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The Extending Access Index: Promoting Global Health

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The Extending Access Index: Promoting Global Health

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Abstract

Many people around the world cannot access essential medicines for diseases like malaria, tuberculosis (TB) and HIV/AIDS. One way of addressing this problem is a Global Health Impact certification system where pharmaceutical companies are rated on the basis of their drugs' impact on global health. The best companies, in a given year, will then be allowed to use a Global Health Impact label on all of their products – everything from lip balm to food supplements. Highly rated companies will have an incentive to use the label to garner a larger share of the market. If even a small percentage of consumers promote global health by purchasing Global Health Impact products, the incentive to use this label will be substantial. An associated Global Health Impact licensing campaign will also have a big impact. Pharmaceutical companies rely, to a large extent, on university research and development. So, if universities only allow companies that agree to use Global Health Impact practices to benefit from their technology, companies will have an incentive to abide by Global Health Impact standards. The Global Health Impact certification system gives companies a reason to produce medicines that will save millions of lives (like a new malaria or HIV vaccine). This paper presents a model rating system that can provide the basis for Global Health Impact certification. It explores some of the methodological choices underlying the construction of this index and explains how the model can be improved with further research.

Key Words: Global Health, Index, Extending Access, Essential Medicines

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1. Extending Access on Essential Drugs

Many people around the world cannot access essential medicines to treat diseases like malaria, tuberculosis (TB) and HIV/AIDS. One way of addressing this problem is a Global Health Impact certification system where pharmaceutical companies are rated on the basis of their drugs' impact on global health. The best companies, in a given year, will then be allowed to use a Global Health Impact label on all of their products – everything from lip balm to food supplements. Highly rated companies will have an incentive to use the label to garner a larger share of the market. If even a small percentage of consumers promote global health by purchasing Global Health Impact products, the incentive to use this label will be substantial. If consumption of Global Health Impact goods reaches 1% of the market in generic and over-the-counter and medications — that will yield about 360 million dollars-worth of incentive for pharmaceutical companies to become Global Health Impact certified.[1] An associated Global Health Impact licensing campaign will also have a big impact. Pharmaceutical companies rely, to a large extent, on university research and development. So, if universities only allow companies that agree to use Global Health Impact practices to

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The model underlying this paper has benefited from significant contributions by the other members of Academics Stand Against Poverty's Global Health Impact working group especially Denise Teo Wei Lin. Angelina Sung, Nathan Lubchenco, George Nardi, Matt Wilson, and Saptarshi Ghose. We would also like to thank Academics Stand Against Poverty, Stanford University, Carnegie Mellon University, the Falk and Berkman Foundation, and Justitia Amplificata for their support during various stages of model construction. Baruch Fishoff, Mark Roberts, Eran Ben-David and others (acknowledged in previous papers on this proposal) also deserve our sincere thanks.
[1] N. Hassoun, "Global Health Impact", Developing World Bioethics (2012): 1471- 8847, <http://onlinelibrary.wiley.com/doi/10.1111/j.1471-8847.2011.00314.x/abstract>, visited on 1 September 2012.

benefit from their technology, companies will have an incentive to abide by Global Health Impact standards. If 1% of universities sign on to a Global Health Impact licensing campaign, that will create 840 million dollars-worth of incentive for pharmaceutical companies to become certified every year.[2] That is more than the cost of developing a new drug, even on the highest estimates, and might double the number of drugs for neglected diseases produced between in 1975-1999 in a similar time-frame.[3] A Global Health Impact certification system will give companies a reason to produce medicines that will save millions of lives (like a new malaria or HIV vaccine).[4] This paper presents a model rating system that can provide the basis for Global Health Impact certification. Several of the assumptions it relies upon require significant refinement. Nevertheless, this paper hopes to illustrate how a good model can be constructed and open the door to debate about the best ways of doing so.

2. Model Rating System

For Global Health Impact certification to be a good idea, the rating system upon which a label relies must be objective and output-based. For the Global Health Impact label, the objective is to design a rating system that can incentivize companies to extend access on essential medicines globally. Towards this end, companies should be able to impact their rating and, if companies' scores improve, that should improve global health.

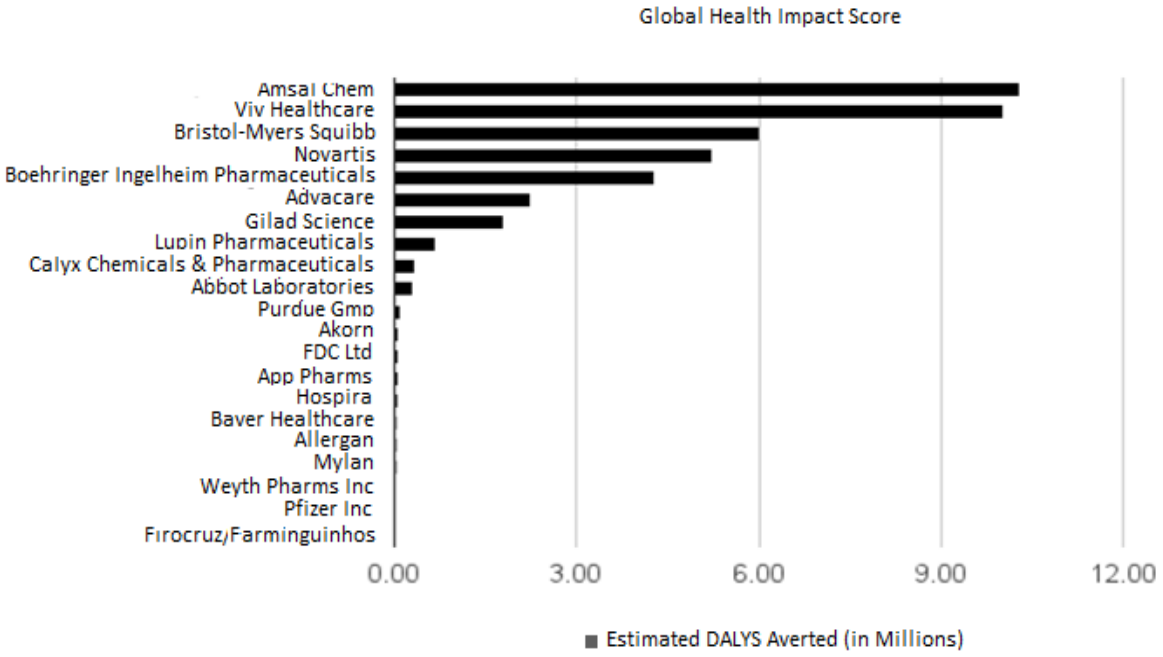
Consider, here, a preliminary model evaluating the impact of all first-line drugs for HIV/AIDS, TB, and (p. falciparum) malaria as they are some of the diseases with the largest global health impact for which good data is available globally.

[2] Ibid

[3] P. Trouiller, E. Torreele, P. Olliaro, N. White, S. Foster, D. Wirth, and B. Pécoul, "Drugs for Neglected Diseases: A Failure of the Market and A Public Health Failure?", *Tropical Medicine and International Health*, 6 (2001): 945-51.

[4] N. Hassoun, "Global Health Impact", *Developing World Bioethics* (2012): 1471 – 8847, <http://onlinelibrary.wiley.com/doi/10.1111/j.1471-8847.2011.00314.x/abstract>, visited on 1 September 2012. N. Hassoun, "Measuring Global Health Impact: Incentivizing Research and Development of Drugs for Neglected Diseases", P. Lenard and C. Straehle (eds.), *Justice and Global Health Inequalities*, Global Justice and Human Rights Series, (Edinburgh University Press, Edinburgh, 2012).

Company Rankings



The model was completed in two (rough) steps. First, we estimated the impact of each drug. Second, we ranked companies by aggregating their drugs' impact on global health. This will allow us to rate companies based on their relative (or absolute standing). Several of the assumptions the model relies upon could benefit from significant refinement. Nevertheless, what follows explains the basic structure of this model.

To evaluate the impact of each drug globally, we consider the impact of each drug in each country where that drug is a first-line therapy. Roughly, this requires information on the need for different essential medicines (e.g. the death and disability due to the diseases they treat), information about access to the drug (e.g. treatment percentages), and information about drug effectiveness (e.g. efficacy estimates). Initially, the drug's impact will be Need*Access*Effectiveness. The need for different essential medicines is calculated in Disability Adjusted Life Years (DALYs) lost to the diseases they treat. Information about access to the drugs is an estimate of the number of people with access to treatment divided by the number of people who need treatment for each drug in each country.[5] In the model, treatment percentages at the country-drug level are sometimes approximated by the percent of people receiving treatment for the disease in a country. Finally, we use estimates of drugs' efficacy from clinical trial data as it is collected in a systematic and comparable way and better data is not available.

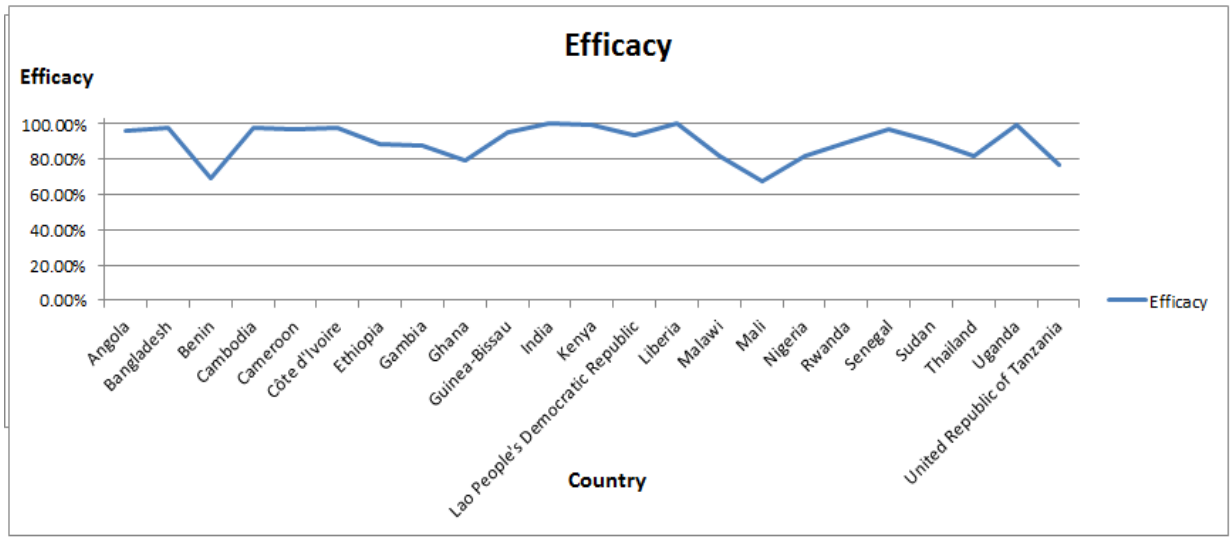
A slightly simplified, hypothetical, example will help explain the basic idea. Again, the drug's impact in the model is, roughly, Need*Access*Effectiveness. Suppose, for instance, 100 million DALYs are lost per annum to a disease treatable with a drug that reduces the

[5] A measure of access over which companies have complete control and responsibility would be even better but it is hard to think of such an indicator.

impact of the disease by 80%, on average. If 50% of the population that needs it has access to it, the drug will save 80 million DALYs (100*.8*.5 = 40).[6]

