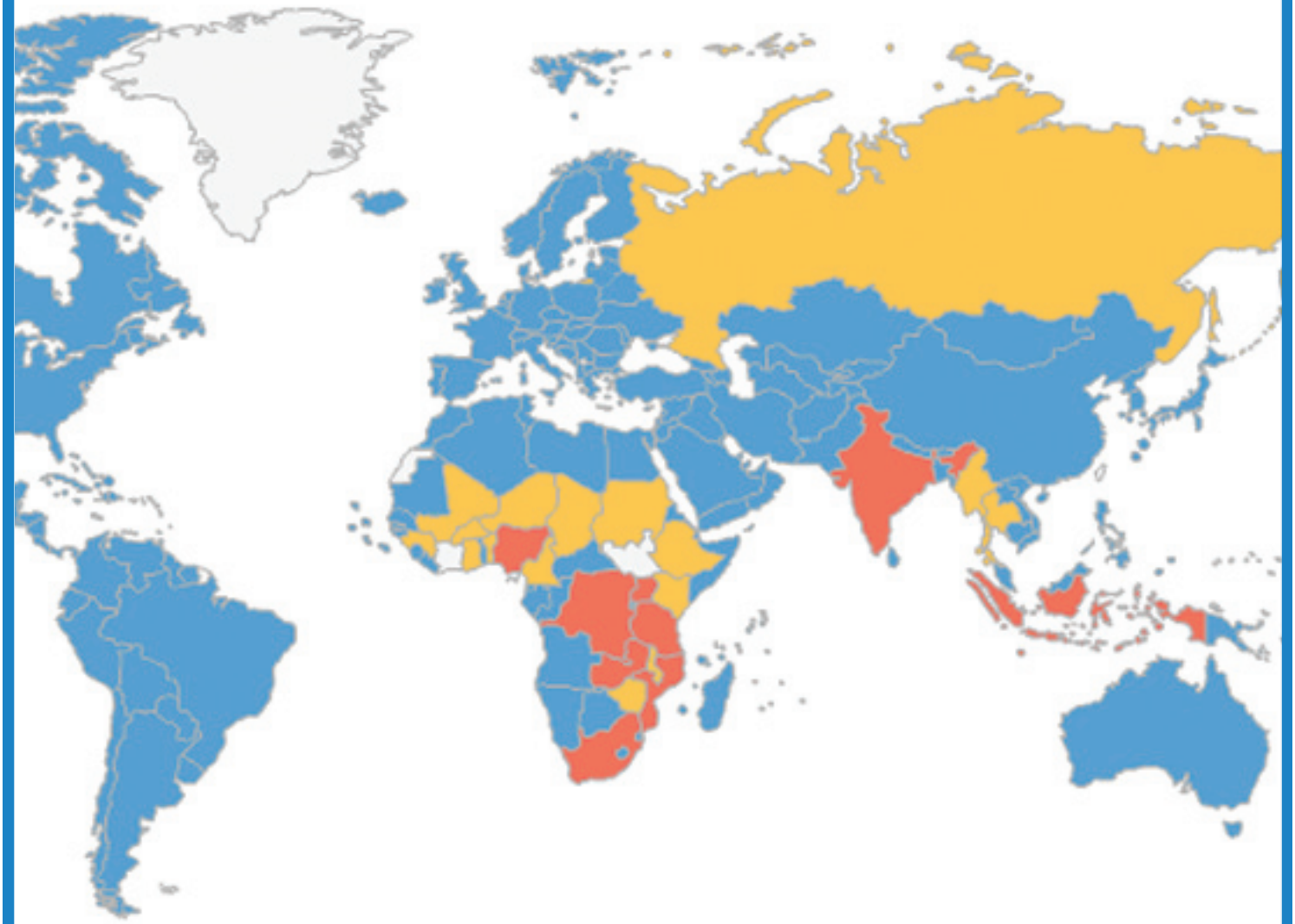
GLOBAL HEALTH Impact



The Extending Access Index: Promoting Global Health

Disclaimer

The information in this paper on the HIV/AIDS portion of the index will be published in a special issue of Public Affairs Quarterly shortly: complete citation information for the final version of the paper will be available on the journal's website at http://paq.press.illinois.edu/28/3/hassoun.html

If you are not redirected to the paper please click here.

Nicole Hassoun

Associate Professor

SUNY Binghamton

Department of Philosophy

4400 Vestal Parkway East

Box 6000

Binghamton, NY 13902-6000

nhassoun@binghamton.edu

Short Bio

Nicole Hassoun is an associate professor in philosophy at SUNY Binghamton. From 2006-2012 she was an assistant professor at Carnegie Mellon University affiliated with Carnegie Mellon's Program on International Relations and the University of Pittsburgh's Center for Bioethics and Health Law. In 2009-2010 she held a postdoctoral position at Stanford University and visited at the United Nation's World Institute for Development Economics Research. She has also been a visiting scholar at the Center for Poverty Research in Austria and the Center for Advanced Studies in Frankfurt. Her book Globalization and *Global Justice: Shrinking Distance, Expanding Obligations* has just appeared with Cambridge University Press. She has published in journals like the *American Philosophical Quarterly, Journal of Development Economics, The Journal of Applied Ethics, The American Journal of Bioethics, Public Affairs Quarterly, The European Journal of Philosophy, Environmental Ethics*, and *Utilitas.*

Abstract

The Extending Access Index: Promoting Global Health

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. This rating system provides essential information for policy makers, researchers, companies, universities, and other stakeholders on companies' global health impact – opening the door to many ways of incentivizing positive change.

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

Content

Drug Abbreviation List

TB Drug Abbreviation	Full Name
3TC	Lamivudine
ABC	Abacavir
AL	Artemether-Lumefantrine
Amk	Amikacin
AS+AQ	Artesunate + Amodiaquine
AS+MQ	Artesunate + Mefloquine
AS+SP	Artesunate + Sulfadoxine-Pyrimethamine
ATV/r	Atazanavir/Ritonavir
AZT	Zidovudine
Cm	Capreomycin
Cs	Cycloserine
DHA-PPQ	Dihydroarteminisin-Piperaquine
ddl	Didanosine
d4T	Stavudine
E (or EMB)	Ethambutol
EFV	Efavirenz
Eto	Ethionamide
FTC	Emtricitabine
Gfx	Gatifloxacin
H (or INH)	Isoniazid
Km	Kanamycin
Lfx	Levofloxacin
LPV/r	Lopinavir with a ritonavir boost
Mfx	Moxifloxacin
NFV	Nelfinavir
NVP	Nevirapine
Ofx	Ofloxacin
PAS	4-aminosalicylic acid
R (or RMP)	Rifampicin
S (or STR)	Streptomycin
TDF	Tenofovir

The Extending Access Index: Promoting Global Health[1]

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. Every year 9 million people are diagnosed with tuberculosis, every day more than 13,400 people are infected with AIDs, every 30 seconds malaria kills a child.[2] One reason for this is that many people cannot access the existing drugs and technologies they need. Even basic medicines, like antibiotics, may be too expensive for people in low income countries making less than the equivalent of what $1,025 a year will buy in the US.[3] Another reason many people around the world lack access to essential medicines is that little of the research and development on new drugs and technologies focuses on the diseases that have the largest impact on global health. Consider research and development (R&D) spending on cardiovascular diseases and diabetes vs. malaria, TB, and HIV/AIDS:

Condition	GDB (Million DALYs)	% of Total GDB	R&D Funding US$ Millions	R&D Funding US$ per DALY
CVD	148.19	9.9	9,402	63.45
Diabetes	16.19	1.1	1,653	102.07
HIV/AIDS	84.46	5.7	2,049	24.26
Malaria	46.49	3.1	288	6.2
TB	34.74	2.3	378	10.88

R&D Spending and the Global Disease Burden (GDB)[4]

There are several ways of trying to address these problems that focus on restructuring the incentives pharmaceutical companies face so that they can extend access on essential drugs to the poor.

Unfortunately, many proposals for increasing access to essential medicines only address the research and development problem and do not ensure that people can actually access these medicines. Prize funds and grants are perhaps the best known alternatives. Organizations like the Gates Foundation often offer individual scientists, or corporations, grants to work on diseases like malaria, TB, and HIV/AIDS. Sometimes

these organizations offer prizes for any individual or corporation that can come up with a new way of addressing global health problems.[5] Other options include Priority Review Vouchers and Target Product Profiles (TPPs). Priority Review Vouchers extend the basic idea behind the Orphan Drug Act by giving companies focusing on essential medicines tradable rights to quicker marketing approval for working on these medicines.[6] TPPs help companies evaluate the promise of new drugs to encourage potentially profitable, but overlooked, research and development on essential medicines.[7] Such proposals may promote new research and development on drugs and technologies that address the global burden of disease. They do not, however, address the access problem -- the medicines that are given priority review, or result from TPPs, prizes, or grants, may still be too expensive for most people to purchase.

Other proposals focus exclusively on helping people access existing medicines. Many governmental, and non-governmental, organizations facilitate access to essential medicines by purchasing these products and distributing them at greatly reduced prices. The Global Fund is, perhaps, the most prominent example of an organization extending access on malaria, TB, and HIV/AIDS medicines globally.[8] Individual companies also increase access to essential medicines via their drug donation programs and differential pricing mechanisms (when they offer reduced-prices in developing country markets). Countries can issue compulsory licenses to produce patented drugs more cheaply if companies refuse to do so.[9] These proposals have had varying degrees of success but do nothing to address the research and development problem.

A few proposals try to both incentivize new research and development and increase access to existing medicines. Many public/private partnerships, such as the International AIDS Vaccine Initiative,[10] promote new drug development.[11] Others, such as the World Health Organization (WHO)/Novartis collaboration to provide Coartem for malaria in Zambia, increase access. Perhaps the most ambitious proposal for addressing both the research and development and access problems is Aiden Hollis' and Thomas Pogge's Health Impact Fund (HIF).[12] The HIF is a global prize system under which companies could register for an alternative kind of patent on essential medicines that would reward them in proportion to the global health impact of their product.

Although there are many good ways of addressing the access to medicines problem, new ideas are desirable because the problem remains. Part of the reason that the existing proposals are not sufficient to solve this problem is that they are expensive to implement. Prize funds and grants require millions of dollars-worth of investments, as do many drug donation programs and price reductions. It would also cost millions, if not billions, to create the HIF.[13] Some proposals, however, are relatively cheap. Most of these proposals, like TPPs, focus on providing essential information about the state of global health and how it might be possible to improve health outcomes.

This paper provides a new, potentially cost-effective, way of addressing the access to medicines problem that might be used in conjunction with, and even buttress, some of the above proposals.[14] It suggests a Global Health Impact rating system where pharmaceutical companies are evaluated on the basis of some of their key drugs' potential impacts on global health. The proposed rating system is similar to, but has some advantages over, the main alternative: The Access to Medicines Index. The Access to Medicines Index considers things like companies' patenting policies, price reductions, public-private partnerships, and charitable contributions. But even the best policies do not guarantee good outcomes. The Global Health Impact

index is grounded in good scientific evidence and measures the potential impact of some of companies' key innovations on global health. It is, thus, a much more promising basis for incentivizing companies to address the access to medicines problem and increase their global health impact.

Such a rating system will open the door to many new ways of incentivizing companies to have a greater impact on global health. Consider just a few possibilities discussed at greater length in several key policy papers on this proposal.[15] On the basis of this rating system the best companies, in a given year, can be licensed a Global Health Impact label to use 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.[16] 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.[17] The rating system can also support a wide range of other initiatives. One possibility is a Global Health Impact licensing campaign. 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. 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.[18] 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.[19] A Global Health Impact certification system will give companies a reason to produce new medicines (like malaria or HIV vaccines) and extend access on existing medicines that will save millions of lives.[20]

Similar labeling and licensing initiatives have had a large impact.[21] There is good experimental, and quasi-experimental, evidence that people are willing to buy a wide variety of products with "ethical" labels and that, when they do so, there are benefits to people around the world.[22] (RED) is, for instance, one of the largest contributors to the Global Fund and, in 2005, the Global Fund provided more than 20% of the international funding for HIV/AIDS programs and about 65% of the funding for tuberculosis and malaria programs.[23] Similarly, university licensing proposals are already starting to take root. Universities Allied for Access to Essential Medicines has, for instance, gotten the University of California Technology Transfer Advisory Committee to issue the following guideline to technology licensing offices on all campuses: "life-saving UC medical research should be licensed to drug companies in ways that make the resulting products affordable to low-income patients in developing countries."[24]

Even if using a global health impact rating system in the ways described above would not be a good idea, the rating system provides extremely useful information in an easily accessible format and may open the door to addressing key global health problems in other ways. It might, for instance, form the basis for corporate social responsibility (CSR) initiatives. Similar CSR initiatives have had a large impact on firm performance and shareholders likely invest more in socially responsible companies.[25] Companies might lobby insurance organizations to give preferential access to highly rated drugs over (medically equivalent) alternatives in creating their formularies. Alternately, researchers or regulators might use the rating system as a standard against which to evaluate new innovations and company efforts. Researchers might also mine the data to figure out which causes, and consequences, of global health innovations will have the most impact (and to answer many other important questions). Presumably the methodology developed here for malaria, TB, and HIV/AIDS medications can be generalized to other drugs and other diseases. These

models may be useful for policy makers interested in trying to improve access to medicines and researchers evaluating policies aimed at doing so.

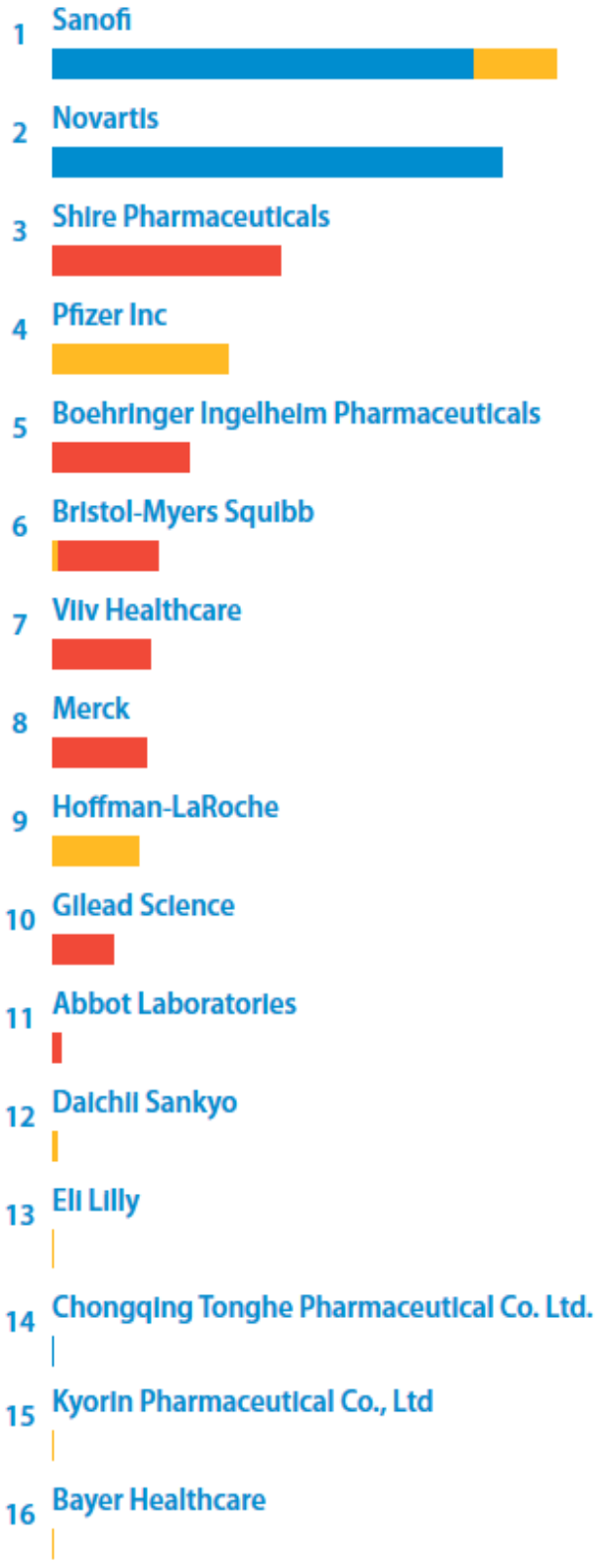
For all of the reasons detailed above, I believe that the model rating system this paper presents is interesting and important. Several of the assumptions the model below relies upon require significant refinement. Nevertheless, this paper hopes to illustrate how a good model can be constructed and open the door to debate about the best ways of doing so.

2. Model Rating System

A good Global Health Impact Index should be objective and output-based to 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.

