announced an intention to expand its mandate to include newer TB medicines.[41] If this is not possible, compulsory licensing could provide an alternative route to enabling generic production.

Conclusions

391 Generic production could make it possible to supply treatments for all cases of MDR-TB with
392 newer medicines and regimens with expenditure equivalent to, or less than, that currently
393 spent on treating a small proportion of cases with second-line medicines.
394
395 When the benefits of new regimens are confirmed, delaying access to, and expansion of,
396 treatment will lead to the loss of lives and forgone savings. Ensuring prompt generic
397 competition can allow greatly improved cost-efficiency and access to treatment.

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Transparency declarations

The funder has not played any decision-making role in the research. Dzintars Gotham, Joseph Fortunak, Anton Pozniak, Saye Khoo, Graham Cooke, and Frederick E Nytko III report no conflicts of interest. Andrew Hill has received consultancy payments from Janssen, not connected with this project, with no other potential conflicts of interest to declare.

Authors' contributions

DG and AH designed the study. DG collected conducted price calculations and drafted the paper. JF and FN analysed the costs of synthesis for bedaquiline, delamanid, and pretomanid. All authors critically reviewed and approved the manuscript.

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520 *Tuberculosis Treatment.* http://www.medicinespatentpool.org/the-medicines-patent-pool-
521 expands-mandate-to-hepatitis-c-and-tuberculosis-treatment/

522 **Tables and figures**

523 **Table 1. Current lowest available prices, estimated generic prices, patent expiry dates, and export volumes of tuberculosis drugs.**

Drug	Patent expiry	Daily dose (mg)[a]	API export volumes, 2015 (kg)		API price per kilogram ($USD)	Estimated generic price per month ($USD)	Lowest currently available price per month (USD)
			SRA	Non-SRA			
Group 1 (first-line)							
Rifampicin	Expired	600	5,525	44,537 kg	108-140	3.4-8.3	$4.1-$4.8
Isoniazid	Expired	300	13,075	87,398 kg	13-36	0.8-3.1	$0.5-$1.6
Pyrazinamide	Expired	1600	20,206	114,206 kg	19-30	3.9-11.3	$2.2-$2.6
Ethambutol	Expired	1200	35,199	265,963 kg	39-58	5.0-12.0	$2.5
Group 2 (injectables)							
Amikacin	Expired	1000	81 (in vials)	2,096 (in vials)	0.24-0.63/vial	7.6-53.7	$38.0-$45.1
Kanamycin	Expired	1000	6 (in vials)	1,547 (in vials)	0.39-1.70/vial	12.2-72.1	$28.0-$48.2
Capreomycin	Expired	1000	188 (in vials)	580 (in vials)	3.44-4.37/vial	105.9-184.2	$106.4-$131.6
Group 3 (fluoroquinolones)							
Levofloxacin	Expired	1000	55,645	44,989	109-200	7.4-16.8	$3.3-$5.4
Moxifloxacin	Expired	400	3,383	37,756	180-270	3.5-7.9	$12.2-$12.3
Group 4 (bacteriostatics)							
Prothionamide	Expired	750	0	50	213-320[b]	6.9-16.9	$10.9-$14.9
Cycloserine	Expired	750	55	186	914-931	23.1-36.2	$15.7-$18.1
Group 5 (novel drugs)							
Bedaquiline	2023	400 QD/200 TIW[c]		[2,030]	2,300-3,450	7.8-17.2	$136.0
Delamanid	2023	200		[3,629]	320-735	4.9-15.6	$283.3
Pretomanid[d]	2016	200		[3,629]	1,280 -2,940	10.8-34.1	No published prices
Linezolid	Expired	600	4,888	14,477	140-210	4.3-9.3	$149.8-$153.4
Sutezolid	Expired	600		[36,288]	140-210	4.3-9.3	No published prices
Clofazimine	Expired	200	4,871	10	214	3.9-10.7	$61.3

Table 1 legend.

Table does not include all TB drugs. No API export data were available for ethionamide, terizidone, or PAS. Patent expiry references in Table S2. For patent expiry, the year of the earliest basic (compound) patent expiry is shown. Numbers in square brackets are global demand estimates based on treatment of half of all of detected MDR-TB cases yearly (108,000 patients). Assumed treatment lengths: Bdq, Dlm, Pa, 6 months; Szd, Pzd, 20 months, based on WHO recommendations for treatment with linezolid[2]. All current available prices are those quoted in the GDF Product Catalogue except delamanid and bedaquiline (references in Table S2). Price for bedaquiline is mean per-month price over 6 months. For bedaquiline and delamanid, doses from WHO interim guidelines.[4,6] Dose for sutezolid assumed equal to linezolid.