Good data is available on all of the components of the rating system but data on efficacy globally is sometimes sparse. We hope to build models that will predict drug efficacy at the country-level when that data is not available from clinical trials. For now, however, we are simply averaging the efficacy estimates from clinical trial data and imputing this to countries missing efficacy information to arrive at a global estimate.[7]

Sample Data: Collected Artemether-Lumafantrine Efficacy Information[8]

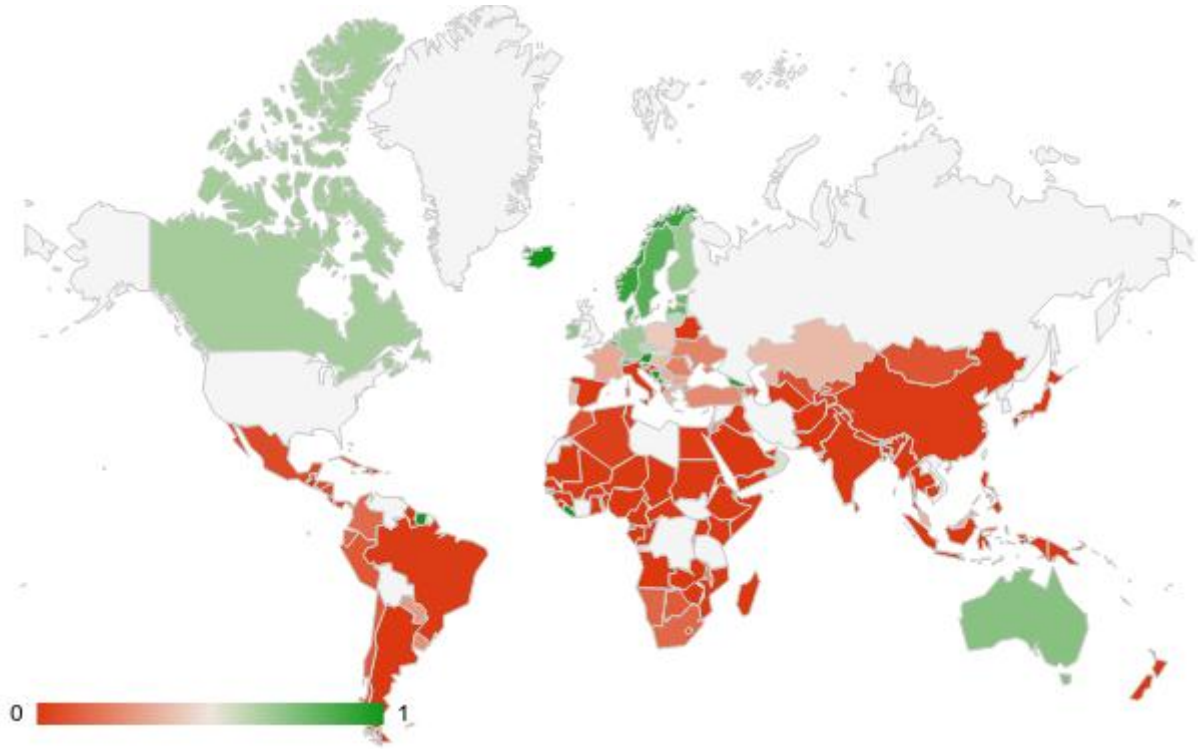


Sample Data: Multi Drug-Resistant Tuberculosis % Treatment Coverage

[6] To deal with the "me-too" problem it is possible to consider drugs' marginal impact. This may be important for some HIV/AIDS medicines but it is also difficult to know where the problem is occurring and to decide on the appropriate comparators. See: J. Bloom, "Me-too? Says Who? (Medical Progress Today)" *Medical Council on Science and Health*, (2012), <http://www.acsh.org/news/newsID.1992/news_detail.asp>, visited on 4 April 2012. Moreover, there are other ways of addressing this problem. Finally, higher-priced but only slightly more effective drugs will probably not attract a large market share and so the percentage of patients receiving me-too drugs may remain small. In any case, we do not try to address that problem here.

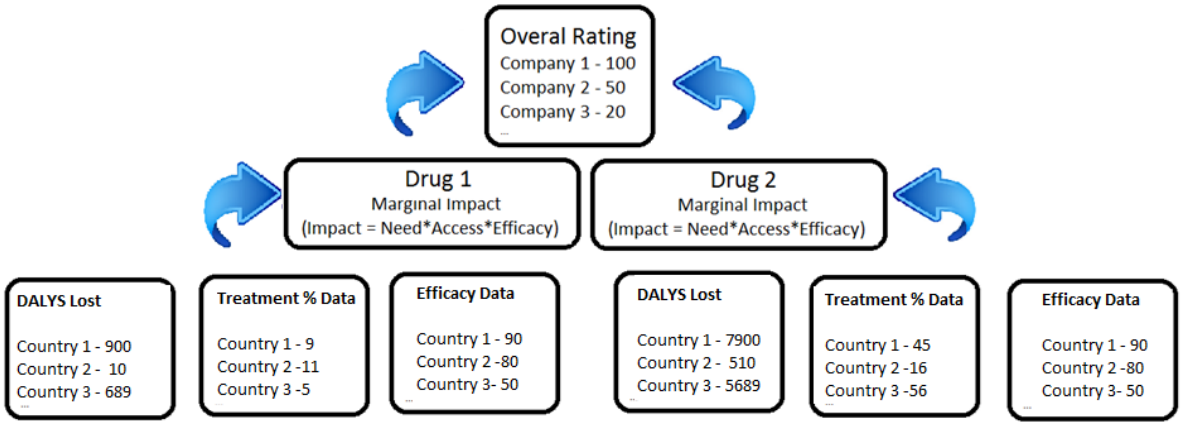
7 So far, we have completed a systematic review of efficacy data for the main first-line drugs for malaria and use estimates for HIV/AIDS and TB.

8 Contact authors for source data.



Colors in each region denote the % treatment coverage for TB: red being 0% treatment coverage and green being 100% treatment coverage.[9]

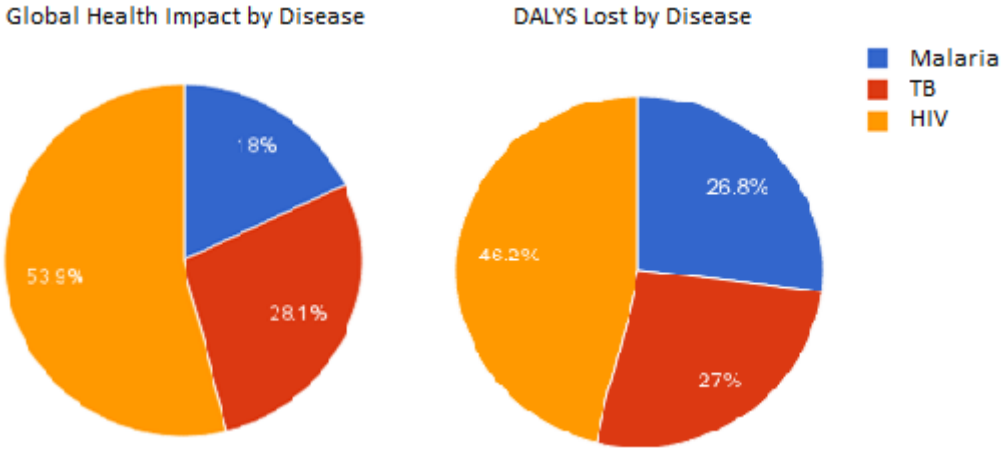
Again, once impact is calculated, companies can be rated on the basis of their drugs' aggregate contribution to alleviating the global burden of disease. Here is a visual illustration of the rating system's main components that feed into the overall rating.



Right now the impact of drugs for HIV/AIDS is most important in our model. This is driven by the DALY and treatment percentage estimates we are using which may be higher for

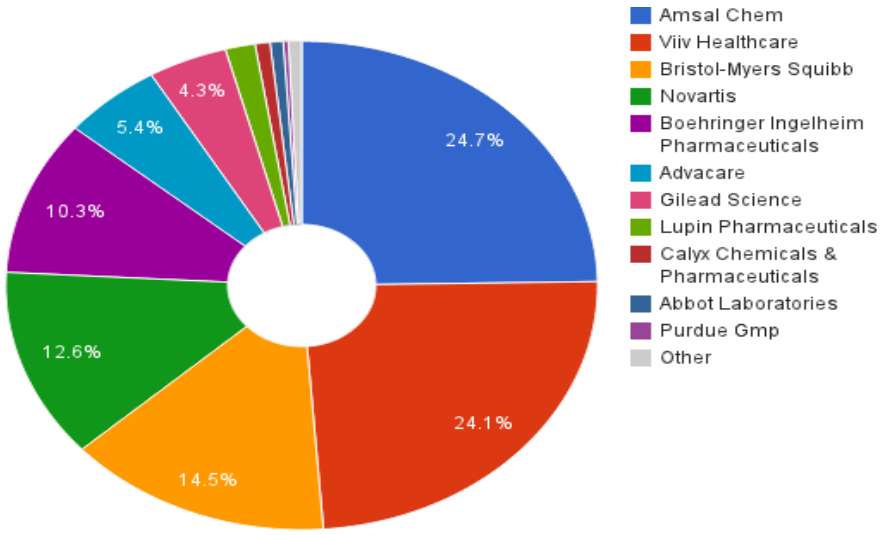
9 Author's calculations from the following source: World Health Organization, "Tuberculosis (TB)", Data for Global Tuberculosis Control 2011. Country Data, Case Notifications, World Health Organization: Geneva, (2012), <http://who.int/tb/country/data/download/en/index.html> visited on 20 August 2012. Columns: e_inc_num on the estimates sheet and dst_mdr_sld, dst_mdr, and dst on the notifications sheet.

diseases like HIV than for diseases like malaria (which are extremely rare in developed countries where better data is available).[10]



Percent DALYs Lost to Each Disease[11] Percent Estimated DALYs Averted for Each Disease

Impact Scores by Company

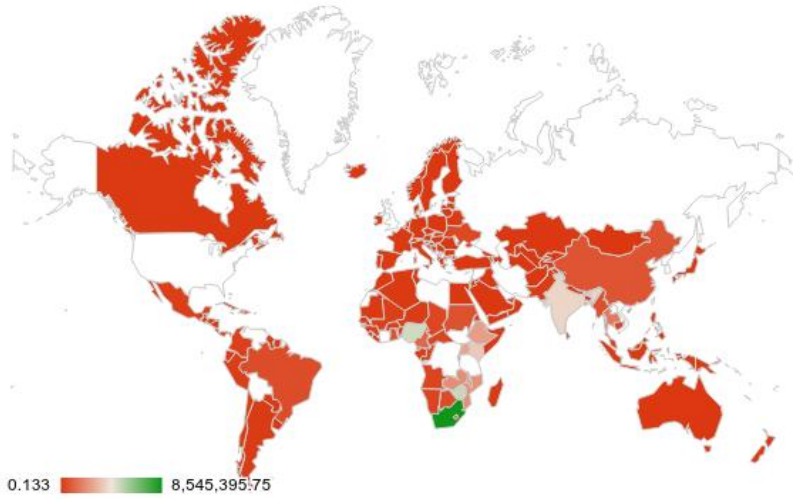


Percent of Total DALYS Averted

DALYs lost to HIV

[10] We have not yet considered drug interactions or side effects. Part of the reason these DALY estimates are poor is that the methods for estimating DALYs lost to p. falciparum malaria (and perhaps TB) in the GBD study probably greatly underestimate the need for these drugs. Better estimates may be available from other sources R. Snow, M. Craig, U. Deichman, and K. Marsh, "Estimating Mortality, Morbidity and Disability due to Malaria Among Africa's Non-Pregnant Population", World Health Organization: Geneva, (1999). R. W. Snow, M. H. Craig, C. R. J. C. Newton, and R. W. Steketee, "The Public Health Burden of Plasmodium Falciparum Malaria in Africa: Deriving the Numbers", *Disease Control Priorities Project*, 11, (2003).