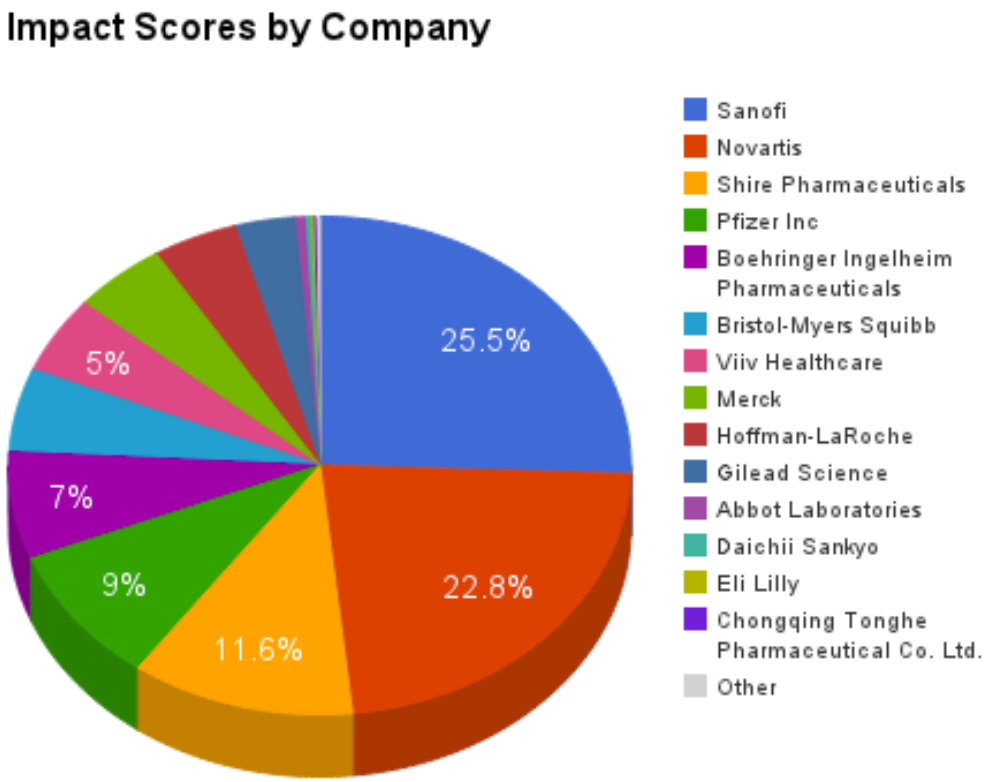
This paper presents a preliminary model that provides an estimate of the impact of key medicines for HIV/AIDS, TB, and Plasmodium Falciparum (p. falc.) malaria in 2011. As the model provides a projection because it focuses on estimating how much of the burden of these diseases is alleviated in 2010, the key drugs will alleviate if they are as accessible and effective in 2011 as the 2010 estimates of treatment percentages and efficacy suggest. The model focuses on these diseases as they are some of the diseases with the largest global health impact for which good data is available globally.[26]

Company By Rank



Company Rank, Areas of Focus, and Drugs

Rank	Company Name	Disease	Drugs
#1	Sanofi	Malaria TB	Artesunate + Amodiaquine, Artesunate + Sulfadoxine-Pyrimethamine, Ethionamide, Rifampicin
#2	Novartis	Malaria HIV	Artemether Lumefantrine, Atazanavir/Ritonavir
#3	Shire Pharmaceuticals	HIV	Lamivudine
#4	Pfizer, Inc.	TB	Cycloserine, Ethambutol, Pyrazinamide
#5	Boehringer Ingelheim Pharmaceuticals	HIV	Nevirapine
#6	Bristol-Myers Squibb	HIV TB	Amikacin, Didanosine, Stavudine, Kanamycin
#7	Viiv Healthcare	HIB	Abacavir, Zidovudine, Nelfinavir
#8	Merck	TB	Efavirenz, Streptomycin
#9	Hoffman-LaRoche	TB	Isoniazid
#10	Gilead Science	HIV	Emtricitabine, Tenofovir
#11	Abbott Laboratories	HIV	Lopinavir with a ritonavir boost, Atazanavir/Ritonavir
#12	Daichii Sankyo	TB	Levofloxacin, Ofloxacin
#13	Eli Lilly	Malaria	Capreomycin
#14	Chongqing Tonghe Pharmaceutical Co., Ltd.	TB	Dihydroartemisinin-Piperaquine
#15	Bayer AG	TB	Moxifloxacin
T#15	Kyorin Pharmaceutical Co., Ltd	TB	Gatifloxacin



Percentage of the Disease Burden Alleviated by Key Malaria, TB and HIV/AIDS Medicines by Company

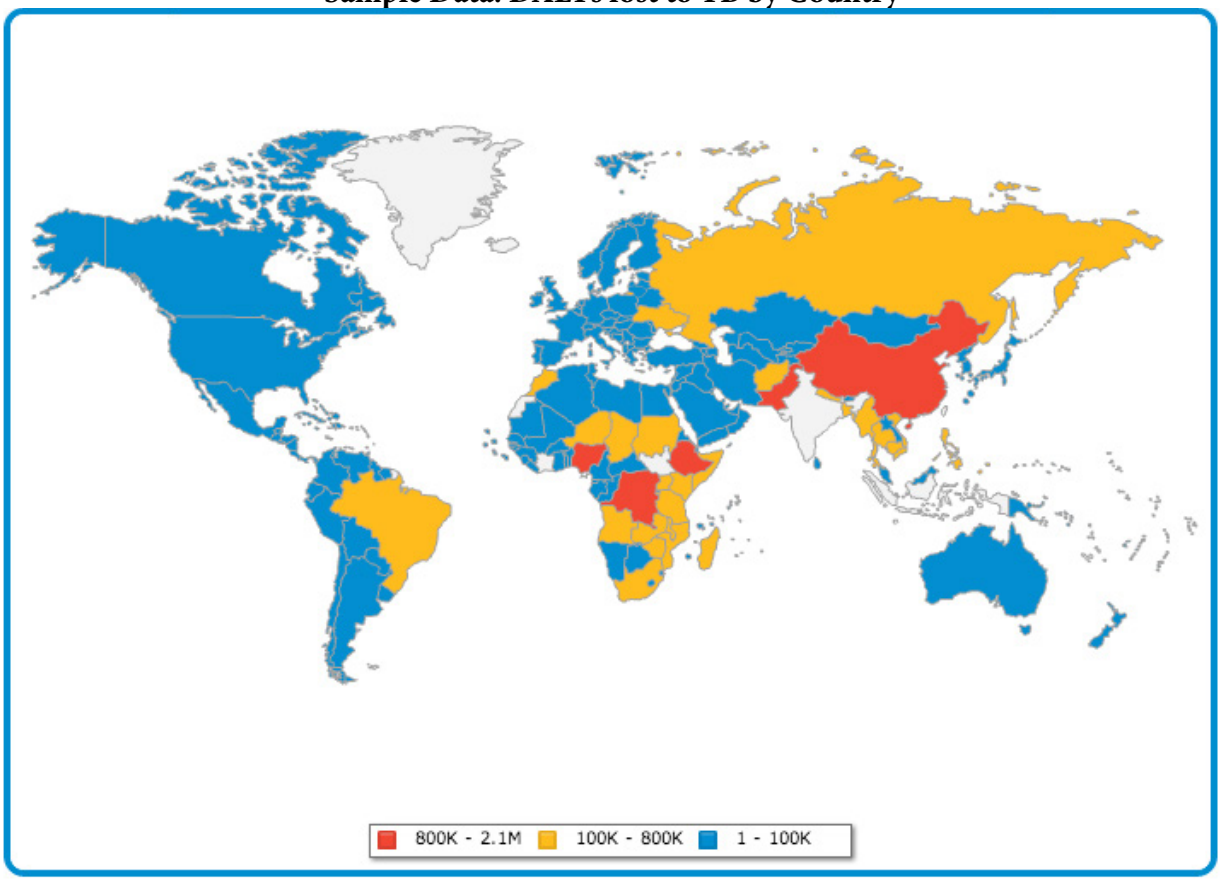
The model was completed in two (rough) steps. First, we estimated the impact of all of the key medicines for HIV/AIDS, TB, and malaria. Second, we ranked companies by aggregating their drugs' estimated impacts on global health. This will allow us to rate companies based on their relative (or absolute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

Consider how we evaluate the impact of each drug globally. 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).

The drug's estimated impact is, roughly, 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. In the model, when country- and drug-specific treatment coverage is not available, the percent of people receiving treatment by a particular drug is estimated at the percent of people who receive treatment for that disease within the country. Rarely, we rely on global estimates of treatment percentages for disease states. Similarly, if country-specific efficacy data for a drug is provided by the WHO, we use this efficacy data. If this information is not available, we use estimates of drugs' efficacy from clinical trial data in other countries or occasionally a global estimate.

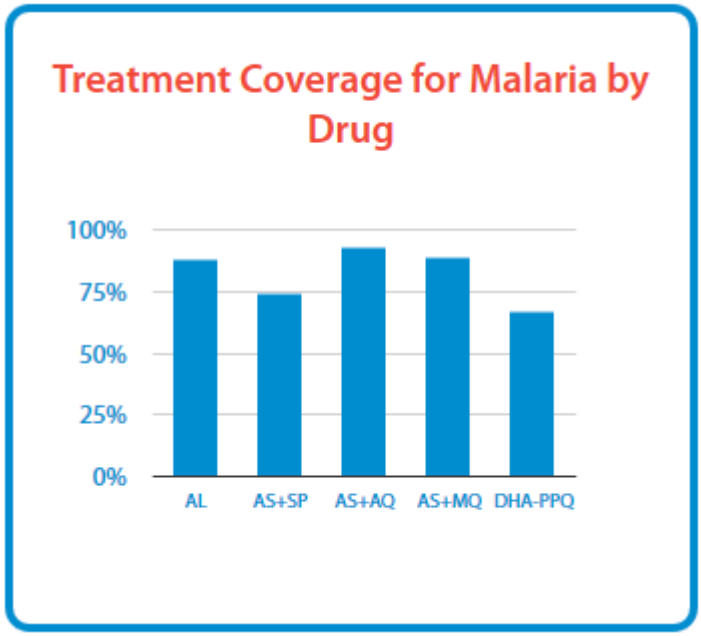
A slightly simplified, hypothetical, example will help explain the basic idea. Again, each drug's impact in the model is, roughly, Need * Access * Effectiveness. Suppose, for instance, 100 million DALYs are lost per annum to a disease treatable with a drug that reduces the impact of the disease by 80%, on average. If 50% of the population that needs it has access to it, we estimate that the drug will save 40 million DALYs (100 * .8 * .5 = 40).

Sample Data: DALYs lost to TB by Country

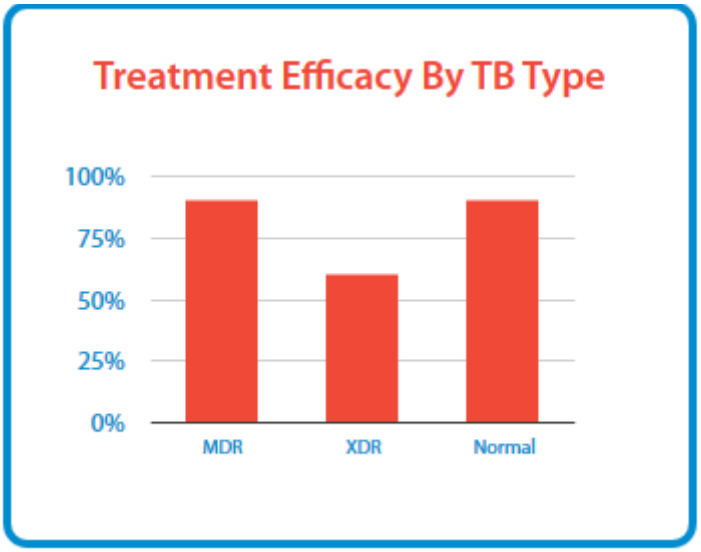


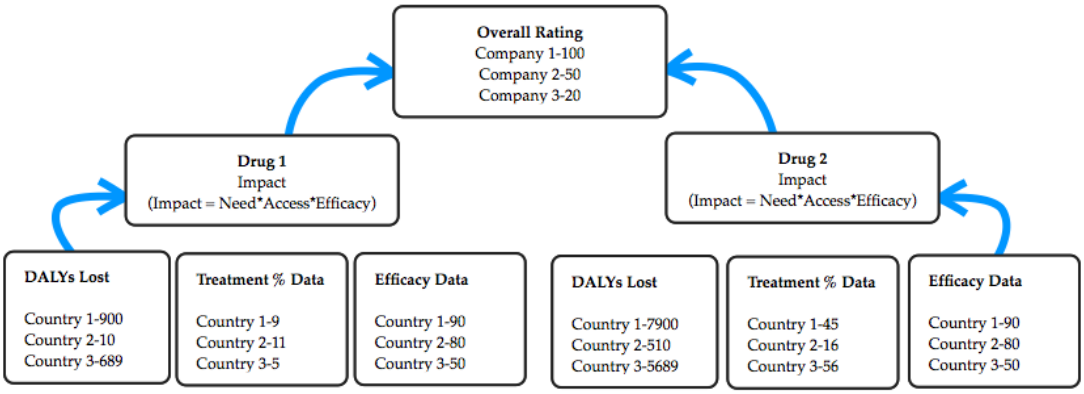
Colors in each region denote DALYs lost to TB: blue indicating a low number of DALYs lost and red indicating a high number of DALYs lost.

Sample Data: Multi Drug-Resistant Tuberculosis % Treatment Coverage



TB Treatment Efficacy





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.

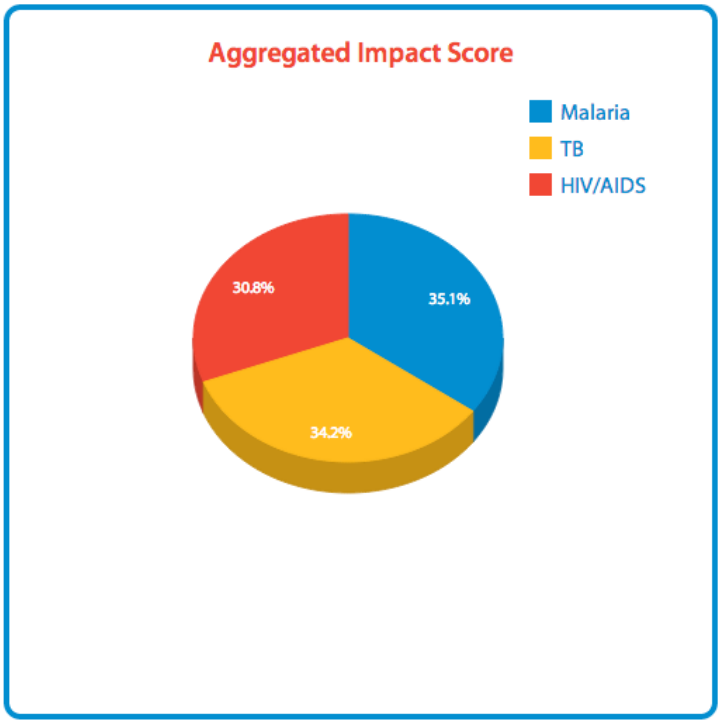
Because the point of the rating system is both to incentivize new innovation and to encourage companies to extend access on existing drugs globally, it is essential to update the model over time (e.g. when the next DALY estimates are released). Companies' scores will improve on the next version of the index insofar as they do something that reduces the burden of disease. Companies can create new efficacious drugs, come up with improvements on existing drugs, or increase access to treatment by reducing prices or increasing their drug donations, etc. Companies will get a lot more credit for widely disseminated drugs and those that are highly efficacious compared to drugs that fewer people can access or that are less effective. Companies focusing on the worst problems, i.e. the disease to which most DALYs are lost, will also get more credit, other things being equal. On the other hand, if a company's interventions are no longer used, e.g. because another company comes up with a better alternative or its interventions' efficacy falls a bit (e.g. due to rising resistance), its score will decline.

It is not a problem with the proposed index that the best available drugs for some diseases have very low efficacy. If the efficacy of HIV drugs was much greater than the efficacy of drugs for malaria, or TB, *and everything else was equal,* the Global Health Impact index would suggest that companies should focus on making HIV drugs first. The rationale for encouraging companies to focus more on some diseases than others is that the expected health impact of focusing on some just happens to be greater than the expected impact of focusing on other diseases. It is possible that companies will do better to make less effective, but highly accessible, drugs than those that are highly effective but (say) very expensive and, so, inaccessible. Of course, it is always true that companies can just be well-placed to work on some diseases as opposed to others, but it is not clear that a good index should reward them for just doing what they are good at if that does not really pay off in terms of global health impact. In any case, the difference in average drug efficacy for the diseases we are focusing on is not that great, so we do not need to consider the issue further here.