[a] Doses/regimen design following WHO recommendations, assuming adult patient weighing 60kg.[2]

[b] As there were no API exports to SRA countries in 2015, we estimated the higher bound of the API price range for prothionamide by multiplying price found for API exported to non-SRA countries by 1.5.

[c] Bedaquiline 400mg daily for 2 weeks, then 200mg three times a week for 22 weeks.

[d] Dosage assumed to be that used in most recent published clinical trial (NCT01498419).

542 **Table 2. Current lowest available prices and calculated generic prices of newer**

543 **tuberculosis regimens.**

Regimen	Dose schedule	Lowest currently available price for full treatment course, $USD	Calculated generic price for full treatment course $USD, (% difference in parentheses)
STREAM arm B (modified Bangladesh) (40 weeks)	Daily, for 40 weeks: moxifloxacin 800mg, clofazimine 100mg, ethambutol 1200mg, pyrazinamide 2000mg. Daily, for first 16 weeks: isoniazid 600mg, prothionamide 750mg, kanamycin 900mg (three times a week from week 12)	734	272-395 (46-63% reduction)
STREAM arm C (40 weeks)	As STREAM arm B, but with kanamycin substituted by bedaquiline: 400mg daily for 2 weeks, then 200mg three times a week for 38 weeks, and moxifloxacin substituted by levofloxacin 1000mg daily	1,799	231-359 (80-87% reduction)
STREAM arm D (28 weeks)	Bedaquiline: 400mg daily for 2 weeks, then 200mg three times a week for 22 weeks. Daily, for 28 weeks: levofloxacin 1000mg, clofazimine 100mg, pyrazinamide 2000mg. Daily, for first 8 weeks: isoniazid 900mg, kanamycin 900mg	1,325	168-262 (80-87% reduction)
PaMZ (assumed 24 weeks)	Daily, for 24 weeks: pretomanid 200mg, moxifloxacin 400mg, pyrazinamide 1500mg	140*	53-114 (19-62% reduction)
BPaZ (assumed 24 weeks)	Bedaquiline 400mg daily for 2 weeks, then 200mg three times a week for 22 weeks. Daily, for 24 weeks: pretomanid 200mg, pyrazinamide 1500mg	967*	84-181 (81-91% reduction)
BPaL (assumed 24 weeks)	Bedaquiline 400mg daily for 2 weeks, then 200mg three times a week for 22 weeks. Daily, for 24 weeks: pretomanid 200mg, linezolid 1200mg	2,749*	120-276 (90-96% reduction)
MDR-END (20 months)	Linezolid 600mg daily for 2 months, then 300mg daily for 18 months. Daily, for 20 months: delamanid 200mg, levofloxacin 750mg, pyrazinamide 1000mg	7,408	238-507 (93-97% reduction)