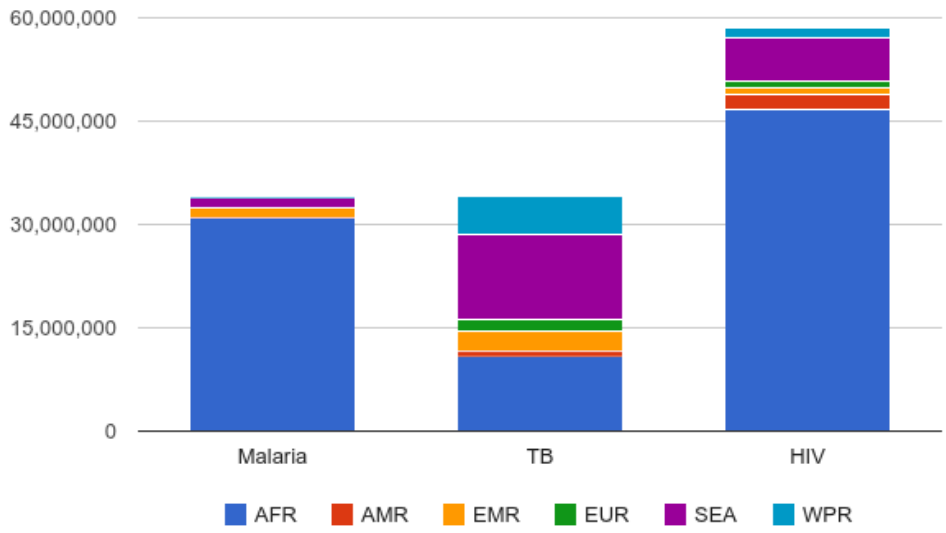
[11] World Health Organization, "Table 2. Estimated Total DALYs ('000), By Cause and WHO Member State, 2004 (a, m)", World Health Organization: Geneva, (2009).



Colors in each region denote DALYs lost to HIV: red being low number of DALYs lost and green being high number of DALYs lost.[12]

The data problems might be more uniform if we considered health impact only in developing countries or the poorest most afflicted region(s) (Africa and/or South-East Asia). However, this focus would exclude much of the burden of TB. Because the distribution of disease does not always track income or region of the world, it seems best not to limit the study in this way.

2004 DALYs by WHO Region



2004 DALYS Lost by WHO Region[13]

[12] World Health Organization, "Table 2. Estimated Total DALYs ('000), By Cause and WHO Member State, 2004 (a, m)", World Health Organization: Geneva, (2009).
[13] World Health Organization, "Table 6. Age-Standardized DALYs per 100,000 By Cause, and Member State, 2004 (a,m,p)", World Health Organization: Geneva, (2009)<http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CFkQFjAA&url=http

3. A Few Concrete Examples: Calculating Novartis', Lupin Pharmaceuticals' and Bristol-Myers Squibb's Scores

It will help to consider some real examples of how companies focusing on malaria, TB, and HIV/AIDS's scores were calculated. (No company in our sample makes drugs for more than one disease but some make more than one drug).

Rank	Company Name	Disease	Drugs
#1	Amsal Chem	TB	Isoniazid
#2	Viiv Healthcare	HIV	Lamivudine, Abacavir, Zidovudine, Nelfinavir
#3	Bristol-Myers Squibb	HIV	Didanosine, Stavudine, Efavirenz
#4	Novartis	Malaria	Artemether-Lumefantrine
#5	Boehringer Ingelheim Pharmaceuticals	HIV	Nevirapine
#6	Advacare	Malaria	Artesunate + Sulfadoxine-Pyrimethamine, Dihydroartemisinin-Piperaquine, Artesunate + Amodiaquine, Artesunate, Artemether
#7	Gilead Science	HIV	Emtricitabine, Tenofovir
#8	Lupin Pharmaceuticals	TB	Rifampicin, Ethambutol, Levofloxacin
#9	Calyx Chemicals & Pharmaceuticals	TB	Pyrazinamide
#10	Abbot Laboratories	HIV	Lopinavir with a ritonavir boost
#11	Purdue Gmp	TB	Cycloserine
#12	Akorn	TB	Capreomycin
#13	FDC Ltd	TB	Ofloxacin
#14	App Pharms	TB	Kanamycin
#15	Hospira	TB	Amikacin
#16	Bayer Healthcare	TB	Moxifloxacin
#17	Allergan	TB	Gatifloxacin
#18	Mylan	HIV	Atazanavir/Ritonavir
#19	Weyth Pharms Inc	TB	Ethionamide
#20	Pfizer Inc	TB	Streptomycin
#21	Fiocruz/Farmanguinhos	Malaria	Artesunate + Mefloquine

3.1 Malaria Example

Consider an example of how Novartis' score was calculated. Novartis is credited only for one anti-malarial: Artemether-Lumefantrine. So its score is based entirely on Artemether-

%3A%2F%2Fwww.who.int%2Fhealthinfo%2Fglobal_burden_disease%2Fgbddeathdalycountryestimates2004.xls&ei=oQ4xUKTqENL46QH5-YCgBQ&usg=AFQjCNFaB2O3wzTGY2HVWp2f-863ErO-Tg&sig2=hOlV5YixqJtK_VHA30a0cg>, visited on 5 September 2012.

Lumefantrine's score. Artemether-Lumefantrine is a first-line drug in Angola, so consider how its impact in Angola was calculated. 784,000 DALYs were lost to malaria in Angola in 2004.[14] 100% of the malaria in Angola was p. falciparum malaria[15] so the full 784,000 DALYs were lost to p. falciparum malaria. The treatment coverage was 11%. Clinical trials in Angola suggested that Artemether-Lumefantrine was 96.4% effective.[16] So the estimated impact of Artemether-Lumefantrine for Angola is (784,000*.11*.964) = 83,135.36 DALYs saved. The above process was repeated for every country where Artemether-Lumefantrine was a first-line drug, so that an impact score for every country was obtained. To get the total impact score for Norvatis, we summed the scores for all of these countries. The total impact score for Novartis was 4,641,166.66 DALYs saved.

Given limited data on clinical trials for p. falciparum malaria in different countries, the malaria scoring model has fall-back data points in cases where specific data is not available. If specific country-level treatment coverage for the first-line drug is not available, the global average treatment coverage for that drug is used instead. If global average treatment coverage for that drug is also unavailable, the country-specific artemisinin-based combination therapy (ACT) treatment coverage is used in place.[17] Finally, if country-specific ACT treatment coverage is unavailable, the global average ACT treatment coverage is used. For instance, if the first-line therapy for, say, Afghanistan is a combination of Artesunate and Sulfadoxine-Pyrimethamine (AS+SP), then first-line therapy efficacy shall reflect the efficacy of AS+SP in Afghanistan. If this efficacy data is not available, the global average efficacy of AS+SP is used instead.

In cases where there are more than one first-line drug for a country, an average is taken across each drug's treatment coverage. For instance, the first-line for Chad is a combination of Artesunate and Amodiaquine (AS+AQ), and Artemether-Lumefantrine (AL). Thus, Chad's first-line drug efficacy reflects the average of AS+AQ's efficacy in Chad and AL's efficacy in Chad.

3.2 TB Example

[14] This is the year of the latest available GBD study data World Health Organization, "Table 6. Age-Standardized DALYs per 100,000 By Cause, and Member State, 2004 (a,m,p)", World Health Organization: Geneva, (2009), <http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CFkQFjAA&url=http%3A%2F%2Fwww.who.int%2Fhealthinfo%2Fglobal_burden_disease%2Fgbddeathdalycountryestimates2004.xls&ei=oQ4xUKTqENL46QH5-YCgBQ&usg=AFQjCNFaB2O3wzTGY2HVWp2f-863ErO-Tg&sig2=hOlV5YixqJtK_VHA30a0cg>, visited on 5 September 2012.

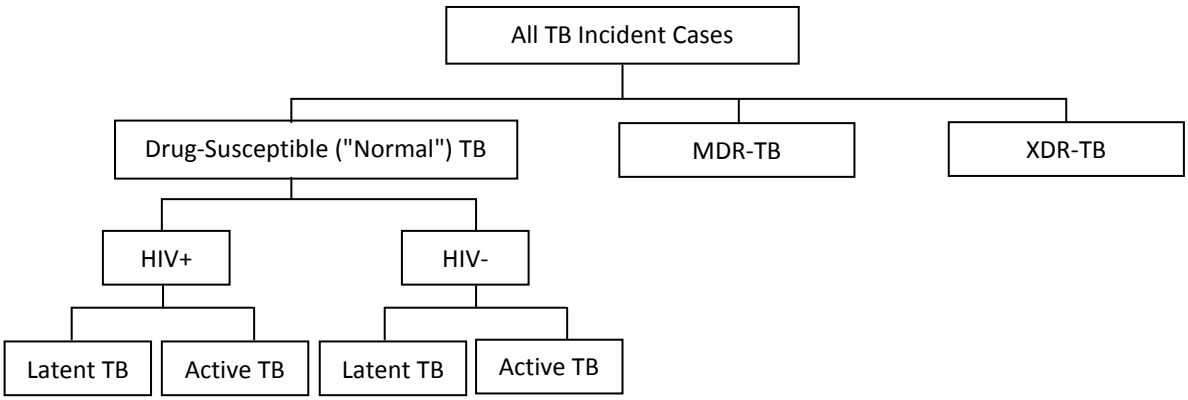
[15] Again, this is the main contributor to the GBD due to malaria and, so, we focused on this kind of malaria in creating our model. World Health Organization World Health Organization, "WHO World Malaria Report 2011", World Health Organization: Geneva, (2011): p. 53.

[16] Please contact authors for relevant data collected via a systematic review of first-line malaria drugs' efficacy.

[17] For relevant treatment coverage data see: World Health Organization. "World Malaria Report 2008" World Health Organization: Geneva, (2008). <http://whqlibdoc.who.int/publications/2008/9789241563697_eng.pdf>, visited on 17 August 2012. Also see: World Health Organization, "Malaria: Country Profiles." World Health Organization: Geneva, (2011). <http://www.who.int/malaria/publications/country-profiles>, visited on 17 August 2012.