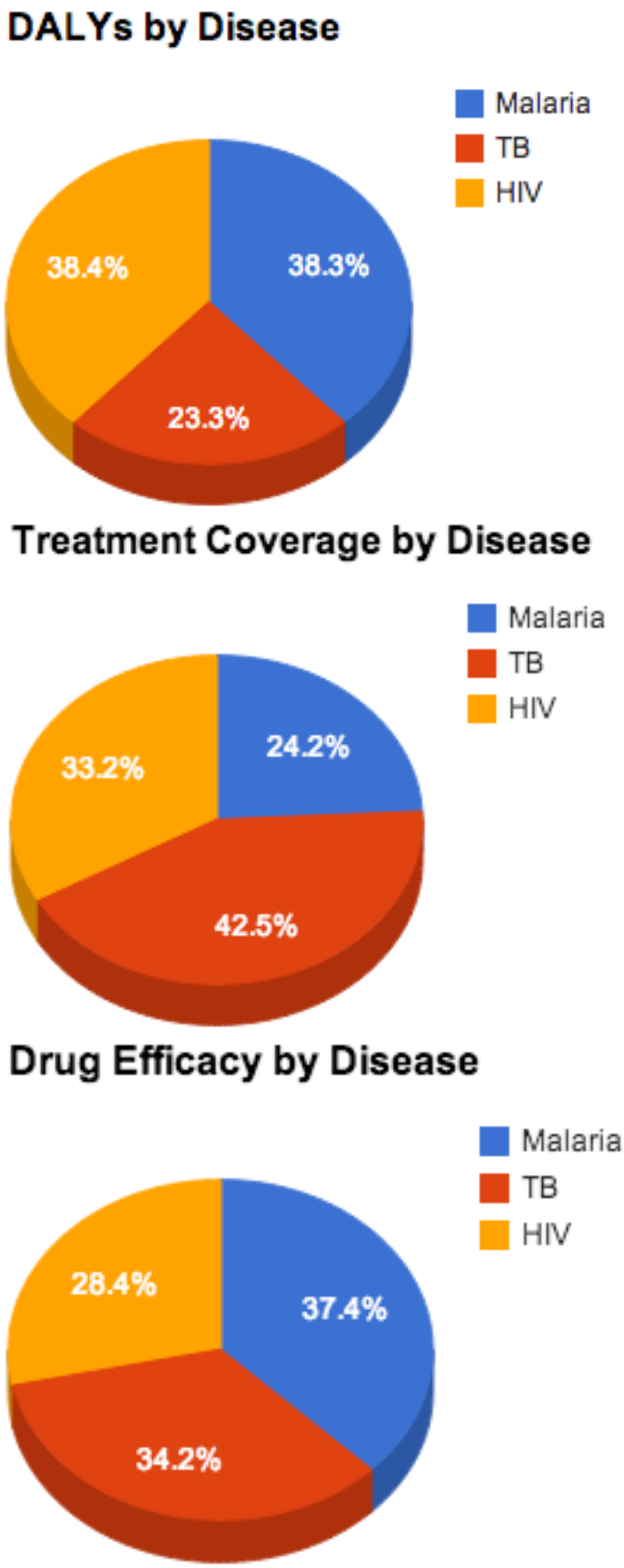
The Global Health Impact index is focused on evaluating companies' global health impacts in a rigorous way, and not on companies' efforts or policies, so companies' scores depend on many other factors besides

their innovations. These other factors include the nature of country-level health systems, inter- national aid efforts, and what other drugs are already around.. To see why, consider one concrete example. Suppose a company offers a new kind of product for a disease that requires expensive genetic testing and there are no programs designed to provide that testing or no agreed upon strategy for doing so. Even if the company makes their drug available for free, its score on the Global Health Impact index may be low because most countries do not have genetic testing in place to identify most of the patients who are candidates for their medicines. Its score may even be lower than a much less generous company's score if that company's drugs had a larger impact because diagnosing the diseases they address is much easier. Nevertheless, that company would get as much credit as its drugs have impact. The company can increase the credit it receives if it can also help people figure out if they have the disease so that more people receive treatment. The company could, presumably, do this in many ways. It might partner with organizations that help developing countries' health systems secure diagnostic services or come up with cheap ways of diagnosing patients that might use their drugs in the private sector, e.g., with something similar to the new home test kits for HIV available in the US.

Right now the impact of drugs for Malaria is most important in our model. There is a much larger need for drugs for both malaria and HIV than for TB, but many more people can access malaria drugs, and they are more efficaious, than drugs for HIV.



Percent Estimated DALYs Averted for Each Disease



Percent DALYs Lost by Disease, Relative Treatment Coverage Proportions, and Relative Efficacy Proportions

3. A Concrete Case: Malaria Example

It will help to consider a real example of how a company's score was calculated. Chongqing Tonghe Pharmaceutical Co. Ltd. is credited only for one anti-malarial: Dihydroartemisinin-piperaquine (DHA-PPQ). So its score is based entirely on DHA-PPQ's score. DHA-PPQ is a first-line drug in Viet Nam, so consider how its impact in Viet Nam was calculated. 63,901.40 DALYs were lost to malaria in Viet Nam in 2010.

About 75% of the malaria in Viet Nam was Plasmodium falciparum malaria, so we estimate that 75% of the 63,901.40—or 47,926.05—DALYs were lost to p. falciparum malaria. DHA-PPQ is used as the first-line treatment of Plasmodium falciparum malaria in Viet Nam.The WHO suggests that DHA-PPQ is 100% effective in Viet Nam. However, DHA-PPQ only has treatment coverage in Viet Nam of 2.6%. The impact of DHA-PPQ in Viet Nam, then, is DALYs * Coverage * Effectiveness. The estimated impact of DHA-PPQ for Viet Nam is (47,926.05 * 2.6% * 100%) = 1,246.08 DALYs saved. The above process was repeated for every country where DHA-PPQ was a first-line drug, so that an impact score for every country was obtained. To get the total impact score for Chongqing Tonghe Pharmaceutical Co. Ltd., we summed the scores for all of these countries. The total impact score for Chongqing Tonghe Pharmaceutical Co. Ltd. is 6,730.11 DALYs saved.

The models used to calculate TB and HIV are much more complex and, so, examples illustrating the necessary calculations for sample companies are relegated to the Appendices.

4. Improving the Index: Questions for Future Research

Further research might improve the model. The structure of the pharmaceutical market is complicated. Some companies have patented drugs that other companies really developed. Some have bought the rights to drugs others have patented. Often companies license out manufacturing and distribution of their drugs to other companies or enter into co-marketing agreements. Different indexes might rate manufacturers, distributors, and innovators. For now we focus on companies with patents on key medications so that the index can incentivize new drug development (see Appendix IV). Moreover, companies that develop a drug are often able to impact their drugs' accessibility. These companies usually have a lot of control over licensing co-marketing, distribution, and manufacturing rights. Taking into account side-effects associated with some drugs may be important in evaluating their impacts. Moreover, as discussed in the appendixes, it may be worth considering 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. Because good data on global health problems even for major diseases like malaria, TB, and HIV/AIDS is often sparse, it may be difficult to improve the model significantly right now. This suggests that it is essential to improve global disease surveillance efforts. Nevertheless, in some cases, it may be possible to:

- Improve our disease models to, for instance, 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 and treatment percentage estimates
- Include estimates of drug interactions/side effects

Sensitivity tests suggest, however, that many of the assumptions our model relies upon have little impact on the overall ranking of companies. We have tested 27 alternate specifications of the model, most either no effect on the rankings or only caused a ranking switch for two adjacent companies. Details of these sensitivity tests and some changes made to the model as a result are included in Appendix III.

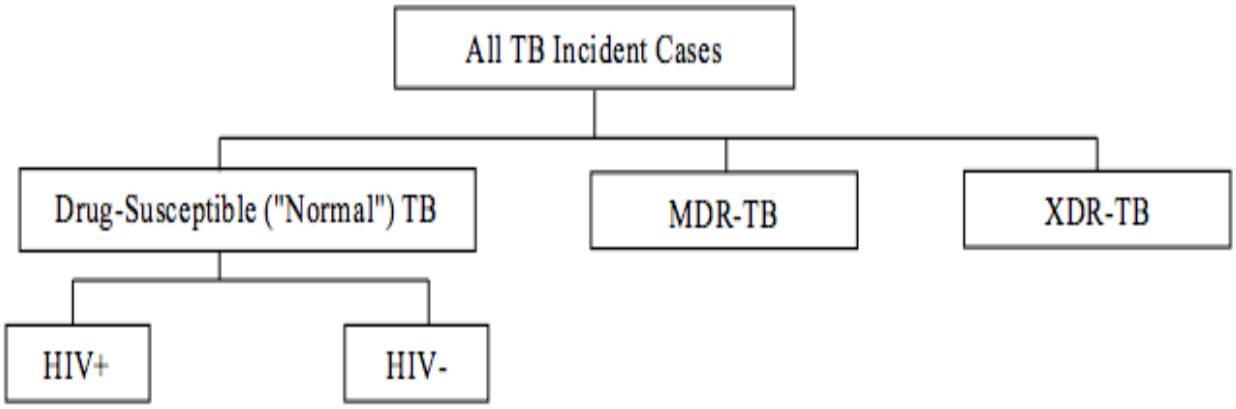
5. Conclusion

There are many difficult issues to resolve in designing a good model rating system for pharmaceutical companies' key innovations' impact on global health. It is possible to refine many of the assumptions the model relies upon further and to update the model as new data on need, access, and efficacy becomes available. One might also expand it in new directions to consider new drugs, diagnostics, vaccines or other diseases or to model the evolution of resistance rates and drug efficacy over time. Alternately, one could try to take into account side effects of the drugs or look at how they impact the transmission potential of each of the diseases. Nevertheless, the model presented here provides some essential information about companies' global health impacts and highlights the need to improve global disease surveillance mechanisms. A good rating system has the potential to foster great improvements to global health. Such a rating system should be of interest to policy makers, researchers, companies, investors, and consumers. It will, for instance, open the door to many new ways of incentivizing companies to have a greater impact on global health. Although this will not solve all of the health problems people face, it may help many people secure essential medicines that can save millions of lives every year.

Appendix I: TB Example

Calculating Pfizer's final impact score was a bit more difficult than calculating Chongqing's score for a few reasons. It makes four anti-TB drugs: Ethambutol, pyrazinamide, cycloserine, and PAS. ethambutol and pyrazinamide are used in combination with two other drugs (Isoniazid and Rifampicin) from other companies for treating (active) drug-susceptible TB. But ethambutol and pyrazinamide (along with rifampicin) are primarily used to prevent resistance from developing to isoniazid. So it is difficult to decide how to credit the different drugs in the combination and extract Ethambutol's and pyrazinamide's impact. A similar problem is also seen when attempting to credit Pfizer for cycloserine since it is used in different combination therapies for multi-drug-resistant (MDR)-, and extremely drug-resistant (XDR)-, TB). Moreover, for TB and HIV/AIDS it is 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 may develop, but protocols differ for different disease states and drugs.

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. Totally drug-resistant (TDR)-TB is excluded from the current model as, thus far, only a small number of TDR-TB cases have been reported.[27] 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 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. 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.[28]

A difficulty that arises with MDR-TB treatment is that different patients are resistant to different drugs. Protocols exist for which treatment to use depending on to which drugs the patient is resistant.[29] Once diagnostic susceptibility testing (DST) has been performed, and MDR-TB is confirmed, there are multiple possible regimens as indicated in the table below:

	Drug Resistance	Treatment Regimen
1	Resistant to isoniazid (H) in combination with rifampicin (R) or rifampicin and ethambutol (E)	Z + S + Lfx + Eto + Cs + PAS
2	Resistance to H+R+E+ pyrazinamide (Z)	S + Lfx + Eto + Cs + PAS
3	Resistance to any of the following: H+R+ streptomycin (S); H+R+E+S; or H+R+E+Z+S	Km + Lfx + Eto + Cs + PAS

According to the National Center for Biotechnical Information, 39.4% of recipients of drug susceptibility tests indicate multiple drug resistance. The resistance patterns are indicated in the following table:[30]

Drug Resistance	Portion of Total
Multidrug Resistance (total)	39.4%
H+R	7.1%
H+R+E	3.3%
H+R+S	11.0%
H+R+E+S	18.6%

Unfortunately, this data does not include pyrazinamide. Pyrazinamide resistance is difficult to test for, so many laboratories do not test for it.[31] Studies in South Africa, however, indicate resistance to pyrazinamide among MDR-TB cases of 42.25%.[32] Given that H+R+E+Z+S is a subset of the H+R+E+S resistance in the second table above, then, we use the figure from South Africa to estimate that resistance to H+R+E+Z+S = 18.6% * 42.25% = 7.86%. We estimate that the remainder, 10.74% (18.6% - 7.86%) of the population, is resistant to H+R+E+S but *not* Z. Similarly, we apply this percentage of 42.25% of those resistant to Z to the percentage of those resistant to H+R+E (3.3%) to get 1.39% resistant to H+R+E+Z and estimate that the remaining 1.91% are resistant to H+R+E, but *not* Z. Therefore, we estimate that resistances and the corresponding treatment regimens are as follows:

	Drug Resistance	Portion of all TB	Portion of MDR-TB[33]	Treatment Regimen[34]	Portion of MDR-TB treatment[35]
1	H+R	7.1%	18.02%	Z + S + Lfx + Eto + Cs + PAS	22.86%
	H+R+E, without Z	1.91%	4.84%		
2	H+R+E+Z	1.39%	3.54%	S + Lfx + Eto + Cs + PAS	3.54%

3	H+R+S	11.0%	27.92%	Km + Lfx + Eto + Cs + PAS	75.13%
	H+R+E+S without Z	10.74%	27.26%		
	H+R+E+Z+S	7.86%	19.95%		

Adjusted to 100%[36], the regimes are as follows:

	Treatment Regimen	Portion of total MDR-TB treatment
1	Z + S + Lfx + Eto + Cs + PAS	22.51%
2	S + Lfx + Eto + Cs + PAS	3.49%
3	Km + Lfx + Eto + Cs + PAS	74.00%

Each drug in each regimen is given equal weight in our model.[37]

The treatment regimen considered for XDR-TB consists of cycloserine, at least one injectable second-line agent, and one fluoroquinolone.[38]

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 above mentioned basis of our model, the first step in calculating Pfizer's impact score is as follows: Taking Botswana as an example country, we see that 18,661.80 DALYs were lost to TB in Botswana.[39] In 2010, 10,000 incident cases of TB were reported according to the WHO[40], 80% of registered cases were tested for HIV status, and 65.43% of TB cases with known HIV status were HIV positive.[41] 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 status, an estimate was derived. This was done by using the global average of 33% of TB cases with a known HIV status.[42] Given that the global average is 33%, and given that we only have data on a proportion of the countries, we derived the necessary average known HIV status for the remaining countries in order to reach the mean of 33%

The next step involves breaking down incident cases into Drug-Susceptible TB, MDR-TB, and XDR-TB. We start with MDR-TB first. The WHO provides data for:

(a) Estimated numbers of MDR-TB cases among notified new cases of pulmonary TB: 120 in Botswana

(b) Estimated number of MDR-TB cases among notified previously treated pulmonary TB cases: 29 in Botswana

(c) Estimated percentage of new TB cases with MDR-TB: 2.5% in Botswana

(d) Estimated percentage of previously treated TB cases with MDR-TB: 7% in Botswana.

Using this data, we determine:

(e) Estimated new cases (any type) = (a) / (c) = 120 / 2.5% = 4,800.00; and

(f) Estimated retreatment cases (any type) = (b) / (d) = 29 / 7% = 414.29

From this, we can calculate:

Overall percent MDR-TB among prevalent TB = [(a) + (b)] / [(e) + (f)]

= (120 + 29) / (4,800.00 + 414.29)

= 2.86%

This percentage is then multiplied by the prevalent cases: 2.86% * 8,100 = 231 MDR-TB cases needing treatment in Botswana in 2010.

The WHO provides data on the number of individuals treated per year. Based on 2010 WHO data, 92 individuals received MDR-TB treatment in Botswana. Our estimated treatment coverage, then, is the 92 individuals who received treatment divided by the 231 individuals needing treatment, or 39.75%.

To compute the DALYs lost to MDR-TB in Botswana, we use the same MDR-TB proportion of 2.86% of the total 18,661.80 DALYs due to TB of any type in Botswana to estimate that 533.27 DALYs were lost in 2010. From this, we then subtract the number of DALYs lost to XDR-TB cases (see below) to reach an estimate of actual DALYs lost to only MDR-TB of 485.27. Because treatment coverage for MDR-TB in Botswana is 39.75%, the impact of any MDR-TB regimen in Botswana, calculated by DALYs lost to MDR-TB * MDR-TB treatment coverage * efficacy of MDR-TB treatment, is 485.27% * 39.75% * 48% : 92.58 is the impact of MDR-TB treatment in Botswana.

For XDR-TB, we know that 9% of all MDR-TB cases are XDR-TB. Multiplying this XDR-TB proportion to the total number of MDR-TB cases in Botswana, we have 9.00% out of 231 MDR-TB cases (or about 21 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. Since 9.00% 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 9.00% of 533.27 DALYs lost to MDR-TB in Botswana in 2010, or 47.99 DALYs were lost to XDR-TB in Botswana. Efficacy of XDR-TB treatment is estimated at 20%. Thus the impact of XDR-TB treatment in Botswana in 2010 is approximately 47.99 DALYs lost * 43% treatment coverage * 20% efficacy = 4.13.