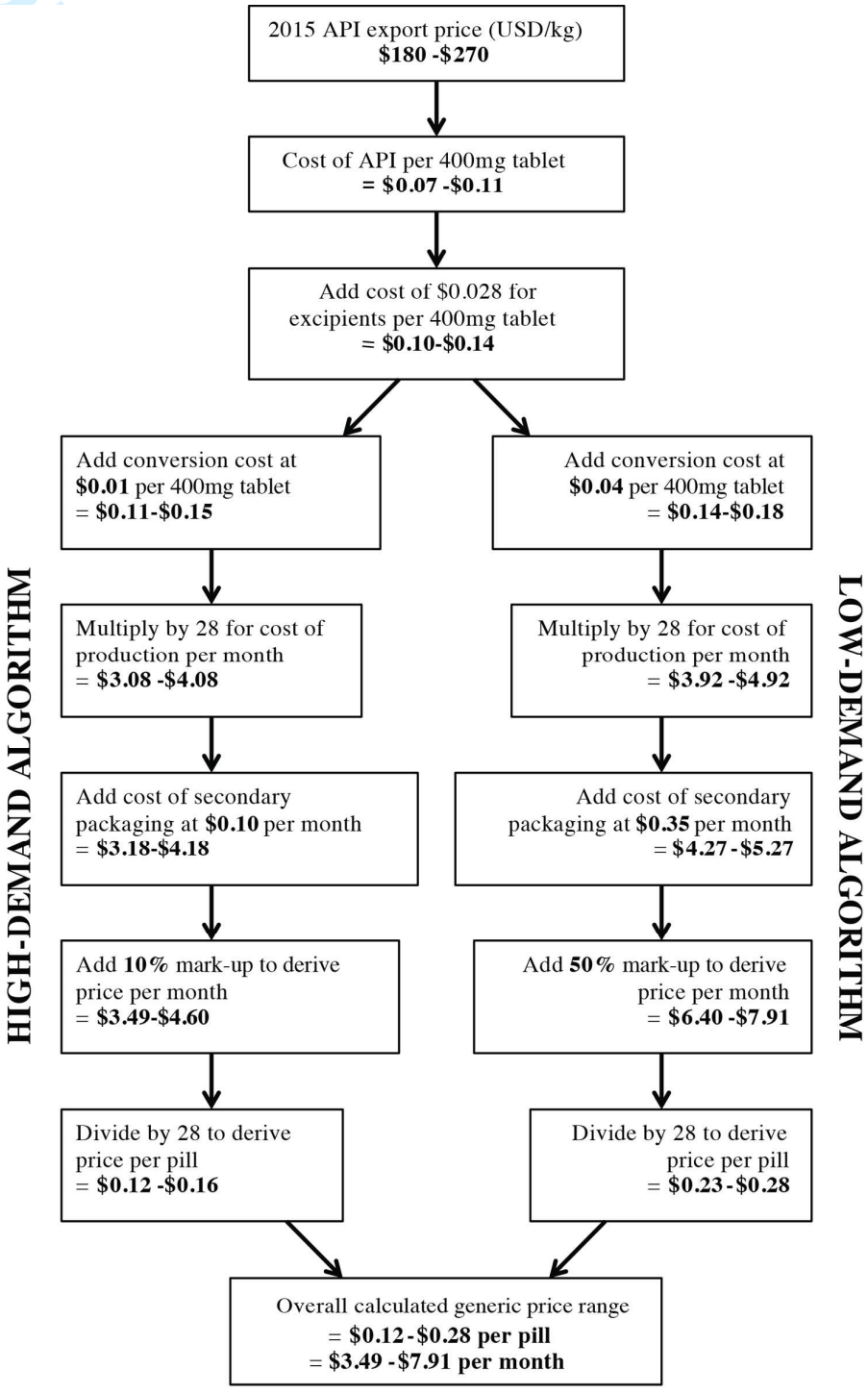
Table 2 legend.

*'Current lowest prices' of pretomanid-containing regimens combine the highest calculated generic price estimate for pretomanid with known current lowest prices for other drugs. All current available prices are those quoted in the GDF Product Catalogue except delamanid and bedaquiline (references in Table S2). Doses/regimen design following recommendations in 'Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberulosis' assuming adult patient weighing 60kg.[2] For bedaquiline and delamanid, doses from WHO interim guidelines.[4,6] For sutezolid, dose assumed equal to linezolid. Regimen details from most recent published clinical trial protocols, trial registration numbers: STREAM NCT02409290, PaMZ NCT01498419, BPaZ NCT02193776 (loading dose schedule for DS-TB used), BPaL NCT02333799, MDR-END NCT02619994 (shortest total duration and lowest doses assumed).[8–12]

556 **Figure 1. Assumptions and calculation algorithms for generic price estimation for**