Calculating Lupin Pharmaceuticals' final impact score was a bit more difficult for three reasons. First, it makes two first-line anti-TB drugs (Rifampicin and Ethambutol) that are used in combination with two other drugs (Isoniazid and Pyrazinamide) from other companies. Lupin also makes one of the second-line anti-TB drugs -- Levofloxacin -- for Extensively Drug-Resistant (XDR) TB treatment that is used with at least one injectable second-line agent and Cycloserine (which are also from other companies). Moreover, Rifampicin, Ethambutol, Isoniazid and Pyrazinamide are used for different lengths of time as a first-line treatment and Rifampicin, Ethambutol, and Pyrazinamide are used primarily to prevent resistance from Isoniazid from developing. So it is difficult to decide how to credit the different drugs in the combination and extract Ethambutol's and Isoniazid's impact. A similar problem is also seen when attempting to credit Lupin Pharmaceuticals for Levofloxacin since it is used in a combination therapy (for XDR-TB). Second, for TB and HIV/AIDS it was also important to consider interactions between the diseases and the drugs. People with HIV/AIDS are highly susceptible to TB and those who contract it should finish their TB medicine, if possible, before starting treatment for HIV/AIDS. Otherwise resistance to the HIV/AIDS medications develops, but protocols differ for different disease states and drugs. Finally, people with different disease-states (e.g. latent versus active TB) and different levels of resistance to different drugs (e.g. Multidrug-Resistant or MDR-TB, Extensively Drug-Resistant or XDR-TB, and Totally Drug-Resistant or TDR-TB) receive different treatment.

In our preliminary TB model, we have attempted to deal with some of these problems. The chart below outlines the breakdown of different patient groups we considered in crediting companies for anti-TB drugs.



Our current model considers three broad categories of drug resistance in TB: Drug-Susceptible (or "Normal") TB, MDR-TB and XDR-TB. TDR-TB is excluded from the current model as, thus far, only a small number of TDR-TB cases have been reported.[18] We attempted to disaggregate the impact of anti-TB drugs into the remaining three levels of resistance. For Drug-Susceptible TB, we also consider the difference in drugs' impacts on

[18]The first two cases of TDR-TB were reported in 2007 in Italy. Subsequently, 15 cases were found in Iran in 2009 and 12 in India since 2009. Z. T. Udwadia, " MDR, XDR, TDR Tuberculosis: Ominous Progression", *Mumbai: Hinduja Hospital and Research Center*, (2008), <http://www.tbonline.info/media/uploads/documents/thoraxjnl-2012-20166.pdf>, visited on 7 June 2012.

HIV+ versus HIV- TB cases. Finally, because different treatment regimens are used for latent and active TB, they were also differentiated in the model.

Most anti-TB treatment is a combination therapy. The contribution of each drug should sum to the overall impact of the therapy. Eventually we hope to extract the impact of individual drugs within a combination therapy along these lines (using the standard treatment for active TB as an example): To calculate the impact of each drug for active TB treatment (Rifampicin+Ethambutol+Isoniazid+Pyrazinamide), we need to construct some estimate of what Isoniazid's efficacy would have been were it used as a monotherapy, and subtract that value from the impact of the combination at any given point in time.[19] We have yet to try to do this. For simplicity sake, we assume that each drug carries equal weight in any given regimen and credit the drugs equally. Each of the four drugs gets a quarter of the credit for the regimen's impact.

Although we lack data on a few countries, most specify that the treatment for active TB is the standard first-line regimen of Rifampicin, Isoniazid, Ethambutol and Pyrazinamide described above. We assume this is the case for all countries.

The treatment regimen for MDR-TB is more complex due to the possibility of patients being resistant to different combinations of first-line anti-TB drugs. The following table summarizes the various types of MDR-TB regimens considered in our model:[20]

For cases before or without Drug Susceptibility Test (DST) results	(Kanamycin or Amikacin or Capreomycin) + Ethambutol + Pyrazinamide + Ofloxacin
For cases resistant to Isoniazid alone or in combination with resistance to Terizidone	Rifampicin + Streptomycin + Pyrazinamide + Ethambutol
For cases resistant to Isoniazid alone or in combination with resistance to Streptomycin and Terizidone	Rifampicin + (Kanamycin or Capreomycin) + Pyrazinamide + Ethambutol
For cases resistant to Isoniazid and Ethambutol	Rifampicin + Streptomycin + Pyrazinamide + (Ethionamide or Ofloxacin)
For cases resistant to Isoniazid, Ethambutol and Streptomycin	Rifampicin + (Kanamycin or Capreomycin) + Pyrazinamide + (Ethionamide or Ofloxacin)
For cases resistant to Isoniazid, Rifampicin and Streptomycin	(Kanamycin or Amikacin or Capreomycin) + Ethionamide + Pyrazinamide + Ofloxacin + Ethambutol
For cases resistant to Isoniazid, Rifampicin, Steptomycin and Ethambutol	(Kanamycin or Amikacin or Capreomycin) + Ethionamide + Pyrazinamide + Ofloxacin + Cycloserine

Like the approach taken with the standard first-line regimen, each drug is given equal weight in its regimen. As we have yet to disaggregate MDR-TB cases into specific resistant cases, we assume for now that each of the seven types of resistant cases has equal prevalence.

The treatment regimen considered for XDR-TB consists of Cycloserine, at least one injectable second-line agent, and one fluoroquinolone.[21]

[19] This is because, as noted above, the other drugs are used primarily to prevent resistance to Isoniazid from developing. We might create the necessary model by estimating how resistance rates would have evolved from past estimates of resistance rates and a model of the relationship between resistance and efficacy.

[20] World Health Organization, "Guidelines for the Management of Drug-Resistant Tuberculosis", World Health Organization: Geneva, (1997): p. 33-35.

Injectable second-line agents	Kanamycin or Amikacin or Capreomycin
Fluoroquinolones	Levofloxacin or Moxifloxacin or Gatifloxacin or Ofloxacin

Each drug in this regimen is given equal weight in our model.

Given the abovementioned basis of our model, the first step in calculating Lupin Pharmaceuticals' impact score is as follows: Taking Botswana as an example country, we see that 16,855.46 DALYs are lost to TB in Botswana.[22]

In 2010, 10,000 incident cases of TB were reported according to the WHO[23], 80% of registered cases were tested for HIV status, and 65.43% of TB cases with known HIV status were HIV positive.[24] So 8,000 (80% of 10,000) TB incident cases were tested for HIV, and the breakdown of HIV positive to HIV negative cases was 5,235 (65.43% of 8,000) to 2,765 (34.57% of 8,000). In countries where data is not available regarding the proportion of TB incident cases with known HIV cases, an estimate was derived. This was done by calculating the average proportion of known HIV status in countries for a particular WHO region where we have data, as well as the average population across these same countries. This was repeated for all six regions.[25] To estimate the proportion of known HIV status in any particular country X, we take the population of X divided by the average population figure for X's region and multiply by the average proportion of known HIV status in that same region.[26]

The next step involves breaking down incident cases into Drug-Susceptible TB, MDR-TB and XDR-TB. We start with MDR-TB first. Drug Susceptibility Tests (DST) on first-line anti-TB drugs are done to confirm if a patient is multidrug-resistant. In Botswana, 947 TB cases received DST in 2010, of which 106 were confirmed to be MDR-TB. This leads to a MDR-TB proportion of 11.19%.[27]

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[21] The possible injectable second-line agents are Kanamycin, Amikacin, and Capreomycin, and the possible floroquinolones include Levofloxacin, Moxifloxacin, Gatifloxacin, and Ofloxacin. This recommendation is based on a study done on XDR-TB treatment in Lima, Peru. C. D. Mitnick, S. S. Shin, K. J. Seung, M. L. Rich, S. S. Atwood, J. J. Furin, and M. C. Becerra, "Comprehensive Treatment of Extensively Drug-Resistant Tuberculosis", *The New England Journal Of Medicine*, 359, 6 (2008), <http://www.nejm.org/doi/pdf/10.1056/NEJMoa0800106>, visited on 7 May 2012.

[22] World Health Organization, "Table 2. Estimated Total DALYs ('000), By Cause and WHO Member State, 2004 (a, m)", World Health Organization: Geneva, (2009).

[23] Estimated number of incident cases (all forms) in 2010. Author's calculations from the following sources: Column e inc num on the estimates sheet World Health Organization, "Tuberculosis (TB)", Data for Global Tuberculosis Control 2011. Country Data, Case Notifications, World Health Organization: Geneva, (2012), <http://who.int/tb/country/data/download/en/index.html> visited on 20 August 2012.

[24] Data from: World Health Organization, "Tuberculosis (TB)", Data for Global Tuberculosis Control 2011. Country Data, Case Notifications, World Health Organization: Geneva, (2012), <http://who.int/tb/country/data/download/en/index.html> visited on 20 August 2012.

[25] The six WHO regions are: African Region (AFR), Region of the Americas (AMR), Eastern Mediterranean Region (EMR), European Region (EUR), South East Asia Region (SEA) and Western Pacific Region (WPR).

[26] In 2010, HIV testing among TB patients reached 34% globally, 59% in the African Region and 75% in 68 countries. World Health Organization, "Global HIV/AIDS Response: Progress Report 2011", World Health Organization: Geneva, (2011).This estimation technique allows us to maintain the 34% global testing rate.

[27] New and re-treatment patients who received diagnostic drug susceptibility testing (DST, including rapid tests) in 2010. Author's calculations from the following source: World Health Organization, "Tuberculosis (TB)", Data for Global Tuberculosis Control 2011. Country Data, Case Notifications, World Health Organization:

Assuming that this is a representative proportion, we extend this same proportion to all TB incident cases in Botswana. In other words, we estimate that 11.19% of 10,000 incident cases in Botswana are MDR-TB cases, working out to 1,119 cases that require MDR-TB treatment. Based on 2010 WHO data, 114 individuals received MDR-TB treatment in Botswana.[28]So our estimated treatment coverage was 10.18%. To compute the DALYs lost to MDR-TB in Botswana, we use the same MDR-TB proportion of 11.19% to estimate that 1,886.67 DALYs were lost in 2010.[29] Because treatment coverage in Botswana is 10.18% (and we assume this is representative across all MDR-TB cases), the impact of any MDR-TB regimen in Botswana comes to 153.72. Impact is calculated by DALYs lost to MDR-TB * MDR-TB treatment coverage * efficacy of MDR-TB treatment. MDR-TB treatment is approximately 80% efficacious.[30] Thus, we estimate that 1,886.67 * 10.18% * 80% or 153.72 DALYs are averted by drugs for MDR TB in Botswana.

For XDR-TB, DSTs are done on second-line anti-TB drugs to confirm if MDR-TB cases are extensively drug-resistant. In Botswana, 24 MDR-TB cases received second-line DST in 2010, and out of which one case was confirmed to be extensively drug-resistant.[31] The proportion of XDR-TB among MDR-cases that received second-line DST thus works out to 4.17%, and again we assume that we can extend this proportion to all MDR-TB cases. Multiplying this XDR-TB proportion to the total number of MDR-TB cases in Botswana, we have 4.17% out of 1,119 MDR-TB cases (or 47 cases) being extensively drug-resistant. We have yet to obtain good data regarding country-level treatment coverage for XDR-TB. Hence, we use global treatment coverage of 43% as an estimate.[32] Since 4.17% of MDR-TB cases are XDR-TB, we assume that this proportion is also representative of the DALYs lost to XDR-TB. Hence, we estimate that 4.17% of 1,886.67 DALYs lost to MDR-TB in Botswana in 2010 or 78.61 DALYs were lost to XDR-TB in Botswana. Efficacy of XDR-TB treatment is estimated at 55%.[33] Thus the impact of XDR-TB treatment in Botswana in 2010 is 78.61 DALYs lost * 43% treatment coverage * 55% efficacy = 18.59.