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 18,128.53. Previously, we calculated the number of HIV+ and HIV- cases among incident cases with known HIV status in Burkina Faso were 5,235 and 2,765 respectively (of 8,000 cases in total). This works out to 65.43% HIV+ and 34.57% HIV-. Thus our DALY breakdown is as follows:

TB/HIV+: 18,128.58 * 65.43% = 11,861.73

TB/HIV-: 18,128.58 * 34.57% = 6,266.80

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 65.9% for all cases. Estimated efficacy for TB/HIV+ treatment is 73% and that for TB/HIV- treatment is 87%. Thus, impact scores for each case are calculated by DALYs lost * treatment coverage * treatment efficacy:

TB/HIV+: 11,861.73 * 65.9% * 73% = 5,706.32

TB/HIV-: 6,266.80 * 65.9% * 87% = 3,592.94

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

TB Case		Impact Score
Drug-Susceptible ("Normal") TB	Latent TB/HIV+	5,706.32
	Active TB/HIV+	3,592.94
Multidrug-Resistant TB (MDR-TB)		92.58
Extensively Drug-Resistant TB (XDR-TB)		4.13

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

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

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

MDR-TB Treatment Regimens

A total of three MDR-TB regimens are considered in this model. As explained above, we estimate the percentage of people with MDR TB receiving each regimen using data based on resistance rates as described above. Within each regimen, we give each drug equal credit. The proportion of credit given to each drug in each of the three regimens is shown in the right column in the table below.

Pyrazinamide + Streptomycin + Levofloxacin + Ethionamide + Cycloserine + PAS	Drug Proportion of Regimen
Pyrazinamide	0.17
Streptomycin	0.17
Levofloxacin	0.17
Ethionamide	0.17
Cycloserine	0.17
PAS	0.17

Streptomycin + Levofloxacin + Ethionamide + Cycloserine + PAS	Drug Proportion of Regimen
Streptomycin	0.20
Levofloxacin	0.20
Ethionamide	0.20
Cycloserine	0.20
PAS	0.20

Kanamycin + Levofloxacin + Ethionamide + Cycloserine + PAS	Drug Proportion of Regimen
Kanamycin	0.20

Levofloxacin	0.20
Ethionamide	0.20
Cycloserine	0.20
PAS	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 Burkina Faso, we disaggregate the scores as follows:

TB Case		**Total Score**	**Score Per Drug**
Drug-susceptible ("Normal") TB	TB / HIV+	5,706.32	Rifampicin: 0.25 * 5,706.32 = 1,426.58 Isoniazid: 0.25 * 5,706.32 = 1,426.58 Ethambutol: 0.25 * 5,706.32 = 1,426.58 Pyrazinamide: 0.25 * 5,706.32 = 1,426.58
	TB / HIV-	3,592.94	Rifampicin: 0.25 * 3,592.94 = 898.24 Isoniazid: 0.25 * 3,592.94 = 898.24 Ethambutol: 0.25 * 3,592.94 = 898.24 Pyrazinamide: 0.25 * 3,592.94 = 898.24

Multidrug-Resistant TB (MDR-TB)	Resistant to isoniazid in combination with rifampicin or rifampicin and ethambutol	20.84[56]	Pyrazinamide: 0.17 * 20.84 = 3.54 Streptomycin: 0.17 * 20.84 = 3.54 Levofloxacin: 0.17 * 20.84 = 3.54 Ethionamide: 0.17 * 20.84 = 3.54 Cycloserine: 0.17 * 20.84 = 3.54 PAS: 0.17 * 20.84 = 3.54
	Resistance to isoniazid with rifampicin, ethamutol, and pyrazinamide	3.23	Streptomycin: 0.20 * 3.23 = 0.65 Levofloxacin: 0.20 * 3.23 = 0.65 Ethionamide: 0.20 * 3.23 = 0.65 Cycloserine: 0.20 * 3.23 = 0.65 PAS: 0.20 * 3.23 = 0.65
	Resistance to: isoniazid with rifampicin and streptomycin; isoniazid with rifampicin, ethamutol, and streptomcin; or resistance to isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin	68.51	Kanamycin: 0.20 * 68.51 = 13.70 Levofloxacin: 0.20 * 68.51 = 13.70 Ethionamide: 0.20 * 68.51 = 13.70 Cycloserine: 0.20 * 68.51 = 13.70 PAS: 0.20 * 68.51 = 13.70
Extensively Drug-Resistant TB (XDR-TB)		4.13	Cycloserine: 0.33 * 4.13 = 1.36 Kanamycin: 0.11 * 4.13 = 0.45 Amikacin: 0.11 * 4.13 = 0.45 Capreomycin: 0.11 * 4.13 = 0.45 Levofloxacin: 0.08 * 4.13 = 0.33 Moxifloxacin: 0.08 * 4.13 = 0.33 Gatifloxacin: 0.08 * 4.13 = 0.33 Ofloxacin: 0.08 * 4.13 = 0.33

An individual drug's score, then, is the sum of each of the proportional score of any regimen in which it is a part. Again, since this example is for Pfizer's impact score, we only focus on the drugs by this company: ethambutol, pyrazinamide, cycloserine and PAS. The impact score for ethambutol, pyrazinamide, cycloserine, and PAS in Botswana is simply the sum of individual scores in the table above that are associated with each drug respectively. The total score for Pfizer is the summation across all countries in the model, which sums up to 13,209,904.58 in all countries in the world.

Appendix II: HIV Example

Consider how we calculate Gilead Science's score. Gilead makes two antiretroviral drugs for HIV: Tenofovir and emtricitabine. Here we do not consider different disease states, and set aside questions about interactions between HIV drugs and others for a rough estimate of impact.

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.[57] 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 AIDS Medicine and Diagnostic Service survey.[58]

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
Botswana	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	Sri Lanka	Grenada
Congo	Sudan	Guyana
Gambia	Suriname	Honduras
Ghana	Swaziland	Nicaragua
Guatemala	Tanzania	Panama
India	Uganda	Paraguay
Iran	Ukraine	Peru
Kenya	United Arab Emirates	Trinidad and Tobago
Lesotho	Viet Nam	Uruguay
Madagascar	Yemen	
Malawi	Zambia	
Malaysia	Zimbabwe	
Mozambique		

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. Conveniently, the Global Health Data Exchange provides such age-specific DALYs informa-

tion.[59] Using Afghanistan as an example, 21,733.66 DALYs were lost by adults to HIV in 2010, and 2,307.78 were lost by children.[60]

The WHO provides data for numbers of individuals (all age groups) needing treatment and number of individuals (all age groups) receiving treatment.[61] Additionally, the same data is provided for children (<15) needing treatment and children receiving treatment.[62] From these numbers, the number of adults needing and receiving treatment can be easily calculated. In Afghanistan, for example, 1600 people (all age groups) need treatment, 550 of which are children. The number of adults needing treatment, then, is the remaining 1,050. Similarly, 46 people are receiving treatment, one of which is a child; the remaining 45, then, are adults. Treatment coverage in Afghanistan, then, is 4.29% for adults (45/1,050) and 0.18% for children (1/550). If country-specific treatment numbers are not provided, then numbers are calculated base on what would be necessary to reach regional averages.

The WHO provides information about what percentage of adults and children are taking first and second line regimens by country group in Group A and B countries. Here is the information for Group A countries.[63]

ADULTS	**Group A**
First-Line Regimens	97.10%
Second-Line Regimens	2.90%

CHILDREN	**Group A**
First-Line Regimens	96.80%
Second-Line Regimens	3.20%

We assume that the DALYs each regimen can recover are proportionate to their use in each population.

The next table lists the first and second line antiretroviral regimens and efficacy information for adults and children in each group.[64]

Antiretroviral Treatment Regimen Proportions and Efficacies[65]

Group A

ADULT First-Line Regimens	Proportion of Adult First-Line Regimens	Efficacy (%)
Stavudine + Lamivudine + Nevirapine	27.70%	69.65%
Zidovudine + Lamivudine + Nevirapine	26.80%	77.00%
Stavudine + Lamivudine + Efavirenz	14.00%	77.50%
Zidovudine + Lamivudine + Efavirenz	11.40%	72.03%
Tenofovir + Lamivudine + Efavirenz	10.60%	76.73%
Tenofovir + Emtricitabine +Efavirenz	3.50%	81.06%
Tenofovir + Lamivudine + Nevirapine	2.70%	75.00%
Tenofovir + Emtricitabine + Nevirapine	2.50%	76.70%
Others	0.80%	69.65%
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%	64.74%
Zidovudine + Lamivudine + Lopinavir/Ritonavir	12.70%	50.00%
Tenofovir + Emtricitabine + Lopinavir/Ritonavir	10.70%	67.00%
Zidovudine + Lamivudine + Tenofovir + Lopinavir/Ritonavir	5.50%	64.74%
Abacavir + Didanosine + Lopinavir/Ritonavir	4.80%	64.74%
Abacavir + Tenofovir + Lopinavir/Ritonavir	2.50%	64.74%
Stavudine + Lamivudine + Lopinavir/Ritonavir	1.90	60.50%
Abacavir + Lamivudine + Lopinavir/Ritonavir	1.10%	63.20%
Others	8.70%	64.74%
CHILDREN First-Line Regiments	**Proportion of Children First-Line Regimens**	**Efficacy (%)**

Stavudine + Lamivudine + Nevirapine	34.90%	100.00%
Zidovudine + Lamivudine + Nevirapine	20.70%	78.50%
Stavudine + Lamuviudine + Efavirenz	15.60%	77.50%
Zidovudine + Lamivudine + Efavirenz	7.20%	72.03%
Abacavir + Lamivudine + Efavirenz	6.20%	59.00%
Stavudine + Lamivudine + Lopinavir/Ritonavir	5.90%	62.00%
Abacavir + Lamivudine + Lopinavir/Ritonavir	5.80%	63.20%
Abacavir + Lamivudine + Nevirapine	1.70%	73.18%
Others	1.50%	73.18%

CHILDREN Second-Line Regiments	**Proportion of Children Second-Line Regimens**	**Efficacy (%)**
Abacavir + Lamivudine + Lopinavir/Ritonavir	26.20%	63.20%
Zidovudine + Didanosine + Lopinavir/Ritonavir	17.20%	65.34%
Abacavir + Didanosine + Lopinavir/Ritonavir	14.80%	65.34%
Zidovudine +Lamivudine + Lopinavir/Ritonavir	12.30%	50.00%
Zidovudine + Didanosine + Efavirenz	6.60%	65.34%
Stavudine + Lamivudine + Lopinavir/Ritonavir	4.60%	60.50%
Tenofovir + Lamivudine + Lopinavir/Ritonavir	2.00%	83.00%
Zidovudine + Abacavir + Lamivudine + Lopinavir/Ritonavir	1.60%	70.00%
Stavudine + Lamivudine + Abacavir	1.40%	65.34%
Others	13.30%	65.34%

Group B

ADULT First-Line Regimens	**Proportion of Adult First- Line Regimens**	**Efficacy (%)**

Zidovudine + Lamivudine + Efavirenz	42.50%	82.00%
Zidovudine +Lamivudine + Lopinavir/Ritonavir	13.60%	50.00%
Zidovudine + Lamivudine + Nevirapine	12.00%	65.33%
Zidovudine + Lamivudine + Atazanavir/Ritonavir	6.40%	72.78%
Tenofovir + Emitricitabine + Efavirenz	6.20%	83.87%
Abacavir + Lamivudine + Efavirenz	2.60%	71.00%
Stavudine + Lamivudine + Nevirapine	2.10%	79.77%
Stavudine + Lamivudine + Efavirenz	1.80%	77.50%
Others	12.90%	72.78%

ADULT Second-Line Regimens	**Proportion of Adult Second-Line Regimens**	**Efficacy (%)**
Tenofovir + Lamivudine + Efavirenz	18.10%	76.73%
Tenofovir + Lamivudine + Lopinavir/Ritonavir	16.60%	83.00%
Tenofovir + Lamivudine + Atazanavir/Ritonavir	13.40%	77.00%
Zidovudine + Lamivudine + Lopinavir/Ritonavir	3.90%	50.00%
Zidovudine + Lamivudine + Tenofovir + Lopinavir/Ritonavir	3.00%	68.75%
Stavudine + Lamivudine + Efavirenz	2.60%	77.50%
Stavudine + Lamivudine + Lopinavir/Ritonavir	2.20%	59.00%
Tenofovir + Lamivudine + Nevirapine	1.70%	58.00%
Zidovudine + Lamivudine + Tenofovir + Atazanavir/Ritonavir	1.40%	68.75%
Others	37.00%	68.75%

CHILDREN First-Line Regiments	**Proportion of Children First-Line Regimens**	**Efficacy (%)**

Zidovudine + Lamivudine + Efavirenz	32.10%	72.35%
Zidovudine + Lamivudine + Lopinavir/Ritonavir	26.70%	50.00%
Zidovudine + Lamivudine + Nevirapine	17.50%	78.50%
Zidovudine + Lamivudine + Nelfinavir	3.50%	66.95%
Zidovudine + Didanosine + Lopinavir/Ritonavir	3.30%	66.95%
Zidovudine + Didanosine + Efavirenz	2.60%	66.95%
Others	14.40%	66.95%

CHILDREN Second-Line Regiments	**Proportion of Children Second-Line Regimens**	**Efficacy (%)**
Zidovudine + Lamivudine + Nevirapine	32.10%	72.03%
Zidovudine +Lamivudine + Lopinavir/Ritonavir	26.70%	50.00%
Zidovudine + Lamivudine + Nevirapine	17.50%	78.50%
Zidovudine + Lamivudine + Nelfinavir	3.50%	66.84%
Zidovudine + Lamivudine + Lopinavir/Ritonavir	3.30%	66.84%
Zidovudine + Lamivudine + Efavirenz	2.60%	66.84%
Others	14.40%	66.84%

In each of these drug regimens, we give equal weight to each of the drugs that make up the regimen. In first-line adult regimens in A countries, for example, efavirenz is credited with 1/3 of the proportion credited to the regimen tenofovir + lamivudine + efavirenz: (1/3) * 10.60% = 3.53%.

Let us look, then, at how Gilead's score is calculated in Afghanistan. In Afghanistan 21,733.66 DALYs were lost in the adult sub-population and 2,307.78 in the child-sub-population in 2010.[66] Afghanistan is classified as an "A" country by the WHO, so its treatment proportions and the efficacies of specific regimens are represented by the "Group A" section of the chart above. Using our basic formula of Need * Efficacy * Coverage, we can calculate tenofovir's and emtricitabine's impact in the various regimens of which they are a part. Let us look at how we calculate tenofovir's score first.

We will begin by calculating the impact of tenofovir in adult first-line treatment regimens. The first adult first-line treatment regimen containing tenofovir is "Tenofovir + Lamivudine + Efavirenz" in adult first-line treatment. Recall that adult DALYs in Afghanistan amount to 21,733.66, and treatment coverage for adults in Afghanistan was calculated to be 4.29% (see above). These are the "Need" and "Treatment Percentage" factors in our equation. We then multiply this by the percent of adults that receive first-line treatment (97.1%), the proportion of those adult first-line treatments that receive Tenofovir + Lamivudine + Efavirenz (10.60%), and the efficacy of that treatment (76.73%). Then, since tenofovir is one of three drugs in the drug regimen, it receives 1/3 of this impact score: 21,733.66 * 4.29% * 97.1% * 10.60% * 76.73% * (1/3) = 24.52. This is then repeated for each regimen of which tenofovir is a part in adult first-line treatment regimens in WHO-classified "A" countries since Afghanistan is an A country:

- Tenofovir + Emtricitabine +Efavirenz:

21,733.66 * 4.29% * 97.10% * 3.50% * 81.06% * (1/3) = 8.55

- Tenofovir + Lamivudine + Nevirapine:

21,733.66 * 4.29% * 97.10% * 2.70% * 75.00% * (1/3) = 6.10

- Tenofovir + Emtricitabine + Nevirapine:

21,733.66 * 4.29% * 97.10% * 2.50% * 76.70% * (1/3) = 5.78

And adult second-line treatment regimens in WHO-classified "A" countries that contain tenofovir are:

- Tenofovir + Lamivudine + Lopinavir/Ritonavir:

21,733.66 * 4.29% * 2.90% * 27.10% * 83.00% * (1/3) = 2.03

- Tenofovir + Emtricitabine + Lopinavir/Ritonavir:

21,733.66 * 4.29% * 2.90% * 10.70% * 67.00% * (1/3) = 0.65

- Zidovudine + Lamivudine + Tenofovir + Lopinavir/Ritonavir:

21,733.66 * 4.29% * 2.90% * 5.50% * 64.74% * (1/4) = 0.24

- Abacavir + Tenofovir + Lopinavir/Ritonavir:

21,733.66 * 4.29% * 2.90% * 2.50% * 64.74% * (1/3) = 0.15

And children second-line treatment regimens in WHO-classified "A" countries contain tenofovir are:

- Tenofovir + Lamivudine + Lopinavir/Ritonavir:

2,307.78 * 0.18% * 3.2% * 2.00% * 83.00% * (1/3) = 0.00.

The overall impact for tenofovir in Afghanistan, then, is:

24.52 + 8.55 + 6. 10 + 5.78 + 2.03 + 0.65 + 0.24 + 0.15 + 0.00 = 48.02.