557 **moxifloxacin 400mg tablets.**

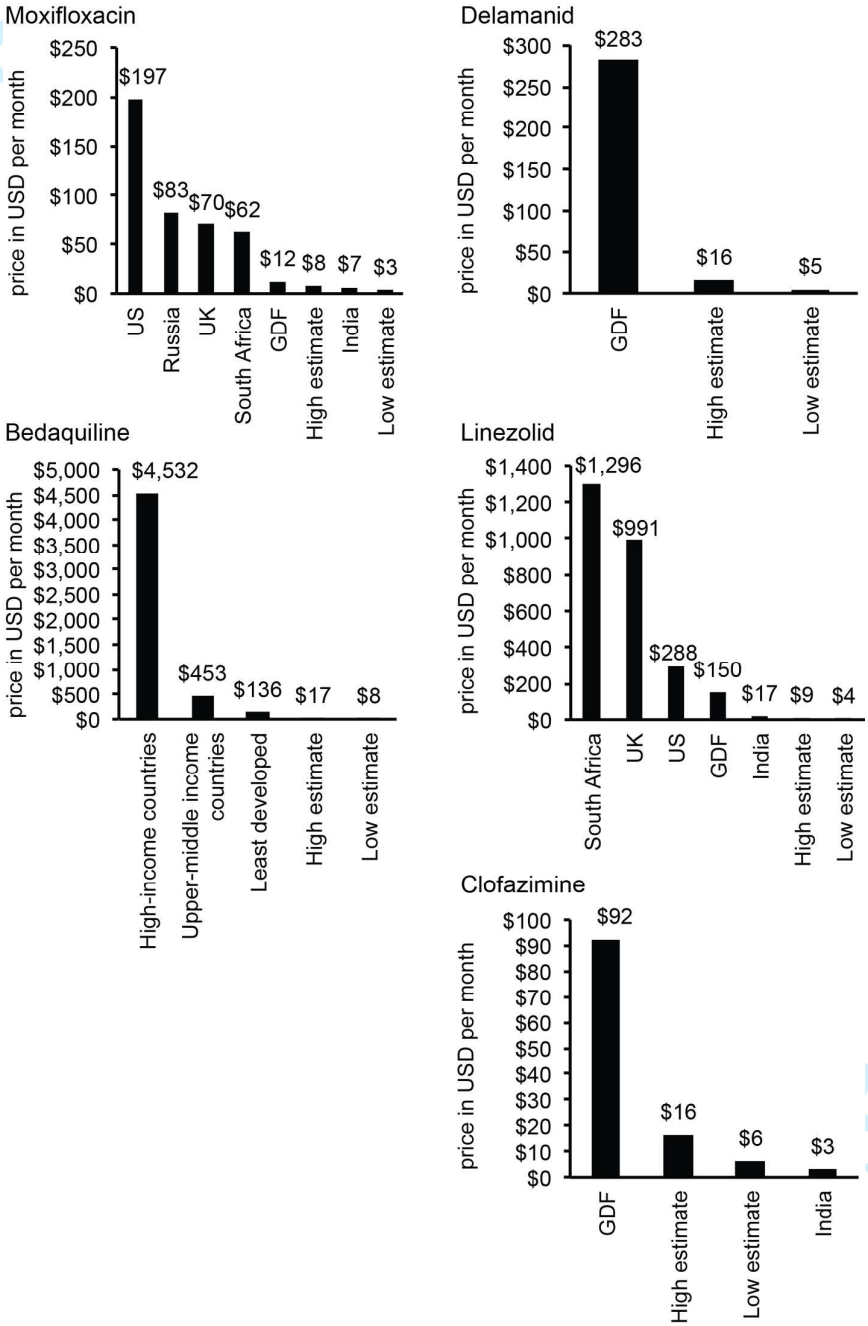
558 (no legend)



559

560 **Figure 2. Lowest currently available prices and estimated generic prices per month**

561 **(USD) for moxifloxacin, bedaquiline, delamanid, linezolid, and clofazimine.**



562

563 Figure 2 legend: GDF – Global Drug Facility. Dosage assumptions given in table 1. Price for

564 bedaquiline is mean per-month price over 6 months. Price categories used for bedaquiline

565 are as described by the originator; country membership of these categories is currently

566 unknown.[14]

Figure 3. Comparison of current and estimated generic prices for Group 1 and 2 (a), Group 3 and 4 (b), and Group 5 (c) tuberculosis drugs (logarithmic).