Geneva, (2012), <http://who.int/tb/country/data/download/en/index.html> visited on 20 August 2012. Columns: dst and dst_mdr on the notifications sheet

[28] Confirmed MDR-TB cases started on treatment with second-line drugs in 2010. Author's calculations from the following sources: Column dst_mdr sld on the notifications sheet World Health Organization, "Tuberculosis (TB)", Data for Global Tuberculosis Control 2011. Country Data, Case Notifications, World Health Organization: Geneva, (2012), <http://who.int/tb/country/data/download/en/index.html> visited on 20 August 2012.

[29] This assumption can be improved upon as more DALYs are probably lost to the average MDR TB case than to drug-susceptible TB (similarly for XDR TB).

[30] The treatment of MDR-TB has reported cure rates over 80%, especially true when fluoroquinolones and adjuvant surgical therapy are used. Sandoz, "MDR-TB", (2006), <http://www.tbdots.com/site/en/doctor_section_tb_mdr.html>, visited on 20 February 2012.Note that in the case of malaria, efficacy data relied upon is based on clinical trial data. Please contact authors for relevant data.

[31] MDR cases that received 2nd-line DST and DR cases that received 2nd-line DST found to have XDR-TB in 2010. Author's calculations from the following sources: World Health Organization, "Tuberculosis (TB)", Data for Global Tuberculosis Control 2011. Country Data, Case Notifications, World Health Organization: Geneva, (2012), <http://who.int/tb/country/data/download/en/index.html> visited on 20 August 2012. Columns: dst mdr sdst and dst_mdr_sldst_xdr on the notifications sheet.

[32] Treatment coverage in 2008 for XDR-TB is estimated at 43 3% globally. World Health Organization, "2007-2008 XDR & MDR Tuberculosis Global Response Plan", World Health Organization: Geneva, (2008).World Health Organization, "Implementing the WHO Stop TB strategy: A Handbook for National Tuberculosis Control Programmes", World Health Organization: Geneva, (2008).

[33] Several countries with good TB control programmes have shown that cure is possible for up to 50–60% of affected people. StopTB, "Extensively Drug-Resistant Tuberculosis (XDR): The Facts", (2007),

Finally, we look at the treatment for Drug-Susceptible (or "Normal") TB. As mentioned earlier, we assume that the DALYs lost to TB in general comes from the DALYs lost to Drug-Susceptible TB, MDR-TB and XDR-TB. Based on this assumption, the DALYs lost to Drug-Susceptible TB for Botswana in 2010 comes to 14,968.78. Approximately 30% of TB patients that are co-infected with HIV have active TB.[34] Previously we calculated that the number of HIV+ and HIV- cases among incident cases with known HIV status in Botswana were 5,235 and 2,765 respectively (of 8,000 cases in total). This means that among 5,235 HIV+ cases in Botswana, there are 3,664 latent TB cases (70% of 5,235) and 1,570 active TB cases (30% of 5,235). It is estimated that 7.5% of HIV- TB cases have active TB.[35] Thus among 2,765 HIV- cases in Botswana, there are 2,558 latent TB cases (92.5% of 2,765) and 207 active TB cases (7.5% of 2,765). Given these figures, we derive that the proportions of latent versus active TB among HIV+ and HIV- cases are as follows:

- Latent TB / HIV+: 3,664 / 8,000 = 45.80%
- Active TB / HIV+: 1,570 / 8,000 = 19.63%
- Latent TB / HIV-: 2,558 / 8,000 = 31.98%
- Active TB / HIV-: 207 / 8,000 = 2.59%

Here we assume that the proportions of each type of TB above can be extended to DALYs lost to each type.[36] With total DALYs lost to Drug-Susceptible TB at 14,968.78 in 2010 in Botswana, DALYs lost to each type of TB are calculated as follows:

- Latent TB / HIV+: 45.80% * 14,968.78 = 6,855.99
- Active TB / HIV+: 19.63% * 14,968.78 = 2,938.28
- Latent TB / HIV-: 31.98% * 14,968.78 = 4,786.43
- Active TB / HIV-: 2.59% * 14,968.78 = 388.09

We have yet to get good treatment coverage data at the country level for each of the above cases. Thus for now we use the WHO's estimate of the prevalence of directly observed treatment short-course (DOTS) coverage of 69.5% for all cases.[37] Estimated efficacy for

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<http://www.stoptb.org/events/world_tb_day/2007/assets/documents/5.5%20XDR%20TB.pdf>, visited on 8 March 2012.

[34] P. P. Gibson, *Evidence-Based Respiratory Medicine* (Oxford: Blackwell, 2005): p. 312.

[35] The risk for HIV negative people of progressing from latent to active TB is about 5-10%. World Health Organization (WHO), "2007-2008 XDR & MDR Tuberculosis Global Response Plan", World Health Organization: Geneva. (2008). World Health Organization (WHO), "Implementing the WHO Stop TB strategy: A Handbook for National Tuberculosis Control Programmes", World Health Organization: Geneva, (2008). For our model we took the average of this range (7.5%).

[36] We recognize that the impact of latent TB on any affected individual is likely to be lower as compared to one infected with active TB. This implies that latent TB contributes to a smaller proportion of DALYs lost as compared to active TB, and the former should ideally be given less weight. However, for now we assume that latent and active TB attribute to DALYs lost with equal weight. Future improvements to the model will account for weight differences.

[37] According to the WHO, there were 8.8 million incident cases of TB in 2010 and of which 5.8 million cases were diagnosed, notified, and treated under the DOTS approach. World Health Organization, "Global Tuberculosis Control 2011", World Health Organization: Geneva, (2011). This is 65.9% coverage (5.8 million out of 8.8 million). For now, we use this as basis for assumption of treatment coverage for Drug-Susceptible TB given that this group makes up the majority of TB cases (MDR-TB, XDR-TB and TDR-TB form a minority proportion of TB incident cases).

latent TB treatment in general is 90%[38] and that for active TB treatment is also 90%.[39] Thus, impact scores for each case are calculated by DALYs lost * treatment coverage * treatment efficacy:

- Latent TB / HIV+: 6,855.99 * 69.5% * 90% = 4,066.29
- Active TB / HIV+: 2,938.28 * 69.5% * 90% = 1,742.69
- Latent TB / HIV-: 4,786.43 * 69.5% * 90% = 2,838.83
- Active TB / HIV-: 388.09 * 69.5% * 90% = 230.18

The following table provides a quick summary for all the scores we have calculated thus far for each scenario for Botswana in 2010:

TB Case		Impact Score[1]
Drug-Susceptible ("Normal") TB	Latent TB / HIV+	4,066.29
	Active TB / HIV+	1,742.69
	Latent TB / HIV-	2,838.83
	Active TB / HIV-	230.18
Multidrug-Resistant TB (MDR-TB)		153.72
Extensively Drug-Resistant TB (XDR-TB)		18.59

(Recall that, in this model, we only consider the breakdown of latent versus active TB for Drug-Susceptible ("Normal") TB while MDR and XDR TB are modeled in a more generic context without such breakdowns.) [40]

The next step is to disaggregate these scores into the corresponding drugs that are involved in the treatment of Drug-Susceptible TB, MDR-TB and XDR-TB.

Drug-Susceptible TB Treatment Regimen (Latent)

Isoniazid	Drug Proportion of Regimen
Isoniazid	1.0

Since latent TB treatment consists of just Isoniazid, Isoniazid receives full credit for the impact in latent TB treatment.

Drug-Susceptible TB Treatment Regimen (Active)

Standard 6-month first-line regimen (2HRZE/4HR)	Drug Proportion of Regimen
Rifampicin	0.25
Isoniazid	0.25
Ethambutol	0.25
Pyrazinamide	0.25

[38] H. M. Blumberg, M. K. Leonard, and R. M. Jasmer, "Update on the Treatment of Tuberculosis and Latent Tuberculosis Infection", *The Journal of the American Medical Association*, 293, 22 (2005), <http://jama.jamanetwork.com/article.aspx?volume=293&issue=22&page=2776#LatentTBInfection>, visited on 9 May 2012.

[39] World Health Organization, "Global Tuberculosis Control 2011", World Health Organization: Geneva, (2011): p. 71.

[40] Again, impact score is calculated as follows: DALYs lost * treatment coverage * treatment efficacy

Again, we assume the impact of each drug in the standard 6-month regimen for active TB is equal.[41]

MDR-TB Treatment Regimens

A total of 7 MDR-TB regimens are considered in this model. We give equal credit to each regimen for MDR-TB treatment (i.e. each regimen gets 1/7 of MDR-TB treatment impact scores) since we have yet to obtain data regarding to what extent each MDR-TB regimen is used for each country. Within each regimen, each drug is also given equal credit. The proportion of credit given to each drug in each of the 7 regimens is shown in the right column in the table below.

[41] It is clear, however, that some of the drugs in combination therapies like this may be more important than others, e.g. if they are included only to prevent resistance from developing and are easily replaceable by alternative drugs.

(Kanamycin or Amikacin or Capreomycin) + Ethambutol + Pyrazinamide + Ofloxacin	Drug Proportion of Regimen
Kanamycin or Amikacin or Capreomycin	0.08 (0.25/3)
Ethambutol	0.25
Pyrazinamide	0.25
Ofloxacin	0.25
Rifamycin + Streptomycin + Pyrazinamide + Ethambutol	Drug Proportion of Regimen
Rifampicin	0.25
Streptomycin	0.25
Pyrazinamide	0.25
Ethambutol	0.25
Rifampicin + (Kanamycin or Capreomycin) + Pyrazinamide + Ethambutol	Drug Proportion of Regimen
Rifampicin	0.25
Kanamycin or Capreomycin	0.13 (0.25/2)
Pyrazinamide	0.25
Ethambutol	0.25
Rifampicin + Streptomycin + Pyrazinamide + (Ethionamide or Ofloxacin)	Drug Proportion of Regimen
Rifampicin	0.25
Streptomycin	0.25
Pyrazinamide	0.25
Ethionamide or Ofloxacin	0.13 (0.25/2)
Rifampicin + (Kanamycin or Capreomycin) + Pyrazinamide + (Ethionamide or Ofloxacin)	Drug Proportion of Regimen
Rifampicin	0.25
Kanamycin or Capreomycin	0.13 (0.25/2)
Pyrazinamid	0.25
Ethionamide or Ofloxacin	0.13 (0.25/2)
(Kanamycin or Amikacin or Capreomycin) + Ethionamide + Pyrazinamide + Ofloxacin + Ethambutol	Drug Proportion of Regimen
Kanamycin, Amikacin or Capreomycin	0.07 (0.20/3)
Ethionamide	0.20
Pyrazinamide	0.20
Ofloxacin	0.20
Ethambutol	0.20
(Kanamycin or Amikacin or Capreomycin) + Ethionamide + Pyrazinamide + Ofloxacin + Cycloserine	Drug Proportion of Regimen
Kanamycin or Amikacin or Capreomycin	0.07 (0.20/3)
Ethionamide	0.20
Pyrazinamide	0.20

XDR-TB Treatment Regimen

Cycloserine + (Kanamycin or Amikacin or Capreomycin) + (Levofloxacin or Moxifloxacin or Gatifloxacin or Ofloxacin)	Drug Proportion of Regimen
Cycloserine	0.33
Kanamycin or Amikacin or Capreomycin	0.11 (0.33/3)
Levofloxacin or Moxifloxacin or Gatifloxacin or Ofloxacin	0.08 (0.33/4)

We also gave proportionate weight to each drug in the above XDR-TB regimen.