This same procedure is followed for emtricitabine in adult first-line treatment regimens in WHO-classified "A" countries:

- Tenofovir + Emtricitabine +Efavirenz:

21,733.66 * 4.29% * 97.10% * 3.50% * 81.06% * (1/3) = 8.55

- Tenofovir + Emtricitabine + Nevirapine:

21,733.66 * 4.29% * 97.10% * 2.50% * 76.70% * (1/3) = 5.78

And in adult second-line regimens in WHO-classified "A" countries:

- Tenofovir + Emtricitabine + Lopinavir/Ritonavir:

21,733.66 * 4.29% * 2.90% * 10.70% * 67.00% * (1/3) = 0.65

The overall impact for emtricitabine in Afghanistan, then, is: 8.55 + 5.78 + 0.65 = 14.98.

The overall impact for Gilead in Afghanistan is the sum of the impacts of tenofovir and emtricitabine: 48.02 + 14.98 = 63 DALYS averted. When this is performed for every country, the overall impact of Gilead on HIV is 2,006,033.09.

Appendix III: Sensitivity Analyses

We report below the results of 27 sensitivity analyses to test the stability of the rating model to key assumptions and methods. Of these, 10 caused no change whatsoever in overall rank. An additional 10 saw only two degrees of change, wherein two companies' positions flipped in ranked position. Only 7 saw more than these two degrees of change. The results of each test follow.

Test #2:
Assumption tested: In the malaria calculations, average global efficacy of a drug is used as fallback data for that drug if efficacy data is not available for a country. Here, we test using maximum or minimum treatment efficacy for the relevant drugs instead of the average.
Response: Minimal changes in score were observed, but no change in overall ranking occurred when using either maximum or minimum treatment efficacy as fallback data points.

Test #5:
Assumption tested: We assumed the proportion of total TB DALYs lost to MDR-is equal to the proportion of total TB cases that are MDR-TB cases.
Response: The model is stable if we attribute up to 59% fewer DALYs to MDR-TB than the corresponding proportion of overall TB cases that are MDR-TB. Similarly, the model is stable with up to a 686% increase in DALYs attributable to MDR-TB than the proportion of overall TB cases. Outside of this range, two companies flip. An additional flip in company rankings is seen at a 72% decrease in the proportion of DALYs in relation to the proportion of MDR-TB cases.

Test #6:
Assumption tested: Sources indicated that MDR-TB treatment is 48% efficacious. We assume this applies to all countries.
Response: The model shows no change in overall rank for MDR-TB treatment efficacy between 13% and 100%. At 13%, there is a flip in company rankings.

Test #8:
Assumption tested: Global XDR-TB treatment is estimated at 43%. Here, we test the impact of greater or lesser XDR-TB treatment percentages.
Response: The model is stable with treatment percentages for XDR-TB between 0% and 100%.

Test #9:
Assumption tested: We assume that the proportion of DALYs attributable to XDR-TB is equal to the proportion of XDR-TB cases among MDR-TB cases. Here we test attributing a greater or lesser proportion of DALYs to XDR-TB than the proportion of XDR-TB cases.
Response: The model is stable with up to a 224% greater proportion of DALYs attributable to XDR-TB than the proportion of cases that are XDR-TB. Beyond that, a flip is seen in company rank. No decrease in the proportion of DALYs attributable to XDR-TB sees a change in ranking.

Test #10:
Assumption tested: XDR-TB treatment efficacy is estimated at 20%. Here, we test the impact of greater or lesser XDR-TB treatment efficacy.
Response: Model is stable with XDR-TB treatment efficacy between 0% and 65%. At 65%, a flip in company rank is observed. No further change in ranking is observed until 87%, at which point an additional

four companies have observed changes in ranking.

Test #12:
Assumption tested: Treatment coverage for "normal" TB is estimated to be 65.9%. Here, we test the impact of increasing or decreasing this estimate of treatment coverage.
Response: Rankings are stable with estimated treatment coverage for "normal" TB between 44% and 68%. Outside of this range flips in ranking are observed between two companies. Additional flips in ranking are observed at 75% and 37%.

Test #16:
Assumption tested: For HIV, the proportion of DALYs recovered due to first-, second-, or third-line treatment is assumed to be equivalent to the proportion of treatments that are first-, second-, or third-line. Here we test extending a greater proportion of DALYs to either first- or second- and third-line treatments.
Response: Model is stable with the proportion DALYs being recovered due to second- and third-line treatment being up to 515% of the proportion of treatment that is second- and third-line. At 516%, a flip in ranking is observed between two companies. Reducing DALYs recovered due to 2nd- and 3rd-line treatment was stable until 34%, at which point a flip in ranking was observed.

Test #17:
Assumption tested: The WHO will occasionally indicate TB incidence in a given country of "<10". When this is the case, we have estimated the incidence of TB within that country as 10 cases. Setting the estimated incidence of TB in these countries at 0
Response: The test caused no change in ranking.

Test #18:
Assumption tested: For HIV, the number needing treatment—both overall (for adults and children) and for children only—is given as a range. We take the mean of the range. Here we test using either the upper or lower bound.
Response: No change in company ranking resulted.

Test #19:
Assumption tested: WHO data indicates some countries have no HIV+ patients among those with TB. Here we see what happens when we assume there are some cases in these countries.
Response: Assuming the average number of HIV+ cases in all countries with zero reported HIV+ caused no change in ranking.

Test #20:
Assumption tested: Treatment regimen for XDR-TB consists of: (1) Cycloserine, (2) an injectable 2nd-line agent, and (3) one fluoroquinolone. Each of these is given equal weight in estimating impact of the treatment regimen. Here, we test giving these three components of the regimen different weights.
Response: The model is stable from 0% to 100% of the weight given to cycloserine.

Test #22:
Assumption tested: Assumption that where ACT coverage exists within a country but no first-line drug is specified, each of the ACTs in our model could eliminate 1/11th of the possible DALYS lost to p. Falciparum malaria in the county. Here, we test not giving any of the ACTs any credit in these countries.

Response: No change in ranking is observed.

Test #25:
Assumption tested: Currently, if efficacy for a particular drug regimen as applied to a specific subgroup of individuals (e.g. first-line adult treatment) is not available, we will use average efficacy for that drug among all subjects. If this data does not exist, we will use the average efficacy for that subgroup of individuals. Here, instead of first turning to average efficacy of the drug for all subjects, we turn to average efficacy for that subgroup.
Response: No change in ranking is observed.

Test #26:
Assumption tested: For malaria efficacy estimates we use data only from the 2010 World Malaria Report. In this test, we include missing data points from older reports.
Response: No change in ranking is observed.

Test #28:
Assumption tested: Proportion of DALYs that could be saved by a particular treatment regimen in a country when there are multiple malaria treatments within a country is currently divided by the number of malaria treatments. Here, we instead calculate the percent of countries wherein each treatment regimen is used. In a country with multiple drug regimens, each drug regimen is credited with the its percentage divided by the total of the percentages of all drugs present (e.g. if two drugs are used in a country, drug A and drug B, and drug A is used in 25% of countries and drug B in 50%, drug A is credited with treating 25% / (25% + 50%) of the DALYs).
Response: Six companies saw changes in ranking.

Test #29:
Assumption tested: The model extends information on HIV WHO group ("A" or "B") to countries that are not classified as such by the WHO. Extrapolated "A" and "B" status is decided by region. Here, we test excluding these countries when calculating either just HIV treatment impact or impact of treatment for all diseases (malaria, TB, HIV).
Response: Excluding countries with missing data in HIV only resulted in change in ranking for five different companies. If these countries were excluded from all disease models, changes in ranking occurred for eight companies.

Test #31:
Assumption tested: The model uses DALYs to calculate impact scores. Here, we test using mortality data instead.
Response: Ten companies see a change in ranking when mortality is used instead of DALYs.

Test #33:
Assumption tested: Impact scores are included for countries of all incomes. Here we test excluding high- and upper middle-income countries, either from HIV alone or from all disease types (malaria, TB, HIV).
Response: When excluding high- and upper-middle income countries from HIV, three companies had a change in ranking. The same three companies had a change in rank when excluding high- and upper-middle income countries from all disease impacts.

Test #34:
Assumption tested: In the model the amount of credit given to each MDR-TB treatment regimen is inversely proportional to the resistance to those drugs. Here, we test giving each MDR-TB treatment regimen equal weight.

Response: No change in ranking observed when giving each MDR-TB treatment regimen equal weight instead of weighting each in inverse proportion to the resistance exhibited to that regimen.

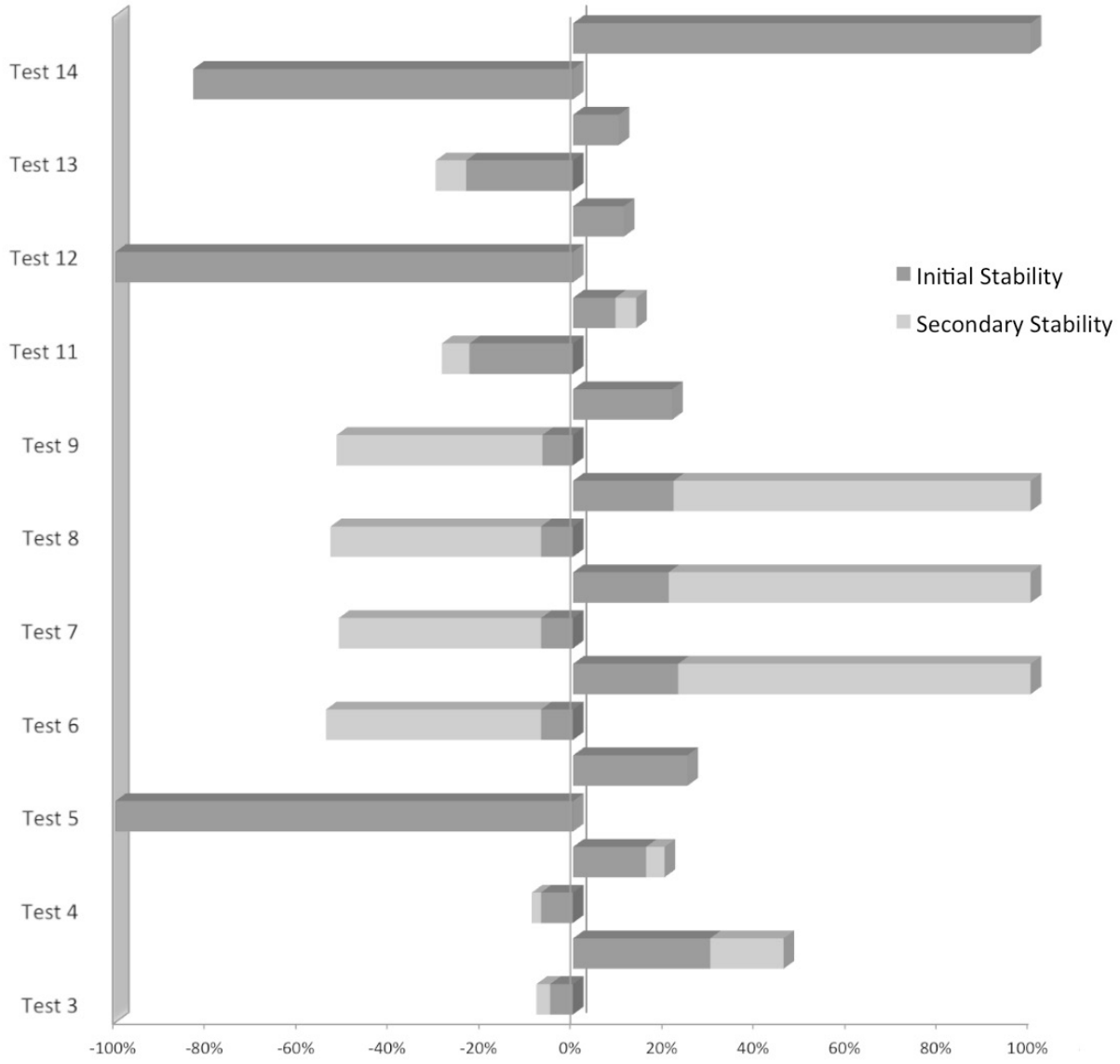
Test #38:
Assumption tested: The four drugs in the standard TB regimen receive equal weight. Here, we test modifying the proportion given to isoniazid, and dividing the remainder equally between rifampicin, ethambutol, and pyrazinamide.
Response: Isoniazid normally receives 25% of the impact of the standard regimen. This is stable between 23% and 29%. Outside of those bounds, a flip in company ranking is observed.

Test #39:
Assumption tested: TB/HIV+ treatment efficacy is estimated at 73%. Here, we test the impact of increasing or decreasing the estimate of treatment efficacy.
Response: The model is stable with TB/HIV- treatment efficacy between 0% and 91%. At 91%, a flip in rank is observed.

Test #40:
Assumption tested: TB/HIV- treatment efficacy is estimated at 87%. Here, we test the impact of increasing or decreasing this estimate of treatment efficacy.
Response: The model is stable with estimated TB/HIV- treatment efficacy between 55% and 90%. Setting efficacy outside of this range saw a flip in ranking between two companies. No further flip is seen with efficacy of up to 100%, but a further flip is seen below 44%.

Test #41:
Assumption tested: Survey data is used for ACT treatment coverage for malaria. If country-specific survey data is not available, then the regional average of available data is used. If no data is available for the region, then the global average is used. Here, we perform three tests: (a) use country-specific survey data first for Malaria treatment efficacy, then global average survey data as fallback (rather than region-specific); (b) use country-specific survey data first, then WHO data if available, then average of all countries where those two data points are available; and (c) use only WHO data--country-specific where available, then average where not.
Response: Each of these tests resulted in one flip in company ranking.

Initial and Secondary Stability



Percent Change in Proportion Associated with Assumption:
Graph Illustrates by What Proportion We Can Change the Assumption until the First (Dark Grey) and Second (Light Grey) Flip in Company Ranking Occurs

Appendix IV: Drug Accreditation

Disease	Drug	Abbreviation	Company	Reference
HIV	Abacavir	ABC	ViiV Healthcare/ GlaxoSmith-Kline	Abacavir was formerly known as 1492u89.[68] The first patent for 1492u89 was by The Wellcome Foundation Limited.[69] The Wellcome Foundation Limited was merged with Glaxo in 1995 to form Glaxo Wellcome.[70] Glaxo Wellcome then merged with SmithKline Beecham in January 2000 to form GlaxoSmithKline.[71] [72] ViiV was created in 2009 as a joint venture between GlaxoSmithKline and Pfizer to take over their HIV operations.[73]
	Atazanavir/Ritonavir	ATV/r	Novartis; Abbott Pharmaceuticals	The earliest patent for Atazanavir, an antiretroviral drug used in HIV/AIDS treatment, was by Novartis in 1995 (Ciba-Geigy, at the time).[74] Ritonavir was first patented by Abbott Laboratories in 1993.[75]
	Didanosine	ddl	Bristol Myers Squibb	Didanosine was developed in the National Cancer Institute (NCI) by Samuel Broder, Hiroaki Mitsuya, and Robert. Given that the NCI cannot market a product, Bristol-Myers Squibb was awarded a ten-yaer exclusive license to market and cell ddl as Videx® tablets by the National Institute of Health.[76]
	Efavirenz	EFV	Merck	First patented by Merck in 1996.[77]
	Emtricitabine	FTC	Gilead Sciences, Inc.	Emtricitabine was first developed by scientists at Emory University.[78] Gilead subsequently paid $525 million for the royalties due to Emory for the drug.[79]
	Lamivudine	3TC	Shire Pharmaceuticals	IAF Biochem first patented Lamivudine in Patent Number 5047407.[80] IAF subsequently changed its name to Biochem Pharma, which was then merged with Shire Pharmaceuticals in 2000.[81]
	Lopinavir with a ritonavir boost	LPV/r	Abbot Laboratories	Patent Number 5541206.[82]
	Nelfinavir	NFV	ViiV Healthcare	Nelfinavir was first developed by the Agouron Institute.[83] Agouron was sold to Warner Lambert in 1998, which subsequently merged with Pfizer.[84] ViiV was created in 2009 as a joint venture between GlaxoSmithKline and Pfizer to take over their HIV operations (see above reference, Abacavir).
	Nevirapine	NVP	Boehringer Ingelheim	Patent Number EP 0667348.[85]
	Stavudine	d4T	Bristol Myers Squibb	Patent Number 5539099.[86]
	Tenofovir	TDF	Gilead Sciences, Inc.	Tenofovir was patented by Gilead Sciences, Inc. in 1998 (filed in 1996).[87]
	Zidovudine	AZT	ViiV	Glaxo filed the first patent for zidovudine in 1992. Through a series of mergers, Glaxo is now GlaxoSmithKline (see abacavir, above). ViiV was created in 2009 as a joint venture between GlaxoSmithKline and Pfizer to take over their HIV operations (see above reference, Abacavir).