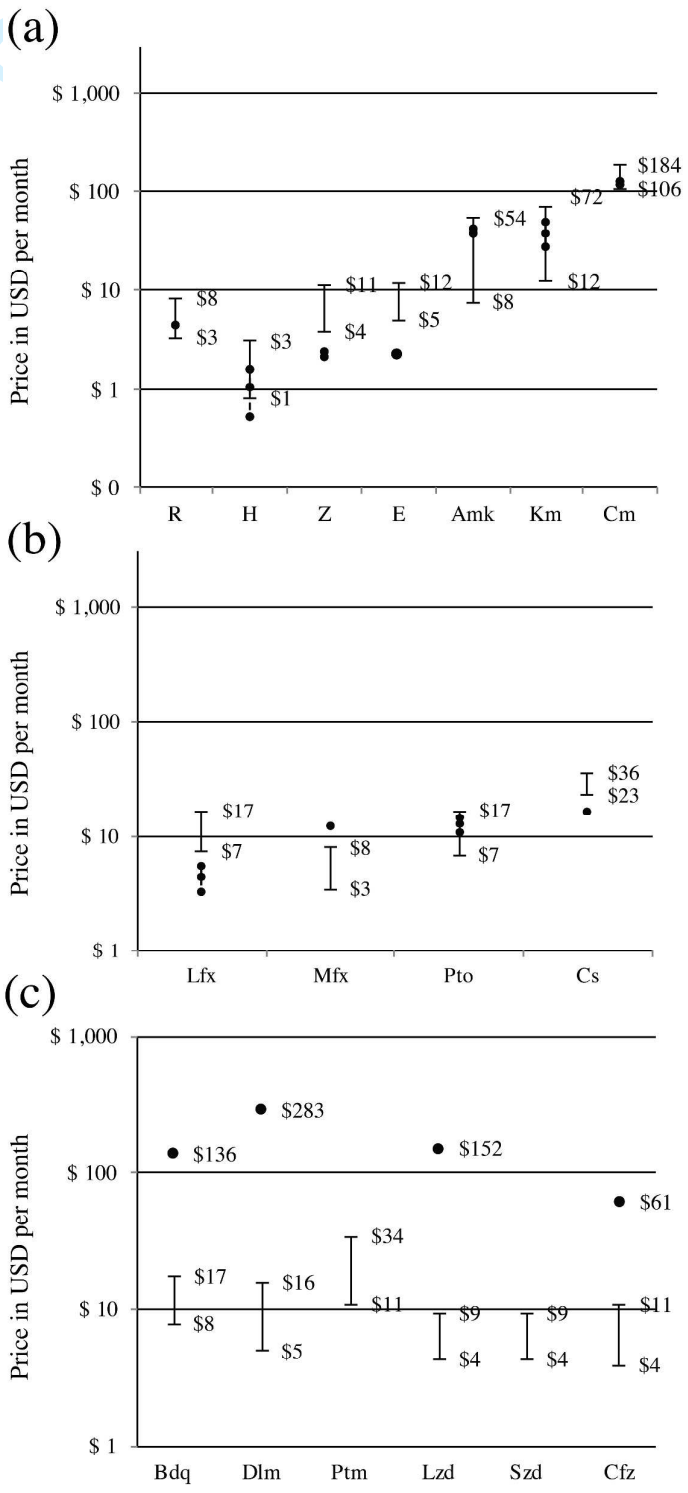
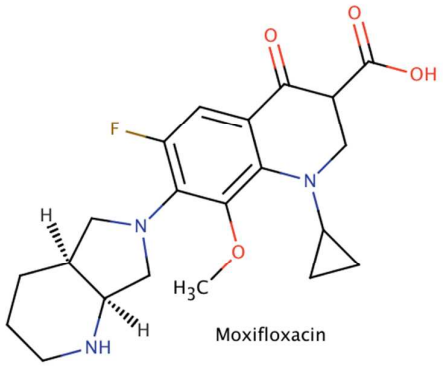
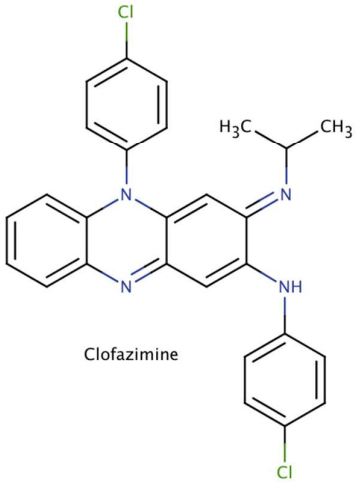
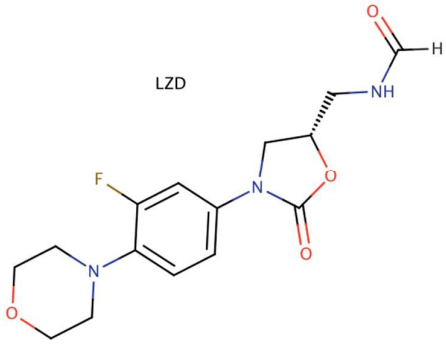
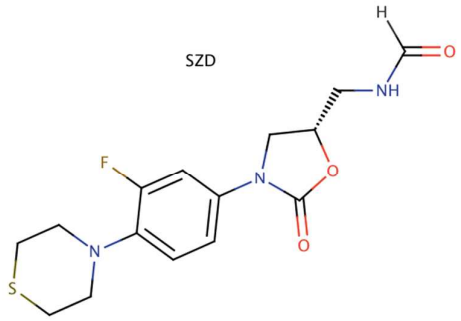
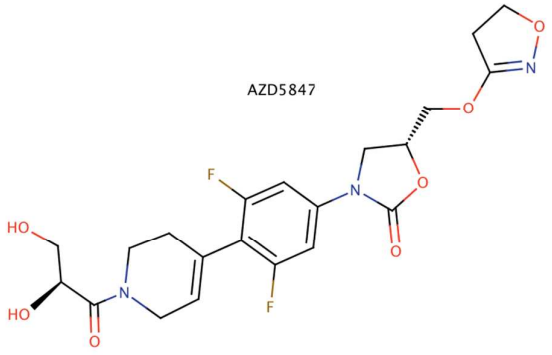
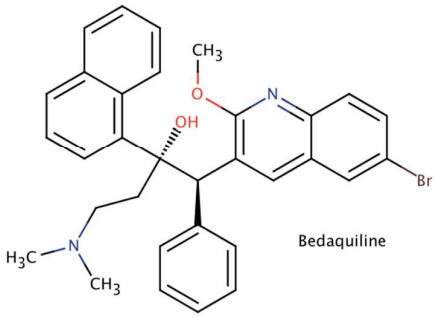
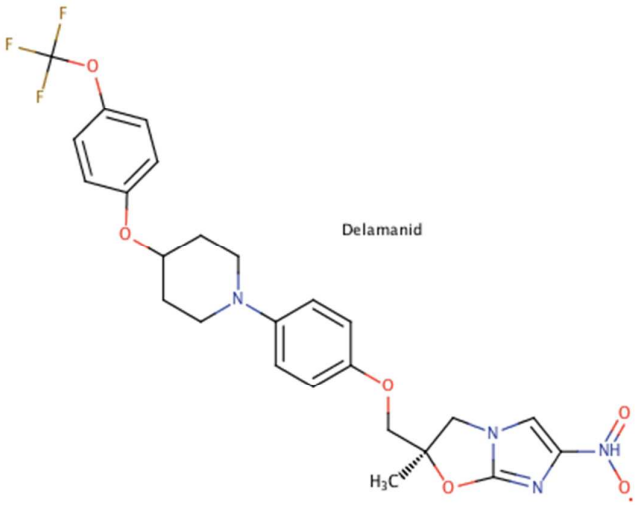
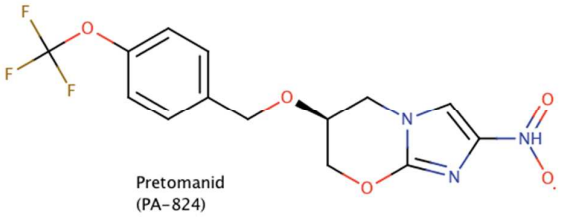