For Botswana, we disaggregate the scores as follows: [42]

TB Case		Total Score	Score Per Drug
Drug-Susceptible ("Normal") TB	Latent TB / HIV+	4,066.29	**Isoniazid: 4,066.29** **Rifampicin:** 0.25*1,742.69= **435.67**
	Active TB / HIV+	1,742.69	**Isoniazid:** 0.25*1,742.69= **435.67** **Ethambutol:** 0.25*1,742.69= **435.67** **Pyrazinamide:** 0.25*1,742.69= **435.67**
	Latent TB / HIV-	2,838.83	**Isoniazid: 2,838.83**
	Active TB / HIV-	230.18	**Rifampicin:** 0.25*230.18 = **57.55** **Isoniazid:** 0.25*230.18 = **57.55** **Ethambutol:** 0.25*230.18 = **57.55** **Pyrazinamide:** 0.25*230.18 = **57.55**
Multidrug-Resistant TB (MDR-TB)		153.72	Each of the 7 regimens gets: 153.72 / 7 = 21.96 Each drug per regimen gets credit of **proportion * 21.96** **Cycloserine:** 0.33*18.59 = **6.13** **Kanamycin:** 0.11*18.59 = **2.04** **Amikacin:** 0.11*18.59 = **2.04**
Extensively Drug-Resistant TB (XDR-TB)		18.59	**Capreomycin:** 0.11*18.59 = **2.04** **Levofloxacin:** 0.08*18.59 = **1.49** **Moxifloxacin:** 0.08*18.59 = **1.49** **Gatifloxacin:** 0.08*18.59 = **1.49** **Ofloxacin:** 0.08*18.59 = **1.49**

Again, since this example is for Lupin Pharmaceuticals' impact score, we only focus on the drugs by this company: Rifampicin, Ethambutol and Levofloxacin. The impact score for Rifampicin, Ethambutol and Levofloxacin in Botswana is simply the sum of individual scores in the table above that are associated with Rifampicin, Ethambutol, and Levofloxacin respectively. The total score for Lupin Pharmaceuticals is the summation across all countries in the model, which sums up to 677,939.57.

3.3 HIV Example

Finally, consider how we calculate Bristol-Myers Squibb's score. Bristol-Myers Squibb makes these antiretroviral drugs for HIV: Didanosine, Stavudine and Efavirenz. Again, we set aside questions about interactions between HIV drugs and others for a rough estimate of efficacy.

[42] Given that an impact score of 153.72 for MDR TB in the table below is to be "shared" (assuming equal "sharing") among seven possible MDR-TB treatment regimens, each regimen gets an impact score of 153.72/7 or 21.96. To breakdown this score further for each drug in each regimen, this score of 21.96 is to be "shared" (assuming equal "sharing" again) among all the drugs in each regimen. Taking the first MDR-TB regimen as an example: (Kanamycin or Amikacin or Capreomycin） + Ethambutol + Pyrazinamide + Ofloxacin --- we divide the score of 21.96 by four (we take "Kanamycin or Amikacin or Capreomycin" as "one drug") such that Ethambutol, Pyrazinamide and Ofloxacin gets 5.49 each. Only one of (Kanamycin or Amikacin or Capreomycin) is used in this treatment regimen, so we give each drug a score of 5.49/3 or 1.83 assuming each drug has an equal one in three chances of being used in this regimen. This same methodology is used to get individual drug scores for all the seven MDR-TB regimens. Then sums for each drug (in all the regimens in which it is used) are calculated.

Finally, consider how we calculate Bristol-Myers Squibb's score. Bristol-Myers Squibb makes these antiretroviral drugs for HIV: Didanosine, Stavudine and Efavirenz. Again, we set aside questions about interactions between HIV drugs and others for a rough estimate of drug efficacy.

The HIV scoring model is based on WHO data collected from mid- and low-income countries affected by HIV that responded to the WHO AIDS Medicines and Diagnostics Service (AMDS) survey.[43] These countries were classified by the WHO as either "Group A" or "Group B" countries. The following table shows the list of countries that responded to the WHO AMDS survey.[44]

Group A *Low- and Middle-Income Countries excluding region of the Americas*		**Group B** *Low- and Middle-Income Countries in the Americas*
Afghanistan	Myanmar	Anguilla
Bangladesh	Namibia	Antigua and Barbuda
Belarus	Nepal	Argentina
Bhutan	Oman	Belize
Bostwana	Papua New Guinea	Bolivia
Burkina Faso	Qatar	Brazil
Burundi	Republic of Moldova	Chile
Cambodia	Romania	Cuba
Cameroon	Saudi Arabia	Dominican Republic
Central African Republic	Sierra Leone	Ecuador
China	Somalia	El Salvador
Democratic Republic of the Congo	Sri Lanka	Grenada
Gambia	Sudan	Guyana
Ghana	Suriname	Honduras
Guatemala	Swaziland	Nicaragua
India	Tanzania	Panama
Iran	Uganda	Paraguay
Kenya	Ukraine	Peru
Lesotho	United Arab Emirates	Trinidad and Tobago
Madagascar	Viet Nam	Uruguay
Malawi	Yemen	
Malaysia	Zambia	
Mozambique	Zimbabwe	

Again the general formula for calculating the impact score for any drug is DALYs * % Treatment Coverage * Drug Efficacy. Because the WHO presents statistics for adults (defined as 15 years of age and above) and children (defined as below 15 years of age) separately, the model starts by calculating impact for these patient groups.

First, we found the following breakdown of DALYs due to HIV by region, gender and age:

[43] We extrapolate to all countries in the world.

[44] Data extracted from World Health Organization, "Antiretroviral Medicines in Low- and Middle-Income Countries: Usage in 2010 with Global and Regional Demand Forecast for 2011 - 2012", World Health Organization: Geneva, (2010): p. 40 (Table 25).

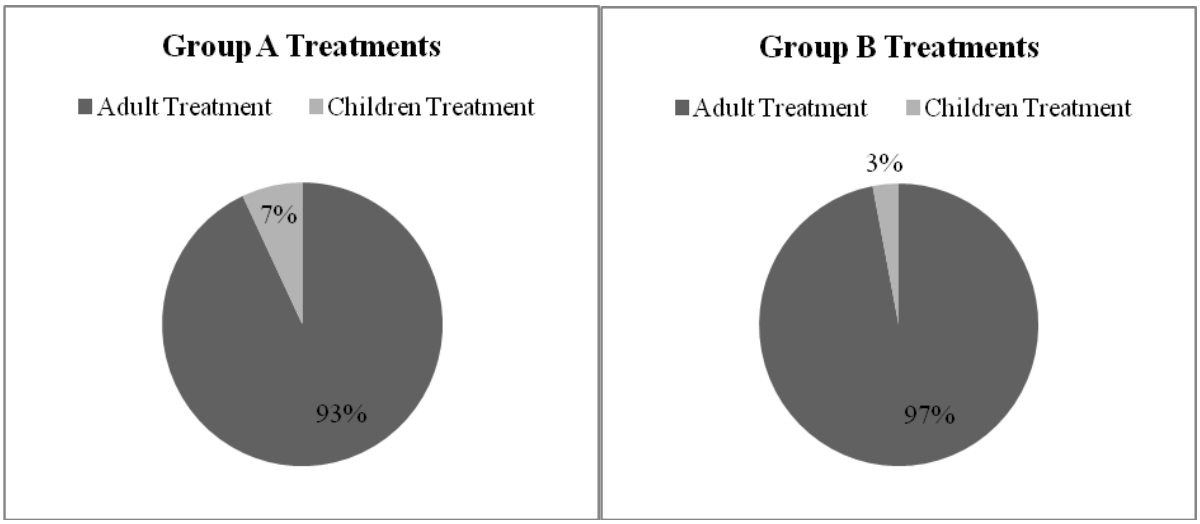
1	2	3	4	5	6	7	8	9
Region	Male Adults	Male Children	Female Adults	Female Children	Adults (Total)	Children (Total)	% Adults	% Children
World	23,247,111.54	5,321,972.13	24,753,057.49	5,190,701.99	48,000,169.03	10,512,674.1	82.03%	17.97%
AFR	15,209,630.58	4,839,669.09	21,865,094.56	4,738,726.42	37,074,725.14	9,578,395.51	79.47%	20.53%
AMR	1,430,238.47	61,599.07	595,117.48	60,184.77	2,025,355.95	121,783.84	94.33%	5.67%
EMR	421,752.36	83,441.93	335,029.83	79,920.72	756,782.19	163,362.65	82.25%	17.75%
EUR	861,384.09	31,090.19	258,095.53	29,265.70	1,119,479.62	60,355.89	94.88%	5.12%
SEA	4,231,941.18	262,298.06	1,360,105.60	242,332.83	5,592,046.78	504,630.89	91.72%	8.28%
WPR	1,060,270.40	41,094.22	314,565.93	37,538.15	1,374,836.33	78,632.37	94.59%	5.41%

Based on the first five columns of data extracted from the Global Burden of Disease 2004 Update Report.[45] we can compute the total number of adults and total number of children burdened by HIV (columns 6 and 7 respectively). We then derive the proportion of all DALYs that are associated with adults (column 6 / sum of columns 6 and 7) and that are associated with children (column 7 / sum of columns 6 and 7) for each region specified in column 1. With these proportions, we can estimate the adult to children DALYs ratio for each country by matching to its respective region and estimate the DALYs lost for adults and children in each country. Using Angola as an example, the total DALYs lost to HIV in 2010 was 308,308.13. Classified under the African Region (AFR), we estimate that the adult to children DALY ratio is 79.47% to 20.53%.[46] Thus, we estimate that 79.47%*308,308.13 = 245,012.47 adult DALYs were lost, and 20.53%*308,308.13 = 63,295.66 child DALYs were lost in Angola in 2010.[47]

Next, we calculated percent treatment coverage for adults and children by country. Again, consider Angola as an example. The total number of people who received antiretroviral treatment in Angola in 2010 was 27,931, out of 86,000 people who needed treatment based on WHO 2010 guidelines.[48] 1,916 children received antiretroviral treatment, out of 19,000 children who needed treatment.[49] Based on these figures, we compute that 26,015 (27,931-1,916) adults received treatment, out of 67,000 (86,000-19,000) adults who needed treatment. Adult percentage treatment coverage in Angola in 2010 thus works out to 26,015/67,000 or 38.83%, while percentage treatment coverage for children is 1,916/19,000 or 10.08%.

The WHO provides information about what treatment regimen adults and children are taking by country group. In Group A countries, 93% of all treatments (first, second, or third line) are for adults, while Group B countries it is 97%.[50]

[45] World Health Organization, "The Global Burden of Disease 2004 Update", World Health Organization: *Geneva*, (2008): Annex A.
[46] We expect that regional averages provide reasonable estimates for a country in that region given that countries in the same region are likely to exhibit similar properties such as life expectancy, age demographics and standard of living.
[47] Again, the reason we consider these groups separately is because the WHO survey data is grouped in this way.
[48] World Health Organization, World Health Observatory Data Repository. Data on HIV/AIDS Response, Antiretroviral Therapy Coverage. < http://apps.who.int/ghodata/?vid=22100 >, Accessed 12 June 2012.
[49] Ibid.
[50] Ibid.