Disease	Drug	Abbreviation	Company	Reference
TB	Amikacin	Amk	Bristol Myers Squibb	Patent Number 4206116 (about the combination of amikacin and penicillin) references amikacin as "those pharmaceutically acceptable acid addition salts disclosed in U.S. Pat. No. 3,781,268 as being included within the scope of the invention claimed therein." Patent 3,781,268 was issued to Bristol Myers Squibb in 1973.
	Capreomycin	Cm	Eli Lilly	Capreomycin was originally isolated by Eli Lilly & Co. in 1961.
	Cycloserine	Cs	Pfizer, Inc.	Patent Gilbert M. Shull et al. first applied for a patent for Cycloserine and the production thereof in 1952 for Pfizer.
	Ethambutol	E	Pfizer, Inc.	The earliest patent for Ethambutol was by the American Cyanamid Company, filed on August 1, 1974 and issued March 16, 1976. American became a subsidiary of American Home Products Corp. in 1995. American Home Products eventually changed its name to Wyeth, and Wyeth was subsequently acquired by Pfizer.
	Ethionamide	Eto	Sanofi	The earliest patent for Ethionamide dates to 1959 (filed 1957) by Chimie et Atomistique. The last patent that belongs to Chimie et Atomistique is from 1962. However, it seems that Francois Albert created the pharmaceutical company "Theraplix (via business at Chimie et Atomistique). Credit for ethionamide going to Theraplix is reinforced by information found in the book Drug Discovery: A History: "The Theraplix company in Paris subsequently introduce ethionamide, but it is now rarely used." Theraplix was taken over by Rhône Poulenc in 1956, and this is now part of Sanofi.
	Gatifloxacin	Gfx	Kyorin Pharmaceutical Co., Ltd.	Patent Number 5880283.
	Isoniazid	H	Hoffman La-Roche	The earliest patent for Isoniazid (formerly isonicotinylhydrazine) is by Hoffman La Roche in 1952. Hoffman La Roche's holding company is Roche Holding, AG.

TB	Kanamycin	Km	Bristol Myers Squibb	Patent Number EP 0525588.
	Levofloxacin	Lfx	Daiichi Sankyo	Levofloxacin was developed by Daiichi and approved by the FDA in 1996.
	Moxifloxacin	Mfx	Bayer	Patent Number 5607942.
	Ofloxacin	Ofx	Daiichi Sankyo	Ofloxacin was first patented by Daiichi Pharmaceutical Co., Ltd. in 1980. Daiichi has since merged with Sankyo Co., Ltd. to form Daiichi Sankyo Co., Ltd.
	PAS	PAS	Pfizer	Jorgen Lehmann developed PAS (4-aminosalicylic acid) while working with Ferrosan. Ferrosan received the first patent for PAS in 1948. Ferrosan is now part of Pfizer.
	Pyrazinamide	Z	Pfizer	The earliest patent for pyrazinamide was granted in 1954 (filed in 1952) by the American Cyanamid Company, which was merged with American Home Products in 1994. This subsequently changed its name to the Wyeth Corporation, and then merged with Pfizer in 2009.
	Rifampicin	R	Sanofi	The earliest patent for Rifampicin was filed in 1965 by Gruppo Lepetit , a subsidiary of Sanofi.
	Streptomycin	S	Merck	Reference: Rutgers developed with Merck funding and they got a license for marketing the drug Patent Number 2449866.

Disease	Drug	Abbreviation	Company	Reference
Malaria	Artemether- Lumefantrine	AL	Novartis	Novartis first patented AL. It sells the drug under the trade name Coartem.
	Artesunate + Amodiaquine	AS + AQ	Sanofi	Robert Sauerwein credits Sanofi for ASAQ in multiple articles. Richerd Haynes also credits Sanofi for ASAQ. DNDi also credits Sanofi for ASAQ. The first patent for ASAQ seems to be one filed in 1988 by Hoechst. The patent concerns "combinations of the antimalarials artemisinin, dihydroartemisinin, arteether, artemether, artesunate or other artemisinin derivatives with one or more of the antimalarials chloroquine, 10-O-methylfloxacrine, quinine, mefloquine, amodiaquine, pyrimethamine, sulfadoxine and primaquine. Synergistic effects are achieved on treatment of mammals, including humans, with subcurative doses of the individual substances." Hoechst is now part of Sanofi.
	Artesunate + Mefloquine	AS + MQ	Public Sector – Military	According to Doctors Without Borders, "ASMQ was developed in the public sector, will not be patented and therefore can be available as a low cost generic immediately."
	Artesunate + Sulfadoxine-Pyrimethamine	AS + SP	Sanofi	The first patent for AS+SP seems to be one filed in 1988 by Hoechst AG. The patent concerns "combinations of the antimalarials artemisinin, dihydroartemisinin, arteether, artemether, artesunate or other artemisinin derivatives with one or more of the antimalarials chloroquine, 10-O-methylfloxacrine, quinine, mefloquine, amodiaquine, pyrimethamine, sulfadoxine and primaquine. Synergistic effects are achieved on treatment of mammals, including humans, with subcurative doses of the individual substances." Hoechst is now part of Sanofi.
	Dihydroarteminisin-Piperaquine	DHA-PPQ	Chongqing Tonghe Pharmaceutical Co. Ltd	A patent for Dihydroartemisinin-Piperaquine for use in treatment of Malaria was first applied for by Chongqing Tonghe Pharmaceutical Co., Ltd in 2000 (US Patent issued 2010).

Note

1. 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, Nick Hall, Angelina Sung, Nathan Lubchenco, George Nardi, Matt Wilson, and Saptarshi Ghose. The author would also like to thank Academics Stand Against Poverty, Binghamton University, Stanford University, Carnegie Mellon University, the Falk and Berkman Foundation, and Justitia Amplificata for their support during various stages of model construction. Baruch Fishoff, Nathaniel Lipkus, Paul Wise, Rajesh Gupta, Clifford Samuel, Briggs Morrison, Art Small, Mark Roberts, Eran Ben-David and others (acknowledged in previous papers on this proposal) also deserve sincere thanks.
2. Center for Disease Control (CDC). 2005. "World TB Day, March 24th 2005." Division of Tuberculosis Elimination. CDC: Atlanta. Accessed 1/31/14. Available at: <http://www.cdc.gov/nchstp/tb/WorldTBDay/2005/resources_progress_elimination.htm>. See also: UNAIDS. 2004. "World AIDS Day 2004: Women, Girls, HIV and AIDS," AIDS Epidemic Update. UNAIDS: Geneva. Accessed 1/31/14. Available at: <http://www.unaids.org/wad2004/report.html>. UNICEF. 2005. "Millennium Development Goals: Combat AIDS/HIV, Malaria, and other Diseases. UNICEF: Geneva. Accessed 2/4/14. Available at: <http://www.unicef.org/mdg/disease.html>.
3. The World Bank. 2013. "How We Classify Countries," The World Bank: Washington D.C. Accessed 1/5/13. Available at: < http://data.worldbank.org/about/country-classifications>.
4. . de Francisco, Andres and Matlin, Stephen eds. 2006. "Monitoring Financial Flows for Health Research 2006: The Changing Landscape of Health Research for Development," Global Forum for Health Research: Geneva. Accessed 2/4/14. Available at < http://www.isn.ethz.ch/Digital-Library/Publications/Detail/?ots591=0c54e3b3-1e9c-be1e-2c24-a6a8c7060233&lng=en&id=46893 >.
5. Bill and Melinda Gates Foundation. 2012. "About the Foundation," Bill and Melinda Gates Foundation: Seattle. Accessed 12/29/12. Available at: < http://www.gatesfoundation.org/about/Pages/overview.aspx>.
6. Ridley, David. 2012. "Priority Review Voucher," Duke University: Durham. Accessed 12/29/12. Available at: <https://faculty.fuqua.duke.edu/~dbr1/voucher/>.
7. Lee, B. and Burke, D. 2010. "Constructing Target Product Profiles (TPPS) to Help Vaccines Overcome Post-Approval Obstacles." Vaccine 28(16), 2806–2809.
8. The Global Fund. 2012. "The Global Fund to Fight AIDs, Tuberculosis and Malaria," The Global Fund: Geneva. Accessed 12/29/12. Available at: < http://www.theglobalfund.org/en/>.
9. World Trade Organization. 2006. "Compulsory Licensing of Pharmaceuticals and TRIPS," World Trade Organization: Geneva. Accessed 12/29/12. Available at: <http://www.wto.org/english/tratop_e/trips_e/public_health_faq_e.htm>.
10. International AIDS Vaccine Initiative. 2012. "Information Center," International AIDS Vaccine Initiative: New York. Accessed 12/29/12. Available at: <http://www.iavi.org/Information-Center/Publications/Pages/About-the-International-AIDS-Vaccine-Initiative.aspx>.
11. The Initiative on Public-Private Partnerships for Health (IPPPH). 2004. "Impact of Public-Private Partnerships Addressing Access to Pharmaceuticals in Selected Low and Middle Income Countries: A Synthesis Report From Studies in Botswana, Sri Lanka, Uganda and Zambia," IPPPH: Switzerland. Accessed 1/5/13. Available at: <http://www.hlsp.org/LinkClick.aspx?fileticket=LIR9H527a1E%3d&tabid=1814&mid=3517>.
12. Hollis, A. and Pogge, T. 2012. The Health Impact Fund: Making Medicines Accessible for All, Health Impact Fund: New Haven. Accessed 1/5/13. Available at <http://healthimpactfund.org/e-library.html>.
13. Hollis, A. and Pogge, T. 2012. "The Health Impact Fund: Making Medicines Accessible for All," Health Impact Fund: New Haven. Accessed 1/5/13. Available at: < http://healthimpactfund.org/e-library.

html>.

14. An expanded rating system might serve as the basis for evaluating global health impact of new medicines for the HIF, for instance. Although the HIF's creators would prefer to gather data on the actual impact of medicines on the ground rather than rely on clinical trial data, the cost of their proposal could be greatly reduced by using the proposed index rather than collecting new data.
15. See, for instance: Hassoun, N. 2012. "Global Health Impact," Developing World Bioethics 12(3), 121-134. Accessed 9/1/12. Available at <http://onlinelibrary.wiley.com/doi/10.1111/j.14718847.2011.00314.x/abstract>.
16. Interviews with key decision makers in pharmaceutical companies suggest that they will seriously consider this proposal and companies with large consumer portfolios may gain a lot form using the label. Hassoun, N. 2011. Phone Interview with Briggs Morrison. September, 2011.
17. Hassoun, N. 2012. "Global Health Impact," Developing World Bioethics 12(3), 121-134. Accessed 9/1/12. Available at <http://onlinelibrary.wiley.com/doi/10.1111/j.14718847.2011.00314.x/abstract>
18. Ibid
19. Trouiller, P. et al. 2001. "Drugs for Neglected Diseases: A Failure of the Market and A Public Health Failure?" Tropical Medicine and International Health 6(11), 945-951.
20. Hassoun, N. 2012. "Global Health Impact," Developing World Bioethics 12(3), 121-134. Accessed 9/1/12. Available at <http://onlinelibrary.wiley.com/doi/10.1111/j.14718847.2011.00314.x/abstract>. Hassoun, N. 2012. "Measuring Global Health Impact: Incentivizing Research and Development of Drugs for Neglected Diseases," in P. Lenard, P. and Straehle, C. Eds. Justice and Global Health Inequalities, Global Justice and Human Rights Series, Edinburgh University Press, Edinburgh.
21. For discussion of similar proposals and their success, see: Hassoun, N. 2012. Globalization and Global Justice: Shrinking Distance, Expanding Obligations. Cambridge University Press, Cambridge. "Hassoun, Nicole. 2012. "Global Health Impact," Developing World Bioethics 12(3), 121-134. Accessed 9/1/12. Available at <http://onlinelibrary.wiley.com/doi/10.1111/j.14718847.2011.00314.x/abstract>
22. Hainmueller, J., Hiscox, M. J., and Sequeira, S. 2011. "Consumer Demand for the Fair Trade Label: Evidence from a Field Experiment," Accessed 12/29/12. Available at <http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1801942>. Hiscox, M., Broukhim, M., and Litwin, C., and Woloski, A. 2011. "Is there Consumer Demand for Fair Labor Standards? Evidence from a Field Experiment on eBay," draft accessed 12/29/12. Available at <http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1811788>. Ruben, R. Eds. 2008. The Impact of Fair Trade. Wageningen Academic Publishers: Wageningen, Netherlands.
23. Komatsu, R. et al. 2010. "Lists Saved by Global Fund Supported HIV/AIDS, Tuberculosis and Malaria Programs: Estimation Approach and Results Between 2003 and End-2007," BMC Infectious Disease 10, 109. Accessed 12/29/12. Available at: <http://www.theglobalfund.org/en/files/about/replenishment/oslo/Resource%20Needs.pdf>. Global Fund, Resource Needs for the Global Fund: 2008-2010. 2007, at
24. <http://www.theglobalfund.org/en/files/about/replenishment/oslo/Resource%20Needs.pdf>. Cited in: Salaam-Blyther, Tiaji. 2008. "The Global Fund to Fight AIDS, Tuberculosis, and Malaria: Progress Report and Issues for Congress," Congressional Research Service: Washington D.C. Accessed 12/29/12. Available at: <http://www.au.af.mil/au/awc/awcgate/crs/rl33396.pdf>. The Henry J. Kaiser Family Foundation (KFF) estimates that Global Fund spending represented about 19% of all international HIV/AIDS commitments in 2005. See Kates, J. and Lief, E. 2006. "International Assistance for HIV/AIDS in the Developing World," US: The Henry J. Kaiser Family Foundation. Accessed 12/29/12. Available at <http://www.kff.org/hivaids/upload/7344-02.pdf>.
25. Collinsworth, B. 2010. "Big Steps Forward for Global Health," Universities Allied for Essential Medicines: Oakland. Accessed 1/5/13. Available at: <http://sandbox.essentialmedicine.org/blog/big-steps-forward-global-health>. Also see: Collinsworth, B. 2012. "University of California Acts to Make Its Medical Breakthrough Affordable," Universities Allied for Essential Medicines: Oakland. Accessed 12/29/12. Available at: <http://essentialmedicine.org/blog/university-california-acts-make-its-medical-breakthroughs-affordable>. Other attempts to encourage universities to address social problems like child labor have also seen some success. See, for instance: United Students Against Sweat Shops. 2012. "What We Do," United Students Against Sweatshops: Washington D.C. Accessed 1/5/13. Available at: <http://usas.org/>.
26. Erhemjamts, O., Li, Q., and Venkateswaran, A. 2012. "Corporate Social Responsibility and its Impact on Firms'

Investment Policy, Organizational Strategy, and Performance," working paper accessed 2/3/14. Available at <http://ssrn.com/abstract=2186627>.

27. We focus, in particular, on first-line drugs (ACTs) for malaria, first- and second- line HIV/AIDS medicines and treatments for drug-susceptible, multi-drug resistant, and extremely drug resistant TB.
28. When possible we do this at the country-level.
29. We have not yet considered drug interactions or side effects.
30. 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: Bloom, J. 2012. "Me-too? Says Who? (Medical Progress Today)" Medical Council on Science and Health. Accessed 4/4/12. Available at <http://www.acsh.org/news/newsID.1992/news_detail.asp>. 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.
31. We do not adopt the suggestion to discount or use prevalence DALYs as recent data with an appropriate discount factor is not available. See, however: Hassoun, N. 2012. "Rating Efforts to Extend Access on Essential Medicines: Increasing Global Health Impact," in Lenard, P. and Straehle, C. Eds. Health Inequalities and Global Justice. Edinburgh University Press: Edinburg.
32. Using treatment percentages as a measure of access is a great improvement over the method of approximating access suggested in: Hassoun, N. 2012. "Rating Efforts to Extend Access on Essential Medicines: Increasing Global Health Impact," in Lenard, P. and Straehle, C. eds. Health Inequalities and Global Justice. Edinburgh University Press: Edinburg. Though, a good measure of access over which companies have complete control and responsibility might be even better.
33. Contact author for details.
34. We estimate what the impact of the drug will be this coming year. We considered taking into account the fact that there would have been more DALYs lost in many cases if the drug was not already in use. After all, the actual DALYs number within a country would be higher were that drug not being used. However, we were not able to determine what the DALYs attributable to a specific disease would have been without treatment, though it may be possible to revisit the issue in the future.
35. Institute for Health Metrics and Evaluation (IHME). 2013. "Global Burden of Disease Study 2010 (GBD 2010) Results 1990-2010. Results by Cause Both Sexes All Ages DALYs 2010," IHME: Seattle, United States. Accessed 10/5/13. Available at: <http://ghdx.healthmetricsandevaluation.org/country_profiles>.
36. World Health Organization. 2012. World Malaria Report 2012. World Health Organization: Geneva.
37. See Corner, C. 2005. "Update on the Treatment of Tuberculosis and Latent Tuberculosis Infection", JAMA: The Journal of the American Medical Association 293(22). Accessed 10/5/13. Available at: <http://jama.jamanetwork.com/article.aspx?articleid=201044#LatentTBInfection>. See also World Health Organization. 2011. "WHO Report 2011: Global Tuberculosis Control". World Health Organization: France. Accessed 10/5/13. Available at: <http://www.who.int/tb/publications/global_report/2011/gtbr11_full.pdf>. For "The treatment of MDR TB has been increasingly successful over the last decade, with reported cure rates over 80% in many settings. This is especially true when fluoroquinolones and adjuvant surgical therapy are used", see Sandoz webpage at <http://www.tbdots.com/site/en/doctor_section_tb_mdr.html>, or Baddour, L. 2008. "Individualized Treatment of XDR-TB", NEJM Journal Watch. Accessed 10/513. Available at: <http://infectious-diseases.jwatch.org/cgi/content/full/2008/806/1>.
38. Of course, it could be harder to come up with improvements in a market where there are already highly effective drugs, but that need not be the case.
39. The GBD study is the best source for global data on a variety of diseases. Institute for Health Metrics and Evaluation (IHME). 2013. "Global Burden of Disease Study 2010 (GBD 2010) Results 1990-2010. Results by Cause Both Sexes All Ages DALYs 2010," IHME: Seattle, United States. Accessed 10/5/13. Available at: <http://ghdx.healthmetricsandevaluation.org/country_profiles>. For other work on the burden of malaria, however, see: Snow, R., Craig, M., Deichman, U., and Marsh, K. 1999. "Estimating Mortality, Morbidity and Disability due to Malaria Among Afric a's Non-Pregnant Population," Bulletin of World Health Organization 77(8), 624-640.