Figure 3 legend: R – rifampicin; H – isoniazid; Z – pyrazinamide; E – ethambutol; Amk – amikacin; Km – kanamycin; Cm – capreomycin; Lfx – levofloxacin; Mfx – moxifloxacin; Pto – prothionamide; Cs – cycloserine; Bdq – bedaquiline; Ptm – pretomanid; Lzd – linezolid; Szd – sutezolid. Calculated generic price ranges are shown as lines bounded by flat caps, wiith maxima and minima labelled with $ values. Superimposed filled dots show lowest currently available prices (range given according to GDF lowest to highest price, except for Bdq and Dlm (Table S2)). Assumptions regarding dosage are as given in table 1. Terizidone, ethionamide, and PAS are not shown, as generic prices could not be calculated due to lack of data on API per-kilogram prices.

Table S1. Chemical structures, formulas, molecular weights, references for excipient content.

Drug, empirical formula, molecular weight	Structure
Moxifloxacin hydrochloride $C_{21}H_{25}FN_3O_4$. HCl Molecular weight*: 401	
Clofazimine $C_{27}H_{22}Cl_2N_4$ Molecular weight: 473	
Linezolid $C_{16}H_{20}FN_3O_4$ Molecular weigh: 337	

Sutezolid $C_{16}H_{20}FN_3O_3S$ Molecular weight: 353	
Posizolid (AZD5847) $C_{21}H_{21}F_2N_3O_7$ Molecular weight: 365	
Bedaquiline fumarate $C_{32}H_{31}BrN_3O_7$ Molecular weight*: 365	