Percent of Treated in Each Group Adult and Child[51]

The table below breaks down each of the four patient groups (Group A adults, Group A children, Group B adults and Group B children) further to show the proportions of first, second, and third line treatments administered.[52]

ADULTS	Group A	Group B
First-Line Regimens	97.10%	69.10%
Second-Line Regimens	2.90%	27.80%
Third-Line Regimens	0.05%	3.10%
CHILDREN	**Group A**	**Group B**
First-Line Regimens	96.80%	72.10%
Second-Line Regimens	3.20%	24.90%
Third-Line Regimens	0.01%	3.00%

Next the model considers the following specific first and second line antiretroviral treatment therapies for Adults in Group A as Angola is a Group A country.[53] For full regimen details, refer to Appendix 2.[54] In the chart below of all the adults receiving first-line antiretroviral therapy 27.70% are receiving a combination of Stavudine + Lamivudine + Nevirapine and we are supposing it is 65.2% efficacious, for instance.[55]

[51] World Health Organization, World Health Observatory Data Repository. *Antiretroviral therapy coverage, data on HIV/AIDS response*. Accessed Jun 12, 2012.

[52] Data extracted from: World Health Organization, "Antiretroviral Medicines in Low- and Middle-Income Countries: Usage in 2010 with Global and Regional Demand Forecast for 2011 - 2012", World Health Organization: Geneva, (2010): p. 4.

[53] We are unable to locate efficacy and proportion data on specific third-line regimens and so do not include them in this version of the model. Given that third-line regimens hold a relatively small proportion out of all antiretroviral treatments, we predict that the impact of third-line regimens will be minimal. Hence, exclusion of third-line regimens from the model due to lack of data should not severely affect final scores.

[54] Regimen breakdown information extracted from World Health Organization, "Antiretroviral Medicines in Low- and Middle-Income Countries: Usage in 2010 with Global and Regional Demand Forecast for 2011 - 2012", World Health Organization: Geneva, (2010): p. 5.

[55] We have yet to do a systematic review of HIV/AIDS or TB drug efficacy. Instead we use either global estimates (for TB) or estimates based on select clinical trials for HIV/AIDS combination therapies' efficacy. The later are probably significantly different from actual global efficacy (as efficacy is likely to vary by region, country, and patient group). So the model can be improved with further data collection.

Group A[56]

ADULT First-Line Regimens	Proportion of Adult First-Line Regimens	Efficacy (%)
Stavudine + Lamivudine + Nevirapine	27.70%	65.20%
Zidovudine + Lamivudine + Nevirapine	26.80%	83.50%
Stavudine + Lamivudine + Efavirenz	14.00%	96.00%
Zidovudine + Lamivudine + Efavirenz	11.40%	76.70%
Tenofovir + Lamivudine + Efavirenz	10.60%	76.60%
Tenofovir + Emtricitabine + Efavirenz	3.50%	90.00%
Tenofovir + Lamivudine + Nevirapine	2.70%	79.00%
Tenofovir + Emtricitabine + Nevirapine	2.50%	84.00%
Others	0.80%	81.38%

Since there exist multiple combination therapies for each patient group and some therapies are used more commonly than others (i.e. have higher proportions in the patient group), weighted efficacies are computed for each patient group. Instead of merely taking the average of all regimen efficacies in a patient group, we give each regimen different weight depending on how commonly it is being used. A regimen with 90% efficacy might be very effective but if it is only used 10% of the time, it should be assigned less weight than another regimen that is used 80% of the time.

Weighted efficacy is the sum of each regime's proportion * each regime's efficacy. For instance, the weighted efficacy for adult first-line treatment in Group A countries is:

((27.70% * 65.20%) + (26.80% * 83.50%) + (14.00% * 96.00%) + (11.40% * 76.70%) + (10.60% * 76.60%) + (3.50% * 90.00%) + (2.70% * 79.00%) + (2.50% * 84.00%) + (.80% * 81.38%)) = 78.77%

The same approach is taken to compute the weighted efficacy for other patient groups. This will yield the following weighted efficacies for treatment in Group A countries:

- Adult First-Line Treatment Efficacy: 78.77%
- Adult Second-Line Treatment Efficacy: 70.47%
- Children First-Line Treatment Efficacy: 75.85%
- Children Second-Line Treatment Efficacy: 70%

We use the above as the estimated weighted efficacies for Angola since it is classified under Group A. Previously, we calculated that 245,012.47 adult DALYs and 63,295.66 child DALYs were lost in Angola in 2010. Recall that we calculated that percentage treatment coverage for adults was 38.83%, while percentage treatment coverage for children was 10.08%. We also previously saw that of all the treatments "Group A Adults" receive, first-line treatments make up 97.10%, second-line treatments 2.90%, and third-line treatments 0.05%. We assume that we can disaggregate adult DALYs in the same proportion (and the same goes for child DALYs). For example, of 245,012.47 adult DALYs, 237,907.11 (97.10% of 245,012.47) can be recovered through first-line treatment, 7,105.36 (2.90% of 245,012.47)

[56] Contact authors for source data.

through second-line treatment and 122.51 (0.05% of 245,012.47) through third-line treatment.[57]

Finally the impact score for each patient group is calculated by potential DALYs recovered * treatment coverage (using adult treatment coverage of 39.83% or children treatment coverage of 10.08%) * weighted efficacy of regimes in the patient group.[58] The impact scores for A countries are as follows:

- Adult First-Line Treatment Impact Score
  = (245,012.47 * 97.10%) * 38.83% ***** 78.77% = 72,767.19

- Adult Second-Line Treatment Impact Score
  = (245,012.47 * 2.9%) * 38.83% ***** 70.47% = 1944.28

- Children First-Line Treatment Impact Score
  = (63,295.66 * 96.80%) * 10.08% * 75.85% = 4684.52

- Children Second-Line Treatment Impact Score
  = (63,295.66 * 3.20%) * 10.08% * 70% =142.92

Again, given the small proportion of third-line treatment regimens in comparison to first- and second-line treatment regimens in general (and the lack of specific data associated with third-line treatment regimens), we only consider first- and second-line treatment scores for adults and children in this model.

Once we have the impact scores for treating each patient group in Angola, the next step is to disaggregate the impact scores to the impact scores associated with each drug. As with drugs in combination therapies for TB, we assume that each drug in any antiretroviral combination therapy receives equal credit.

ADULT First-Line Regimens (Angola, Group A)	Proportion of Adult First-Line Regimens	Each Drug's Weight
Stavudine + Lamivudine + Nevirapine	27.70%	9.23%
Zidovudine + Lamivudine + Nevirapine	26.80%	8.93%
Stavudine + Lamivudine + Efavirenz	14.00%	4.67%
Zidovudine + Lamivudine + Efavirenz	11.40%	3.80%
Tenofovir + Lamivudine + Efavirenz	10.60%	3.53%
Tenofovir + Emtricitabine + Efavirenz	3.50%	1.17%
Tenofovir + Lamivudine + Nevirapine	2.70%	0.90%
Tenofovir + Emtricitabine + Nevirapine	2.50%	0.83%
Others	0.80%	0.27%

Consider, for instance, how we calculate Stavudine's score in Angola's adult population receiving a first-line regimen. Again, we know that 72,767.19 is the final impact score for adult first-line regimen treatments in Angola in 2010. Stavudine only occurs in these two

[57] Note that the sum of DALYs saved through first, second and third line treatment for adults in Group A does not add up exactly to 245,012.47 as the breakdown of treatment proportions provided by WHO (first line = 97.1%, second line = 2.9%, third-line = 0.05%) adds up to 100.05%, possibly due to rounding of decimals.

[58] Multiplying each regimen's efficacy by the regimen's proportion in effect moves some information necessary for calculating treatment percentages at the country-drug level with each regimen into the weighted efficacy result, but running the calculation in this way was much more efficient given our data structure.

combinations (highlighted in the table). For the first combination therapy in the table above, there are three drugs (Stavudine, Lamivudine and Nevirapine) and this combination therapy makes up 27.70% of all adult first-line treatments in Angola. So each of the three drugs has a weight of 27.70%/3 = 9.23%. For the third combination therapy in the table above, there are also three drugs (Stavudine + Lamivudine + Efavirenz) but this combination therapy makes up only 14% of all adult first-line treatments in Angola. So each drug receives a weight of 4.67%. So the total weight for Stavudine is 9.23% + 4.67% = 13.9% among Angola's adult first-line treatment regimens. Thus, Stavudine's impact here is 13.9% of 72,767.19 = 10,114.63.

The same procedure is repeated to get each drug's impact for all regimens and patient groups in each country. The scores are then summed up for each drug across all the countries. Since Bristol-Myers Squibb makes Didanosine, Stavudine and Efavirenz, its total score of 5,570,674.58 reflects the sum of each drug's score.

4. Improving the Index: Questions for Future Research

Further research is necessary to improve the model. It is not always clear, for instance, which company should receive credit for a drug's impact. The structure of the pharmaceutical market is complex. Some companies have patented drugs that other companies really developed. Some have bought the rights to drugs others have patented and developed. Often companies license out manufacturing and distribution of their drugs to other companies or enter into co-marketing agreements. Ideally, it might be best to try to figure out which companies have marketing rights to which drugs in different areas of the world or which companies are really responsible for drug development. Those companies that have control over licensing co-marketing, distribution, and manufacturing rights have a lot of control over access to drugs and have often developed the drugs. Those companies that develop a drug are able to control much that happens to it downstream (for the life of their patents). It is difficult, however, to secure information about which companies market where (globally) or even to isolate which company is really responsible for a drug's development. For now, we are relying primarily on FDA patent applications and companies' annual reports to determine which companies to credit.

We also need to address the issues described above. Further information about treatment protocols is necessary, for instance, to determine which people should get which drugs and how much credit to give each drug in countries where more than one drug is prescribed. Taking into account side-effects associated with some drugs may also be important in evaluating their impacts. Moreover, as noted above, we need to consider further interactions between TB and HIV, and how to appropriation credit for different drugs in combination when one company does not make all of the drugs.