Snow, R., Craig, M., Newton, C., and Steketee, R. 2003. "The Public Health Burden of Plasmodium Falciparum Malaria in Africa: Deriving the Numbers," Disease Control Priorities Project 11. Accessed 2/4/14. Available at < http://archives.who.int/prioritymeds/report/append/610snow_wp11.pdf>.

40. Institute for Health Metrics and Evaluation (IHME). 2013. "Viet Nam Global Burden of Disease Study 2010 (GBD 2010) Results 1990-2010. Results by Cause Both Sexes All Ages DALYs 2010," IHME: Seattle, United States. Accessed 10/5/13. Available at: <http://ghdx.healthmetricsandevaluation.org/country_profiles>.
41. For relevant sources see discussion below.
42. Institute for Health Metrics and Evaluation (IHME). 2013. "Viet Nam Global Burden of Disease Study 2010 (GBD 2010) Results 1990-2010. Results by Cause Both Sexes All Ages DALYs 2010," IHME: Seattle, United States. Accessed 10/5/13. Available at: <http://ghdx.healthmetricsandevaluation.org/country_profiles>
43. The model focuses on this kind of malaria as it is the main contributor to the GBD due to malaria. World Health Organization World Health Organization. 2011. "WHO World Malaria Report 2011", World Health Organization: Geneva, p. 53.
44. We use 2010 as the base year for the model. If WHO data exists for country-specific effectiveness for a drug, then that data is used. For relevant efficacy data see: World Health Organization. 2010. Global Report on Antimalarial Efficacy and Drug Resistance: 2000-2010. World Health Organization: Geneva. Available at: <http://www.who.int/malaria/publications/atoz/9789241500470/en/>. When data from this report was not available we used data from the follow source preferring more recent data to less recent data as close to the base year as possible: World Health Organization. 2012. World Malaria Report 2012. World Health Organization: Geneva. Available at: <http://www.who.int/malaria/publications/world_malaria_report_2012/en/>. When WHO data is not available, we used the data from a systematic review of clinical trial data. For each study we use data for (or closest to) day 28 and prefer data controlling for recrudescence and for intention to treat populations to unadjusted data or data from select patients that followed the protocol. World Health Organization. 2008. "Methods and Techniques for Clinical Trials on Antimalarial Drug Efficacy: Genotyping to Identify Parasite Populations," World Health Organization; Geneva, Switzerland. Accessed 12/14/13. Available at: <http://www.who.int/malaria/publications/atoz/9789241596305/en/ >. Bloland, P., Ringwald P., and Snow, R. 2003. "Assessment and Monitoring of Antimalarial Drug Efficacy for the Treatment of Uncomplicated Falciparum Malaria," World Health Organization: Geneva. Accessed 12/14/13. Available at: <http://www.cdc.gov/malaria/resources/pdf/drug_resistance/who2003_monitoring.pdf>. World Health Organization. 1996. "Assessment of Therapeutic Efficacy of Antimalarial Drugs for Uncomplicated Falciparum Malaria in Areas with Intense Transmission" World Health Organization: Geneva. Accessed 12/14/13. Available at: <http://apps.who.int/iris/handle/10665/63295>. We are simply averaging the efficacy estimates from clinical trial data when we have multiple data points and imputing this to countries missing efficacy information to arrive at a global estimate when a global estimate is unavailable. For, even doing a systematic review of first-line malaria drug efficacy, we were unable to obtain enough data to build a good model to predict drug efficacy at the country-level when that data is not available from clinical trials.
45. World Health Organization. 2010. "Global Report on Antimalarial Drug Efficacy and Drug Resistance: 2000-2010," World Health Organization: Geneva, p.102. Accessed 12/13/13.Available at: <http://whqlibdoc.who.int/publications/2010/9789241500470_eng.pdf>.
46. For Children under 5 with fever being treated with anti-malarial drugs, See Index Mundi webpage which contains data from DHS and MICS surveys: <http://www.indexmundi.com/vietnam/malaria-treatment.html, found in index mundi>. See also World Health Organization. 2012. "World Malaria Report," WHO: Geneva. Accessed 2/4/14. Available at: <http://www.who.int/malaria/publications/world_malaria_report_2012/en/>. Again, we prefer more recent data to less recent data as close to the base year as possible.
47. We only examine the impacts of the five main ACTs as the others' impacts are negligible. If no data for first-line drug treatments exists within a country, but some DALYs are lost to Plasmodium falciparum malaria, then each of the ACTs in our model receives credit for 1/11th of the total ACT treatment coverage (as there are 11 available ACTs). In Algeria, for example, no first-line treatment data exists however, 10,780 DALYs are lost to Plasmodium falciparum malaria. As such, the overall ACT coverage in Algeria (69%) is divided by 11, and the five ACTs included on the overall ratings sheet each get credit for 1/11 of this coverage (6.27%).

48. Companies are doing less of their own research and development on new drugs and producing fewer new drugs, in part, because they are effectively outsourcing these tasks. However, they still invest a lot in drug development. Rafols, I. et al. 2012. "Big Pharma, Little Science? A Bibliometric Perspective on Big Pharma's R&D Decline," working paper accessed 2/4/2014. Available at SSRN: http://ssrn.com/abstract=2012878 or http://dx.doi.org/10.2139/ssrn.2012878
49. To credit companies, we are relying primarily on FDA patent applications, patent searches, and companies' annual reports. See Appendix IV.
50. 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. Udwadia, Z. T. 2012. " MDR, XDR, TDR Tuberculosis: Ominous Progression", Thorax 67, 286-288. Accessed 7/7/12. Available at <http://www.tbonline.info/media/uploads/documents/thoraxjnl-2012-20166.pdf>.
51. It might be possible 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 would 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. We have yet to try to do this. Additionally, although we lack data on a few countries, most specify that the treatment for active drug-susceptible TB is the standard regimen of Rifampicin, Isoniazid, Ethambutol and Pyrazinamide described above. We assume this is the case for all countries. Note that sensitivity analysis suggests this makes a big difference. If (a) isoniazid were to receive 40% of the credit and the remaining credit (60%) were split equally between the other three drugs, Hoffman-LaRoche would jump three spots in overall rank. If we were to (b) give isoniazid 60% of the credit and split the remaining 40% equally between the other three drugs, ViiV and Merck would lose one spot in rank, Pfizer would lose 3, and Hoffman-LaRoche would gain five. If we were to (c) give isoniazid 40% of the credit, rifampicin 30%, and split the remaining 30% between the other two drugs, Pfizer would lose two spots in rank, ViiV, Merck, and BMS would each lose one, Boehringer would gain one, and Hoffman-LaRoche would gain 4.
52. These protocols are found in World Health Organization. 2009. "Management of MDR-TB: A field guide," World Health Organization: Italy, pp. 20-23. Accessed 12/20/13. Available at <http://whqlibdoc.who.int/publications/2009/9789241547765_eng.pdf>.
53. Shah, S. et al. 2007. "Worldwide Emergence of Extensively Drug-resistant Tuberculosis," Emerging Infectious Diseases,13(3), 380-387, Table 1. Accessed 12/24/12. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2725916/>.
54. Mphahlele, M. et al. 2008. "Pyrazinamide Resistance among South African Multidrug-Resistant Mycobacterium tuberculosis Isolates," 46(10), 3459-3464. doi:10.1128/JCM.00973-08. Accessed 1/4/13. Available at <http://jcm.asm.org/content/46/10/3459.full>.
55. Ibid. Table 2: 30/71.
56. Calculated as percentage of total TB divided by percentage of total TB that is MDR-TB (39.4%).
57. Abbreviations are as follows: pyrazinamide (Z), streptomycin (S), levofloxacin (Lfx), ethionamide (Eto), cycloserine (Cs), and kanamycin (Km).
58. This number represents the sum of the relevant "portion of MDR-TB" numbers for each treatment regimen. The first treatment regimen, for example, is the sum of 18.02% and 4.84%, or 22.86%.
59. Regimens must be adjusted, as the original data added up to more than the total for MDR-TB of 39.4% (7.1% + 3.3% + 11.0% + 18.6% = 40%, not 39.4%). This is not due to an error on anyone's part but due to the fact that the total number tested for MDR in general was greater than the number tested for sub-types of MDR and we can conclude from this that there is a small difference in tested and untested populations. The tested populations have slightly higher chances of resistance but we do not attempt to account for this in the model. Shah, S. et al. 2007. "Worldwide Emergence of Extensively Drug-resistant Tuberculosis," Emerging Infectious Diseases 13(3), 380-387, Table 1. Accessed 12/14/12. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2725916/>.
60. Km, for example, receives one-fifth of the total percentage of the third treatment regimen, since that regimen consists of five drugs. (1/5) * (74.00%) = 14.80% of the effects of all MDR-TB is credited to Km as part of the third treatment regimen. This process is repeated for each drug in each regimen.

61. 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. See Mitnick, C. et al. 2008. "Comprehensive Treatment of Extensively Drug-Resistant Tuberculosis," The New England Journal of Medicine 359, 563-574. Accessed 5/7/12. Available at <http://www.nejm.org/doi/pdf/10.1056/NEJMoa0800106>.
62. Institute for Health Metrics and Evaluation (IHME). 2013. "Botswanna Global Burden of Disease Study 2010 (GBD 2010) Results 1990-2010. Results by Cause Both Sexes All Ages DALYs 2010," IHME: Seattle, United States. Accessed 10/5/13. Available at: <http://ghdx.healthmetricsandevaluation.org/country_profiles>.
63. 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. 2012. "Tuberculosis (TB)", Data for Global Tuberculosis Control 2011. Country Data, Case Notifications," World Health Organization: Geneva. Accessed 8/20/12. Available at <http://who.int/tb/country/data/download/en/index.html>.
64. Data from: World Health Organization. 2012. "Tuberculosis (TB)", Data for Global Tuberculosis Control 2011. Country Data, Case Notifications," World Health Organization: Geneva, Accessed 8/20/12. Available at <http://who.int/tb/country/data/download/en/index.html>.
65. World Health Organization. 2011. "TB/HIV Facts 2011". World Health Organization: Geneva. Accessed 8/20/12. Available at <http://www.who.int/tb/challenges/hiv/factsheet_hivtb_2011.pdf> or at Google Doc. <https://docs.google.com/a/binghamton.edu/file/d/0By3X5BXUH_fbcGc5VnBUY2tXR28/edit>.
66. To do this, we took the prevalence of TB in cases with any known HIV status data as a proportion of total global prevalence, and determined the percentage of those with known HIV status within these countries: We have data for known HIV status for 68.15% of the prevalent cases. The prevalent cases in countries without known HIV status data, then, account for 31.85% of the total. We then determine the percent within this 68.15% that have known HIV status given numbers from the WHO: 21.46%. So, to reach a global known HIV status of 33%, we can determine the percentage with known HIV status in countries for which we do not have data: (68.15%) * (21.65%) + (31.85%) * (x) = 33%; x = 37.29%.
67. Column e_new_mdr_num on the estimates sheet World Health Organization. 2012. "Tuberculosis (TB)", Data for Global Tuberculosis Control 2011. Country Data, Case Notifications," World Health Organization: Geneva. Accessed 8/20/12. Available at <http://who.int/tb/country/data/download/en/index.html>.
68. Column e_ret_mdr_num on the estimates sheet World Health Organization. 2012. "Tuberculosis (TB)", Data for Global Tuberculosis Control 2011. Country Data, Case Notifications," World Health Organization: Geneva. Accessed 8/20/12. Available at <http://who.int/tb/country/data/download/en/index.html>.
69. Column e_new_mdr_pcnt on the estimates sheet World Health Organization. 2012. "Tuberculosis (TB)", Data for Global Tuberculosis Control 2011. Country Data, Case Notifications," World Health Organization: Geneva. Accessed 8/20/12. Available at <http://who.int/tb/country/data/download/en/index.html>.
70. Column e_ret_mdr_pcnt on the estimates sheet World Health Organization. 2012. "Tuberculosis (TB)", Data for Global Tuberculosis Control 2011. Country Data, Case Notifications," World Health Organization: Geneva. Accessed 8/20/12. Available at <http://who.int/tb/country/data/download/en/index.html>.
71. Column e_prev_num on the estimates sheet World Health Organization. 2012. "Tuberculosis (TB)", Data for Global Tuberculosis Control 2011. Country Data, Case Notifications," World Health Organization: Geneva. Accessed 8/20/12. Available at <http://who.int/tb/country/data/download/en/index.html>.
72. Confirmed MDR-TB cases started on treatment with second-line drugs in 2010. Author's calculations from the following sources: Column conf_mdr_tx on the notifications sheet World Health Organization. 2012. "Tuberculosis (TB)", Data for Global Tuberculosis Control 2011. Country Data, Case Notifications. World Health Organization: Geneva. Accessed 8/20/13. Available at <http://who.int/tb/country/data/download/en/index.html>.
73. This assumption is hard to evaluate, although more DALYs are probably lost to the average MDR TB case than to drug-susceptible TB (similarly for XDR TB) this is probably due to varying treatment efficacy.
74. World Health Organization. 2013, Global Tuberculosis Report 2013. World Health Organization: Geneva, page 45.
75. "About 9% of MDR-TB cases also have resistance to two other classes of drugs, or extensively drug-resistant TB (XDR-TB)." See WHO. 2013. WHO Tuberculosis Fact Sheet. Accessed 04/01/14. Available at <http://www.who.

int/tb/challenges/mdr/MDR_TB_FactSheet.pdf>

76. Treatment coverage in 2008 for XDR-TB is estimated at 43% globally. World Health Organization. 2008. "2007-2008 XDR & MDR Tuberculosis Global Response Plan," World Health Organization: Geneva.World Health Organization. 2008. "Implementing the WHO Stop TB strategy: A Handbook for National Tuberculosis Control Programmes," World Health Organization: Geneva. This data is available as of 2011, so the data will be more precise when data is updated.
77. "Among a subset of 795 XDR-TB patients in 26 countries, treatment success was 20% overall"
78. WHO. 2013. Global Tuberculosis Report 2013. p. 56. Accessed 04/01/14. Available at: <http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf>.
79. According to 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. (See World Health Organization. 2011. "TB/HIV Facts 2011," accessed 8/20/12. Available at <http://www.who.int/tb/challenges/hiv/factsheet_hivtb_2011.pdf>.) This comes up to a coverage of 65.9% (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 this group makes the majority of TB cases (MDR-TB, XDR-TB and TDR-TB form a minority proportion of TB incident cases). World Health Organization (WHO). 2011. WHO Report: Global Tuberculosis Control 2011. WHO: Geneva.
80. "The treatment success rate for all new HIV-positive TB patients was 73% compared with 87% among HIV-negative TB patients."Source: WHO. 2013, Global Tuberculosis Report 2013. p. 44. Accessed 04/01/14. Available at <http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf?ua=1>
81. 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.
82. These numbers represent the total score for MDR-TB multiplied by the proportion of the overall treatment used in each case.
83. We extrapolate to all countries in the world.
84. Data extracted from World Health Organization. 2010. "Antiretroviral Medicines in Low- and Middle-Income Countries: Usage in 2010 with Global and Regional Demand Forecast for 2011 - 2012," World Health Organization: Geneva, p. 40 (Table 25).
85. "Estimated percentage of eligible children under the age of 15 currently receiving antiretroviral therapy." World Health Organization. 2010. Estimated Antiretroviral Therapy Coverage Among Children. Accessed 10/5/13. Available at < http://apps.who.int/gho/indicatorregistry/App_Main/view_indicator.aspx?iid=2966>.
86. Institute for Health Metrics and Evaluation (IHME). 2013. Global Burden of Disease Study 2010 (GBD 2010) Results 1990-2010. Results by Cause, Summing Ages 0-14 and 15+, DALYs 2010. IHME: Seattle, United States. Accessed 10/5/13.Available at: <http://ghdx.healthmetricsandevaluation.org/country_profiles>.
87. World Health Organization. 2010. Data on the HIV/AIDS response: Antiretroviral therapy coverage. Accessed 10/5/13. Available at <http://www.who.int/hiv/data/en/>, Annex 4.
88. World Health Organization. 2010. Data on the HIV/AIDS response: Antiretroviral therapy coverage. Accessed 10/5/13. Available at http://apps.who.int/ghodata/?vid=22100 > HIV/AIDS > Data on the HIV/AIDS response > Antiretroviral therapy coverage
89. Regional averages provided by UNAIDS. 2011. "UNAids data tables 2011." Accessed 10/5/13. Available at: <http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC2225_UNAIDS_datatables_en.pdf>. See also World Health Organization. 2011. "Global HIV/AIDS Response". Accessed 10/5/13. Available at: <http://whqlibdoc.who.int/publications/2011/9789241502986_eng.pdf. The percentage of each region (by population) for which we are missing data is calculated, and then the treatment coverage required to bring the total regional treatment coverages to those provided by the WHO and UNAIDS is calculated; the missing treatment coverage data is capped at 0% and 100%.
90. Data extracted from: World Health Organization. 2010. "Antiretroviral Medicines in Low- and Middle-Income Countries: Usage in 2010 with Global and Regional Demand Forecast for 2011 - 2012", World Health Organization: Geneva, p. 4.
91. We have yet to do a systematic review of HIV/AIDS or TB drug efficacy. Instead we use global estimates for TB

and estimates based on a survey we completed of 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. Because efficacy data is scarce, we use fallback data points to approximate missing efficacy information. Specifically, we use the average efficacy of a regimen if we lack data on the efficacy of a regimen in a region or patient group etc. (e.g. we use the average of all Stavudine + Lamivudine + Nevirapine data to approximate the efficacy of missing region/patient group data on Stavudine + Lamivudine + Nevirapine efficacy). If there is no data on the efficacy of a regimen we use the average efficacy of drugs that are in the same categories -- drug designation (first/second line), patient group (adults/children), and region (group A/group B). Additionally, 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. Regimen breakdown information is 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.