Delamanid $C_{25}H_{25}F_3N_3O_6$ Molecular weight: 534	
Pretomanid (PA-824) $C_{14}H_{12}F_3N_3O_5$ Molecular weight: 359	
Data and structures from PubChem. *Molecular weight not including salt.	
References used for excipient contents	
Rifampicin	Sanofi. Rifadin®. http://products.sanofi.us/rifadin/Rifadin.pdf (accessed Jul 8, 2015).
Isoniazid	Drugs.com. Isoniazid Tablets. http://www.drugs.com/pro/isoniazid-tablets.html (accessed Jul 8, 2015).
Pyrazinamide	World Health Organization. Package Leaflet. http://apps.who.int/prequal/whopar/whoparproducts/TB172part3v1.pdf (accessed Jul 8, 2015.
Ethambutol	World Health Organization. Package Leaflet. http://apps.who.int/prequal/whopar/whoparproducts/TB134part3v1.pdf (accessed Jul 8, 2015).
Levofloxacin	Food and Drug Administration. Levaquin® prescribing information. http://www.fda.gov/downloads/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/UCM133684.pdf (accessed Jul 8, 2015).
Moxifloxacin	Merck. Avelox® prescribing information. https://www.merck.com/product/usa/pi_circulars/a/avelox/avelox_pi.pdf (accessed Jul 8, 2015).
Prothionamide	Lupin Pharmaceuticals. Suprax®. http://www.lupinpharmaceuticals.com/pdf/09/SUPRAX%20Common%20PI%20.pdf (accessed Jul 8, 2015).
Cycloserine	Pfizer. Trecator®. http://labeling.pfizer.com/showlabeling.aspx?id=473 (accessed Jul 8, 2015).
Bedaquiline	World Health Organization. Sirturo™. http://www.who.int/tb/challenges/mdr/Package_insert_bedaquiline.pd

	f (accessed Jul 8, 2015).
Delamanid (same assumed for pretomanid)	European Medicines Agency. Summary of product characteristics. http://ec.europa.eu/health/documents/community-register/2015/20150424131446/anx_131446_en.pdf (accessed Jul 8, 2015).
Clofazimine	Novartis. Lamprene®. https://www.lamprene.com/fileadmin/pharmaworld/lamprene/lamprene_packing_insert.pdf (accessed Jul 8, 2015).
Linezolid (same assumed for sutezolid and posizolid)	Food and Drug Administration. Zyvox®. http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021130s016,021131s013,021132s014lbl.pdf (accessed Jul 8, 2015).

Table S2. Sources of current price and patent data.	
Price data sources	
US	GoodRx. http://www.goodrx.com/
UK	British National Formulary. https://www.medicinescomplete.com/mc/bnf/current/
Russia	Государственный реестр предельных отпускных цен http://grls.rosminzdrav.ru/PriceLims.aspx
South Africa	South African Medicine Price Registry. Database of Medicine Prices. Available from: http://www.mpr.gov.za/Publish/ViewDocument.aspx?DocumentPublicationId=1761
India	DrugsUpdate.com. http://www.drugsupdate.com/
Bedaquiline	MSF Access campaign. DR-TB drugs under the microscope: Sources and prices for drug-resistant tuberculosis medicines. 2016. Available at: http://www.msfaccess.org/sites/default/files/TB_report__DR-TB_DRUGS_UTM__4th_edition_2016.pdf. Accessed 22 March 2016.
Delamanid	Stop TB Partnership. Stop TB Partnership's Global Drug Facility jumpstarts access to new drugs for MDR-TB with innovative public-private partnerships. 2016. Available at: http://www.stoptb.org/news/stories/2016/ns16_005.asp. Accessed 15 March 2016.
Patent data sources	
Group 1-4 drugs	US Food and Drug Administration. Orange Book. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.
Bedaquiline	UNITAID. A Review of the Bedaquiline Patent Landscape: A scoping report. 2013.
Delamanid	UNITAID. A Review of the Delamanid Patent Landscape. 2014.
Pretomanid	UNITAID. A Review of the PA-824 Patent Landscape. 2014.
Sutezolid	UNITAID. A Review of the Sutezolid (PNU-100480) Patent Landscape. 2014.
Posizolid	UNITAID. A Review of the AZD5847 Patent Landscape. 2014.
Linezolid, moxifloxacin, clofazimine	MSF Access campaign. DR-TB drugs under the microscope: Sources and prices for drug-resistant tuberculosis medicines. 2016. Available at: http://www.msfaccess.org/sites/default/files/TB_report__DR-TB_DRUGS_UTM__4th_edition_2016.pdf. Accessed 22 March 2016.
Moxifloxacin	Merck & Co. Inc. Form 10-K: Annual report pursuant to section 13 or 15(d) of the securities exchange act of 1934 [Internet]. 2013. Available from: http://www.sec.gov/Archives/edgar/data/310158/000119312513084618/d438975d10k.htm

Figure S1. Moxifloxacin exports from India by price, destination region, and size of shipment, 2010-2016 (logarithmic).