5. Conclusion

Indicators are powerful because they can focus attention and legal or political effort on achieving important goals.[59] This paper has sketched the prospects for creating a new kind of indicator – one that measures the global health impact of essential medicines -- that can be

[59] B. Kingsbury, "Indicators and Law in Global Governance", 8th Viterbo GAL Seminar "Indicators in Global Governance: Legal Dimensions", Istituto di Ricerche sulla Pubblica Amministrazione: Rome, Italy.

used to encourage pharmaceutical companies and others in positions of power to better address global health needs.[60] Of course, what impact this indicator will have d**e**pends on how it is used.[61] There is a lot of good work on potential pitfalls to avoid in constructing good indicators and evaluating potential uses.[62] It is necessary to consider the prospects and potential draw-backs of the proposed indicator carefully to maximize its chances of providing useful information that can promote global health. It is important that the indictor really track what it is supposed to track (in this case global health impact) and that its assumptions are made explicit and tested.[63] To improve the model sketched above, amongst other changes, we hope to:

- Improve our disease models to better deal with interaction effects between drugs and disease states.
- Model resistance rates to mono-therapies to better credit drugs in combination therapies
- Improve efficacy estimates
- Determine which companies it is best to credit for innovations
- Include estimates of drug interactions/side effects

We are also working on some sensitivity analysis of our model to figure out which of its simplifying assumptions has a large impact on the overall rating of companies (and what we might focus on improving). We must also consider how update the indicator over time if it is to provide a stable basis for fruitful philanthropic, governmental and non-governmental action.[64]

No indicator is perfect and different indictors are appropriate for different purposes, but we believe a good Global Health Impact indicator can have a major impact.[65] By making the goals we would like this indicator to help achieve explicit and keeping them in mind in developing the model, we have tried to address some of the design issues necessary for creating a good indicator. Further analysis will help us determine what proposed uses for the

[60] For work on other global health indicators and their importance see: M. Samson, "Indicators as a monitoring tool for the implementation of Global Health Law", 8th Viterbo GAL Seminar "Indicators in Global Governance: Legal Dimensions", Istituto di Ricerche sulla Pubblica Amministrazione: Rome, Italy.

[61] K. Davis, B. Kingsbury, and S. Merry, "Indicators as a Technology of Global Governance", Public law & Legal Theory Research Paper Series. Working Paper No. 10-26 and Law & Economics Research Paper Series Working paper no. 10-13. New York University School of Law. B. Kingsbury, "Indicators and Law in Global Governance", 8th Viterbo GAL Seminar "Indicators in Global Governance: Legal Dimensions", Istituto di Ricerche sulla Pubblica Amministrazione: Rome, Italy. For discussion of some uses of indictors in law, see: K. Davis, "Legal Indicators: Potential and Perils", 8th Viterbo GAL Seminar "Indicators in Global Governance: Legal Dimensions", Istituto di Ricerche sulla Pubblica Amministrazione: Rome, Italy.

[62] Ibid.

[63] For discussion of the importance of this point in a different context, see: N. Hassoun, "Free Trade, Poverty and Inequality", *Journal of Moral Philsophy*, 8: 5-44.

[64] Kevin E. Davis and Benedict Kingsbury, "Indicators as Interventions: Pitfalls and Prospects in Supporting Development Initiatives," Rockefeller Foundation Working Paper, December 14, 2011.

[65] K. Davis, B. Kingsbury, and S. Merry, "Indicators as a Technology of Global Governance", Public law & Legal Theory Research Paper Series. Working Paper No. 10-26 and Law & Economics Research Paper Series Working paper no. 10-13. New York University School of Law. Also see: B. Kingsbury, "Indicators and Law in Global Governance", 8th Viterbo GAL Seminar "Indicators in Global Governance: Legal Dimensions", Istituto di Ricerche sulla Pubblica Amministrazione: Rome, Italy.

indicator are most promising. The discussion and contestation academic publication can bring is important for improving the end result.[66]

If it is possible to develop and maintain a good rating system, it will have a significant impact on global health. Such a rating system will support Global Health Impact certification, where highly-rated pharmaceutical companies are allowed to use a Global Health Impact label on all of their products. This will give companies a large incentive to become highly rated as they can use the label to garner a larger share of the market for their over-the-counter medications and other consumer products. An associated Global Health Impact licensing campaign would also have a big impact. Again, the idea is that universities might give preference in licensing their products to highly rated companies. This would give companies an even greater incentive to abide by Global Health Impact standards. If the proposed Global Health Impact indicator is successful, it will provide the basis for effective interventions that can help us address some of the most complex, changing, and devastating global health problems people face.[67]

[66] G. Dimitropoulos, "Global Administrative Law as "Enabling Law": How To Monitor And Evaluate Indicator-Based Performance", 8th Viterbo GAL Seminar "Indicators in Global Governance: Legal Dimensions", Istituto di Ricerche sulla Pubblica Amministrazione: Rome, Italy.

[67] Kevin E. Davis and Benedict Kingsbury, "Indicators as Interventions: Pitfalls and Prospects in Supporting Development Initiatives," Rockefeller Foundation Working Paper, December 14, 2011.

Appendix 1: Anti-TB Drug List

Abbreviation	Full Name
2HRZE/4HR	6-month first-line regimen (active TB)
Amk	Amikacin
Amx	Amoxicillin
Cfz	Clofazimine
Clr	Clarithromycin
Clv	Clavulanate
Cm	Capreomycin
Cs	Cycloserine
E (or EMB)	Ethambutol
Eto	Ethionamide
Gfx	Gatifloxacin
H (or INH)	Isoniazid
Ipm	Imipenem
IPT	Isoniazid Preventive Treatment
Km	Kanamycin
Lfx	Levofloxacin
Lzd	Linezolid
Mfx	Moxifloxacin
Ofx	Ofloxacin
PAS	p-aminosalicylic acid
Pto	Prothionamide
R (or RMP)	Rifampicin
S (or STR)	Streptomycin
Thz	Thioacetazone
Trd	Terizidone
Z (or PZA)	Pyrazinamide

Appendix 2: Antiretroviral Treatment Regimen Proportions and Efficacies[68]

Group A

ADULT First-Line Regimens	Proportion of Adult First-Line Regimens	Efficacy (%)
Stavudine + Lamivudine + Nevirapine	27.70%	65.20%
Zidovudine + Lamivudine + Nevirapine	26.80%	83.50%
Stavudine + Lamivudine + Efavirenz	14.00%	96.00%
Zidovudine + Lamivudine + Efavirenz	11.40%	76.70%
Tenofovir + Lamivudine + Efavirenz	10.60%	76.60%
Tenofovir + Emtricitabine + Efavirenz	3.50%	90.00%
Tenofovir + Lamivudine + Nevirapine	2.70%	79.00%
Tenofovir + Emtricitabine + Nevirapine	2.50%	84.00%
Others	0.80%	81.38%
ADULT Second-Line Regimens	**Proportion of Adult Second-Line Regimens**	**Efficacy (%)**
Tenofovir + Lamivudine + Lopinavir/Ritonavir	27.10%	83.00%
Zidovudine + Didanosine + Lopinavir/Ritonavir	25.00%	65.80%
Zidovudine + Lamivudine + Lopinavir/Ritonavir	12.70%	65.80%
Tenofovir + Emtricitabine + Lopinavir/Ritonavir	10.70%	67.00%
Zidovudine + Lamivudine + Tenofovir + Lopinavir/Ritonavir	5.50%	65.80%
Abacavir + Didanosine + Lopinavir/Ritonavir	4.80%	65.80%
Abacavir + Tenofovir + Lopinavir/Ritonavir	2.50%	65.80%
Stavudine + Lamivudine + Lopinavir/Ritonavir	1.90%	61.00%
Abacavir + Lamivudine + Lopinavir/Ritonavir	1.10%	63.20%
Others	8.70%	65.80%
CHILDREN First-Line Regimens	**Proportion of Children First-Line Regimens**	**Efficacy (%)**
Stavudine + Lamivudine + Nevirapine	34.90%	65.20%
Zidovudine + Lamivudine + Nevirapine	20.70%	83.50%
Stavudine + Lamivudine + Efavirenz	15.60%	96.00%
Zidovudine + Lamivudine + Efavirenz	7.20%	76.70%
Abacavir + Lamivudine + Efavirenz	6.20%	76.68%
Stavudine + Lamivudine + Lopinavir/Ritonavir	5.90%	62.00%
Abacavir + Lamivudine + Lopinavir/Ritonavir	5.80%	76.68%
Abacavir + Lamivudine + Nevirapine	1.70%	76.68%
Others	1.50%	76.68%
CHILDREN Second-Line Regimens	**Proportion of Children Second-Line Regimens**	**Efficacy (%)**
Abacavir + Lamivudine + Lopinavir/Ritonavir	26.20%	70.00%
Zidovudine + Didanosine + Lopinavir/Ritonavir	17.20%	70.00%
Abacavir + Didanosine + Lopinavir/Ritonavir	14.80%	70.00%
Zidovudine + Lamivudine + Lopinavir/Ritonavir	12.30%	70.00%
Zidovudine + Didanosine + Efavirenz	6.60%	70.00%

Group B

[68] Regimen breakdown information extracted from World Health Organization, "Antiretroviral Medicines in Low- and Middle-Income Countries: Usage in 2010 with Global and Regional Demand Forecast for 2011 - 2012", World Health Organization: Geneva, (2010): p. 5. This efficacy information is currently the weakest in our model as it is from selected clinical trial data (and we either use a data point from a different region/patient group or the average for each treatment regimen type (e.g. first line) for each patient and country group when we are not able to locate an appropriate trial).

ADULT First-Line Regimens	Proportion of Adult First-Line Regimens	Efficacy (%)
Zidovudine + Lamivudine + Efavirenz	42.50%	76.70%
Zidovudine + Lamivudine + Lopinavir/Ritonavir	13.60%	78.07%
Zidovudine + Lamivudine + Nevirapine	12.00%	83.50%
Zidovudine + Lamivudine + Atazanavir/Ritonavir	6.40%	78.07%
Tenofovir + Emtricitabine + Efavirenz	6.20%	90.00%
Abacavir + Lamivudine + Efavirenz	2.60%	59.00%
Stavudine + Lamivudine + Nevirapine	2.10%	65.20%
Stavudine + Lamivudine + Efavirenz	1.80%	96.00%
Others	12.90%	78.07%
ADULT Second-Line Regimens	**Proportion of Adult Second-Line Regimens**	**Efficacy (%)**
Tenofovir + Lamivudine + Efavirenz	18.10%	76.60%
Tenofovir + Lamivudine + Lopinavir/Ritonavir	16.60%	86.30%
Tenofovir + Lamivudine + Atazanavir/Ritonavir	13.40%	86.30%
Zidovudine + Lamivudine + Lopinavir/Ritonavir	3.90%	86.30%
Zidovudine + Lamivudine + Tenofovir + Lopinavir/Ritonavir	3.00%	86.30%
Stavudine + Lamivudine + Efavirenz	2.60%	96.00%
Stavudine + Lamivudine + Lopinavir/Ritonavir	2.20%	86.30%
Tenofovir + Lamivudine + Nevirapine	1.70%	79.00%
Zidovudine + Lamivudine + Tenofovir + Atazanavir/Ritonavir	1.40%	86.30%
Others	37.00%	86.30%
CHILDREN First-Line Regimens	**Proportion of Children First-Line Regimens**	**Efficacy (%)**
Zidovudine + Lamivudine + Efavirenz	32.10%	76.70%
Zidovudine + Lamivudine + Lopinavir/Ritonavir	26.70%	80.10%
Zidovudine + Lamivudine + Nevirapine	17.50%	83.50%
Zidovudine + Lamivudine + Nelfinavir	3.50%	80.10%
Zidovudine + Didanosine + Lopinavir/Ritonavir	3.30%	80.10%
Zidovudine + Didanosine + Efavirenz	2.60%	80.10%
Others	14.40%	80.10%
CHILDREN Second-Line Regimens	**Proportion of Children Second-Line Regimens**	**Efficacy (%)**
Zidovudine + Lamivudine + Efavirenz	32.10%	76.70%
Zidovudine + Lamivudine + Lopinavir/Ritonavir	26.70%	80.10%