92. Regimen breakdown information is extracted from: World Health Organization. 2010. "Antiretroviral Medicines in Low- and Middle-Income Countries: Usage in 2010 with Global and Regional Demand Forecast for 2011 - 2012". World Health Organization: Geneva, p. 5.
93. From Country Profiles on GHDx website: See Institute for Health Metrics and Evaluation (IHME). 2013. "Global Burden of Disease Study 2010 (GBD 2010) Results 1990-2010. Results by Cause Both Sexes All Ages DALYs 2010," IHME: Seattle, United States. Accessed 10/5/13. Available at: <http://ghdx.healthmetricsandevaluation.org/country_profiles>.
94. World Health Organization. 2010. "Antiretroviral Medicines in Low- and Middle-Income Countries: Usage in 2010 with Global and Regional Demand Forecast for 2011 - 2012", World Health Organization: Geneva.
95. Shah, S. et al. 2007. "Worldwide Emergence of Extensively Drug-resistant Tuberculosis," Emerging Infectious Diseases,13(3), 380-387, Table 1. Accessed 12/24/12. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2725916/>.
96.
97. Hughes, W. et al. 1999. "Safety and Single-dose Pharmacokinetics of Abacavir (1592u89) in human immunodeficiency virus type 1-infected children." *Antimicrob Agents Chemother* 43(3), 609-615. Accessed 2/15/13. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10049275>.
98. Barry, W. 1995. "Synergistic Combinations of zidovudine, 1592u89 and 3tc." Patent Number 6417191. Accessed 2/15/13. Available at <http://www.google.com/patents/EP0817637B1, http://www.google.com/patents/US6417191>.
99. Author Unknown. 1995. "FTC Approves Glaxo-Wellcome Merger." Chicago Tribune. Accessed 2/15/13. Available at <http://articles.chicagotribune.com/1995-03-16/news/9503170329_1_glaxo-wellcome-glaxo-plc-wellcome-plc>.
100. Author Unknown. 2000. "Profile: Glaxo Wellcome." BBC News. Accessed 2/15/13. Available at <http://news.bbc.co.uk/2/hi/business/606752.stm>.
101. Author Unknown. 2000. "Pharmaceutical Giants Glaxo and SmithKline Finally Merge." The Telegraph. Accessed 2/15/13. Available at <http://www.telegraph.co.uk/finance/4476425/Pharmaceutical-giants-Glaxo-and-SmithKline-finally-merge.html>.
102. ViiV Company Website. Accessed 2/15/13. Available at <http://www.viivhealthcare.com/about-us/heritage.aspx?sc_lang=en>.
103. Reuters, T. 2011. "Patent Landscape Report on Atazanavir." World Intellectual Property Organization, page 6. Accessed 1/12/13. Available at <http://www.wipo.int/export/sites/www/freepublications/en/patents/946/wipo_pub_946_2.pdf>.
104. Ip, L. 2011. "Patent Landscape Report on Ritonavir." World Intellectual Property Organization, page 7. Accessed 1/12/13. Available at < http://www.wipo.int/export/sites/www/freepublications/en/patents/946/wipo_pub_946.pdf>.

105. Author Unknown. N.D. The Medical Dictionary Online. Accessed 3/8/13. Available at <http://the-medical-dictionary.com/didanosine.htm>.
106. Young, S. et al. 1995. "Benzoxazinones as Inhibitors of HIV Reverse Transcriptase." Patent Number 5519021. Accessed 3/8/13. Available at <http://www.google.com/patents/US5519021>.
107. Liotta, D. et al. 1993. "Method for the Synthesis, Compositions, and Use of 2'-Deoxy-5-Fluoro-3'-Thiacytidine and Related Compounds." Patent Number 5814639. Accessed 3/8/13. Available at <http://www.google.com/patents/US5814639>.
108. Author Unknown. 2005. "Gilead Sciences and Royalty Pharma Announce $525 Million Agreement with Emory University to Purchase Royalty Interest for Emtricitabine." Emory University Website. Accessed 3/8/13. Available at <http://www.emory.edu/news/Releases/emtri/>.
109. Belleau, B. et al. 1989. "2-substituted-5-substituted-1,3-oxathiolanes with antiviral properties." Patent Number 5047407. Accessed 3/7/13. Available at <http://www.google.com/patents/US5047407>.
110. Author Unknown. 2000. "BioChem Pharma agrees to $13-billion merger." CBC News. Accesed 3/7/13. Available at <http://www.cbc.ca/news/business/story/2000/12/11/biochem001211.html>.
111. Kempf, D. et al. 1993. "Retroviral Protease Inhibiting Compounds." Patent Number 5541206. Accessed 3/2/13. Available at <http://www.google.com/patents/US5541206>.
112. Dressman, B. et al. 1994. "HIV Protease Inhibitors." Patent Number 5484926. Accessed 3/4/13. Available at <http://www.google.com/patents/US5484926>.
113. Company Website. Accessed 3/4/13. Available at <http://www.agi.org/history.html>.
114. Christmann, A. et al. 1994. "Process for the Preparation of Nevirapine." Patent Number EP 0667348. Accessed 3/5/13. Available at <http://www.google.com/patents/EP0667348B1>.
115. Skonezny, P. et al. 1994. "Process for large-scale preparation of 2',3'-didehydro-2',3'-dideoxynucleosides." Patent Number 5539099. Accessed 3/8/13. Available at <http://www.google.com/patents/US5539099>.
116. Bischofberger, N. 1996. "PMPA preparation." Patent Number 5733788. Accessed 1/28/13. Available at <http://www.google.com/patents/US5733788>.
117. Roberts, T. et al. 1992. "Crystalline Oxathiolane Derivatives." Patent Number 5905082. Accessed 3/7/13. Available at <http://www.google.com/patents/US5905082>.
118. Naito, T. et al. 1978. "Novel Penicillins." Lines 53-56. Patent Number 4206116. Accessed 3/8/13. Available at <http://www.google.com/patents/US4206116>.
119. Kawaguchi, H. et al. "Antibiotic Derivatives of Kanamycin." Patent Number 3781268. Accessed 3/8/13. Available at <http://www.google.com/patents/US3781268>.
120. Kraus, C. et al. 2003. "Aerosolized Capreomycin for Inhibition of Pulmonary Tuberculosis." Patent Number 20070128124. Accessed 3/8/13. Available at <http://www.google.com/patents/US20070128124>.
121. Shull, G. 1952. "Cycloserene and Production Thereof." Patent Number 2773878. Accessed 3/8/13. Available at <http://www.google.com/patents/US2773878>.
122. Singh, B. et al. 1974 "Synthesis of Ethambutol." Patent Number 3944618. Accessed 2/5/13. Available at <http://www.google.com/patents/US3944618>.
123. Author Unknown. 1997. "FTC Settles Charges with American Cyanamid; Agency Alleged Company had Fixed Prices and Restricted Competition." Federal Trade Commission. Accessed 2/4/13. Available at <http://www.ftc.gov/opa/1997/01/amcy.shtm>.
124. Peterson, M. 2002. "American Home Products Is Changing Name to Wyeth." NY Times. Accessed 2/4/13. Available at < http://www.nytimes.com/2002/03/11/business/american-home-is-changing-name-to-wyeth.html>.
125. Pfizer official web page. Accessed 2/4/13. Available at <http://www.pfizer.com/welcome/>.
126. Liberman, D. et al. 1957. "Certain 2-Substituted Isonicotinic Thioamides." Patent Number 2901488. Accessed 2/15/13. Available at <http://www.google.com/patents/US2901488>.
127. Redel, J. 1959. "New Derivatives of Trioxo-2,4,6-Piperidine and the Process of Preparing Same." Patent Number 3048590. Accessed 3/15/13. Available at <http://www.google.com/patents/US3048590>.
128. Translation of Biography. Accessed 3/15/13. Available at <http://translate.google.com/translate?hl=en&sl=fr&u=http://www.academie-francaise.fr/les-immortels/francois-albert-buisson&prev=/sea

rch%3Fq%3DFran%25C3%25A7ois%2BAlbert-Buisson%2Btheraplix%26hl%3Den%26safe%3Doff%26biw%3D1190%26bih%3D547&sa=X&ei=lnxDUamuBo_G4AOZ-oDgCg&ved=0CFAQ7gEwBA>.
129. Sneader, W. 2005. Drug Discovery: A History. John Wiley & Sons, Lt. Page 396. Accessed 3/15/13. Available at <http://books.google.com/books?id=jglFsz5EJR8C&pg=PA396&lpg=PA396&dq=Theraplix+ethionamide&source=bl&ots=DE1f4A8V3c&sig=cnSsHTjdDZHPBLpEoYnslJH7F2g&hl=en&sa=X&ei=13lDUbObApK04AONloGIAg&ved=0CGAQ6AEwCQ#v=onepage&q=Theraplix%20ethionamide&f=false>.
130. Author Unknown. "Rhone Poulenc" Sanofi Company Website. Accessed 3/15/13. Available at <http://en.sanofi.com/history/ajax/en_rhone_poulenc.html>.
131. Matsumoto, T. et al. 1997. "8-Alkoxyquinolonecarboxylic Acid Hydrate With Excellent Stability and Process for Producing the Same." Patent Number 5880283. Accessed 3/8/13. Available at <http://www.google.com/patents/US5880283>.
132. Fox, H. 1951. "Process of and Compositions for Combating Tuberculosis." Patent Number RE 23947. Accessed 2/21/13. Available at < http://www.google.com/patents/USRE23947>.
133. Furumai, T. et al. 1991. "Production of Pradimicin Antibiotics by Actinomadura Strain." Patent Number EP 0525588. Accessed 3/8/13. Available at <http://www.google.com/patents/EP0525588A2>.
134. Bullmont, J. et al. 2006. "Process for the Preparation of an Antibacterial Quinolone Compound." Patent Number EP 1939206. Accessed 2/28/13. Available at <http://www.google.com/patents/EP1939206A1?cl=en>.
135. Peterson, U. et al. 1995. "7-(1-pyrrolidinyl)-3-quinolone- and - naphthyridone-carboxylic acid Derivatives as Antibacterial Agents and Feed Additives." Patent Number 5607942. Accessed 3/13/13. Available at <http://www.google.com/patents/US5607942>.
136. Janssen-Ortho Inc. and Daiichi Pharmaceutical Co., Inc vs. Novopharm Limited 2006, 2006 FC 1234, Paragraph 24. Accessed 2/4/13. Available at <http://decisions.fct-cf.gc.ca/en/2006/2006fc1234/2006fc1234.html>.
137. Ryan, F. 1992. Tuberculosis: The Greatest Story Never Told. Swift Publishers Ltd.
138. Karl-Gustaf, R. 1947. "Process for producing a 4-amino salicylic acid." Patent Number US 2445242. Accessed 2/8/14. Available at <https://www.google.com/patents/US2445242>.
139. Company website. Accessed 1/8/14. Available at <http://www.ferrosan.com/>.
140. Williams, J. et al. 1952. " Tubekculostatic agent." Patent Number 2677641. Accessed 11/1/12. Available at <http://www.google.com/patents/US2677641>.
141. Sensi, P. et al. 1965. "Derivatives of Rifamycin." Patent Number 3342810. Accessed 1/5/13. Available at <http://www.google.com/patents/US3342810>.
142. Official Sanofi Website. Accessed 1/5/13. Available at <http://en.sanofi.com/our_company/worldwide/italy.aspx>.
143. Waksman, S. 1945. "Streptomycin and Process of Preparation." Patent Number 2449866. Accessed 3/6/13. Available at <http://www.google.com/patents/US2449866>. See also Kingston, W. 2004. "Streptomycin, Schatz v. Waksman, and the Balance of Credit for Discovery." Journal of the History of Medicine 59(3), 441-62.
144. Thomas, A. and Helmut, W. 1998. "Benflumetol derivatives, intermediates thereof and their use against parasitical protozoa and trematodes." Patent Number EP1089961. Accessed 3/8/14. Available at <https://www.google.com/patents/EP1089961A1>.
145. Company website. Accessed 3/13/14. Available at <http://www.novartis.com/newsroom/feature-stories/2011/04/malaria-initiative-1.shtml>.
146. Sauerwein, R. "Malaria." Radboud University Nijmegen Medical Centre. Accessed 11/22/12. Available at <https://docs.google.com/a/binghamton.edu/viewer?a=v&q=cache:l0UdpgVgaOQJ:www.edctpforum.org/wp-content/uploads/presentations/03_Robert_Sauerwein.pdf+&hl=en&gl=us&pid=bl&srcid=ADGEESgTPgUY-xyPbw6XurnsdJde8xhUISxsa3KZvdhLcHoMd0LajuVk3ctMowCXYS84LmNVxdTAKfDKy7Qbq9hbFcuZs7oXJy4fHux3SY1jU9EAkuFEaO5x4g8AJrJXH1G3lwuAveq3M&sig=AHIEtbSO7CqrnUt0eAwR5OcDHYpopWdLhQ>, slide 6.
147. Bousema, J. et al. 2006. "Moderate Effect of Artemisinin-Based Combination Therapy on Transmission of Plasmodium falciparum." The Journal of Infectious Diseases 193, 1151-1159. Accessed 11/23/12. Available at <http://jid.oxfordjournals.org/content/193/8/1151.full.pdf>, page 1152.
148. Haynes, R. 2009. "Artemisinins: Remarkable Antimalarial Drugs, Usages, and Problems, and a New Deriva-

tive – Artemisone." AREA Science Park Seminar. Accessed 11/22/12. Available at <AREA Science Park Seminar.ppt - International Centre for Science>, slide 11.
149. Author Unknown. N.D. DNDi. Geneva, Switzerland. Accessed 11/22/12. Available at <http://dndi.org/component/content/article/347-about-dndi/key-accomplishments/1212-malaria.html?highlight=YToyOntpOjA7czo0OiJhc2FxIjtpOjE7czo2OiJzYW5vZmkiO30=>. We also gives credit to companies for ASMQ.
150. Chatterjee, D. et al. 1988. "Drug Mixture for Prophylaxis and Therapy of Malaria." Patent Number EP0290959 A2. Accessed 11/16/12. Available at <http://www.google.com/patents/EP0290959A2?cl=en&dq=artesunate+amodiaquine&hl=en&sa=X&ei=DhfCUIqFLMeC0QGYxoCoBw&ved=0CDcQ6AEwAA>. Emphasis added.
151. Kumar, D. et al. 1988. "Drug mixture for prophylaxis and therapy of malaria. EP 0290959 A2. Accessed 3/10/13. Available at <https://www.google.com/patents/EP0290959A2>.
152. Author Unknown. 2008. "MSF Welcomes New Fixed-Dose Combination Against Malaria." Doctors Without Borders. Accessed 12/3/12. Available at <http://www.doctorswithoutborders.org/press/release.cfm?id=2619>.
153. Chatterjee, D. et al. 1988. "Drug Mixture for Prophylaxis and Therapy of Malaria." Patent Number EP0290959 A2. Accessed 11/16/12. Available at <http://www.google.com/patents/EP0290959A2?cl=en&dq=artesunate+amodiaquine&hl=en&sa=X&ei=DhfCUIqFLMeC0QGYxoCoBw&ved=0CDcQ6AEwAA>. Emphasis added. See also Kumar, D. et al. 1988. "Drug mixture for prophylaxis and therapy of malaria." Patent Number Patent Number EP 0290959 A2. Accessed 11/16/12. Available at <http://www.google.com/patents/EP0290959A2?cl=en&dq=artesunate+amodiaquine&hl=en&sa=X&ei=DhfCUIqFLMeC0QGYxoCoBw&ved=0CDcQ6AEwAA >.
154. Li, G. and Song, J. 2004. "Composition Containing Artemisinin for Treatment of Malaria." US Patent Number 7851512. Accessed 1/1/13. Available at <http://www.google.com/pateßnts/US7851512>.