Each bubble represents one shipment; bubble area scaled to the size in kilograms of the shipment (inset legend for bubble size). Colours represent the region of the recipient country. For clarity, the regions Africa, Central Asia, and Oceania are not shown as they represent a negligible proportion of exports (0.3% of total volume).

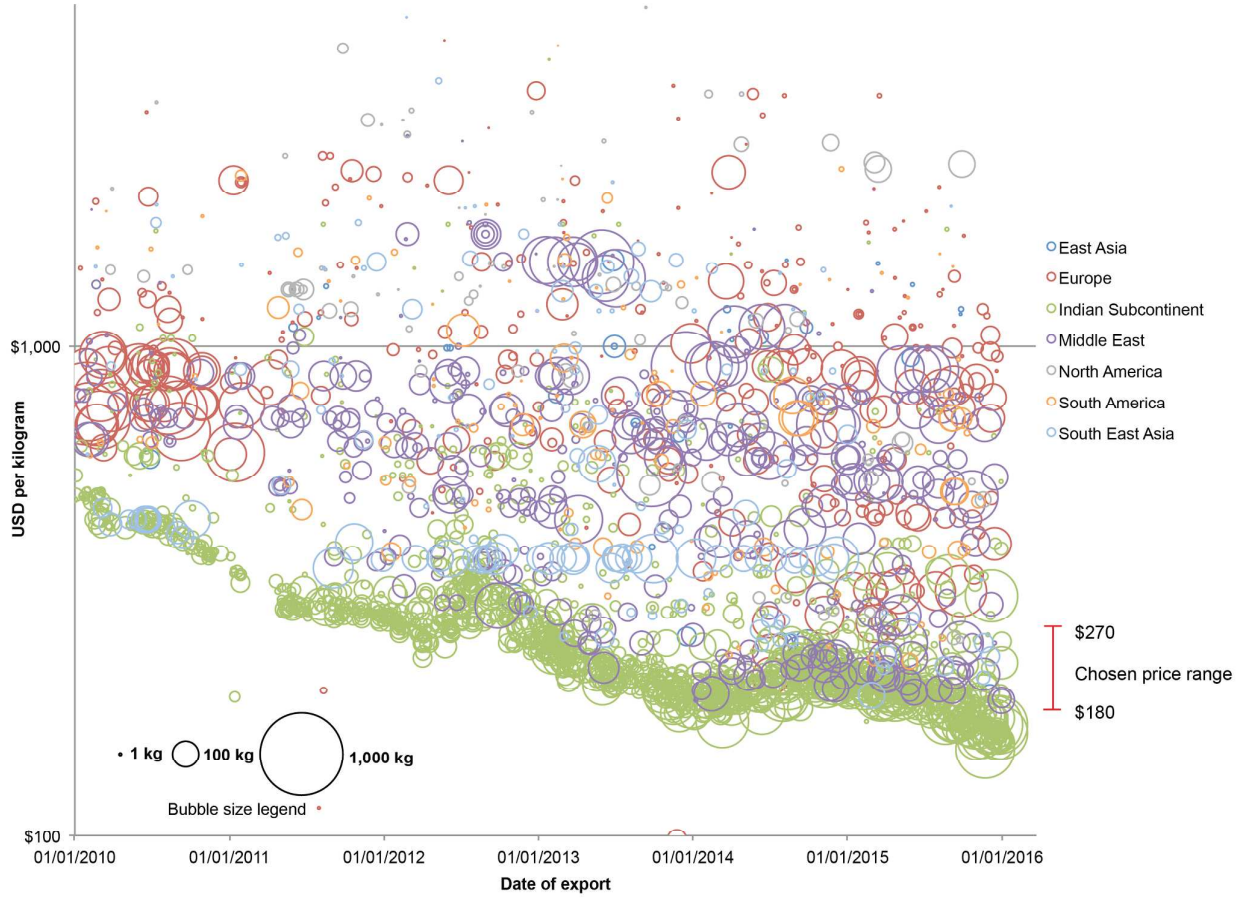


Figure S2. Linezolid exports from India by price, region, and size of shipment, 2010-2016 (logarithmic).

Each bubble represents one shipment; bubble area scaled to the size in kilograms of the shipment (inset legend for bubble size). Colours represent the region of the recipient country. For clarity, the regions Africa, Central Asia, and Oceania are not shown as they represent a negligible proportion of exports (0.04% of total volume).