

Supporting Information

A framework for assessing the impact of disease treatment

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This Supporting Information contains two sections: (1) additional model details describing the methods used to calculate disease impact scores for target diseases with sub-sections for TB, HIV, malaria, NTDs and a description of how we aggregate drug scores—focusing, in particular, on how we locate originator companies and estimate manufacturing companies' drug distributions; and (2) results from Monte Carlo sensitivity analyses testing several of the modelling assumptions and demonstrating the stability of the models.

1. MODEL DETAILS AND METHODS

TB model

Our current TB model investigates the impact of drugs on three patient groups: those with drug-susceptible TB (DS-TB), multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). The model also makes a distinction between the drug impact of treatment for DS-TB on patients with HIV/AIDS and without.

To illustrate how we calculate TB impact scores, we will walk through a demonstration for the Dominican Republic in 2013. This section first explains how the inputs for the total DS-TB impact score were derived, then computes the impact score, and finally disaggregates the score among the drugs used to treat each case. This explanation is repeated for the MDR-TB and XDR-TB impact scores.

To calculate the final impact score for DS-TB we must first determine DALYs lost to DS-TB/HIV+ and DS-TB/HIV-. Approximately 18,000 DALYs were lost to TB in the Dominican Republic in 2013 [15]. We assume that DALYs lost to TB are the sum of DALYs lost to DS-TB, MDR-TB, and XDR-TB. We estimate that DALYs lost to MDR-TB and XDR-TB are 1,958.06 and 207.94, respectively. We explain the derivation of these estimates later in this section. Thus, we can infer that 15,834.01 DALYs were lost to DS-TB ($18,000 - 1,958.06 - 207.94$). We still need to decouple DS-TB/HIV+ DALYs from DS-TB/HIV- DALYs lost. The WHO reported 4,331 incident cases of TB with known HIV status: with 24.72% testing positive and 75.28% testing negative [17]. Therefore, we estimate that 39,139.97 DALYs and 11,920.04 DALYs were lost to DS-TB/HIV+ and DS-TB/HIV-, respectively.

We also require data on treatment coverage and efficacy to calculate DS-TB impact. We lack accurate treatment coverage data for the Dominican Republic so we utilise the WHO's estimate of directly observed treatment coverage of 58% for every case [17]. The WHO's 2014 Global Tuberculosis Report estimates 73% effectiveness for HIV+ cases and 88% effectiveness for HIV- cases [25].

The data collected previously can now be inserted into the overall impact formula to derive the final impact score for both diseases.

$$I_{DS-TB/HIV+} = \frac{3,913.97 * 58% * 73%}{1 - 58% * 73\%} = 2,874.05$$

$$I_{DS-TB/HIV-} = \frac{11,920.04 * 58% * 88\%}{1 - 58\% * 88\%} = 12,426.44$$

Consider, next, how the DS-TB impact score is split up to estimate individual drugs' impact on HIV+ and HIV- patients. DS-TB is characterised by the absence of resistance to first-line TB drugs and is treated using a 6-month rifampicin-based regimen involving 2 months of isoniazid (H) + rifampicin (R) + ethambutol (E) + pyrazinamide (Z) and 4 months of H+R, (2HRZE/4HR) [18]. For DS-TB, we assume that the impact of each drug in the standard 6-month regimen is equal. So we divide the total DS-TB impact score for the Dominican Republic by four, crediting each drug equally.

To calculate the impact score for MDR-TB we must differentiate MDR-TB cases from TB cases. The WHO tells us that there are an estimated 30 MDR-TB cases among newly treated TB cases and an estimated 62 MDR-TB cases among previously treated TB cases [19]. The WHO also tells us that 6.6% of new TB cases were MDR-TB while 20% of previously treated TB cases were MDR-TB [19]. Dividing the number of MDR-TB cases among newly treated TB cases (30) by the percentage of new TB cases that were MDR-TB (6.6%) gives us 454.55 or, in other words, the estimated new cases of any type of TB. Dividing MDR-TB cases among previously treated TB cases by the percentage of previously treated TB cases that were MDR-TB gives us the number of retreatment cases of any type, 310. We can then calculate the overall percentage of MDR-TB among prevalent TB: $(30 + 62)/(454.55 + 310) = 12.03\%$. To expand, the numerator contains new and retreatment cases of MDR-TB, and the denominator contains all new and retreatment TB cases. Therefore, dividing the numerator by the denominator gives us the percentage of MDR-TB cases among all TB cases. If the WHO reports zero new and retreatment MDR-TB cases at the country level, the model will substitute the global average of the proportion of new and retreated MDR-TB cases out of total TB cases. Countries with these fall-back data will maintain a total MDR-TB impact score, but we do not further disaggregate impact among treatment regimens for these countries as we lack resistance rate data for new and retreated MDR-TB cases at the country level. We can then multiply the percentage of MDR-TB among prevalent TB cases by the total DALYs lost due to TB of all types: $12.03\% \times 18,000 = 2,167.02$. We subtract 207.94 from 2,167.02, the number of DALYs lost to XDR-TB, to reach an estimate of 1,958.06 DALYs lost to MDR-TB that is not XDR-TB. The calculation to derive the number of XDR-TB DALYs lost can be found later in this section.

Next, we estimate treatment coverage and efficacy for MDR-TB. The WHO estimates that there are 7,600 prevalent cases of TB in the Dominican Republic [19]. Multiplying this by the overall percentage of MDR-TB among prevalent TB cases (12.03%) yields 915, the number of MDR-TB cases needing treatment. Data from the WHO state that 105 Dominican Republic citizens received treatment for MDR-TB in 2013 [19]. This number allows us to then estimate treatment coverage in the Dominican Republic: 105 individuals receiving treatment divided by 7,600 individuals needing treatment, or 11.48%. The WHO's Global Tuberculosis 2016 Report suggests that MDR-TB treatment is 52% effective [20].

We can now use the overall impact formula to calculate the final 2013 impact of MDR-TB treatment in the Dominican Republic. Given that MDR-TB treatment typically takes 2 years, we divide the estimated impact scores by two to arrive at an estimate for a single year [21]:

$$I_{MDR-TB} = \frac{1,958.06 * 11.48\% * 52\%}{1 - 11.48\% * 52\%} / 2 = 6$$

Now that we have derived the overall impact of all three MDR-TB regimens in 2013, we can give credit to the individual regimens (and drugs within the regimens). MDR-TB is treated with one of three regimens, which is appropriate for a given individual depends on how their disease resists treatment with particular drugs. So we use resistance rates to estimate the proportion of people who receive each regimen [19]. The WHO provides country-level information on the number of individuals who test positive for MDR-TB in both new and retreatment cases as well as the overall number of individuals who are tested for drug resistance [19]. Therefore, we are able to estimate the percentage of cases that are MDR-TB as the proportion of those who have been tested who are resistant.

A summary of the regimens and their respective drug resistance rates can be found in an analysis done by the Global Project on Anti-Tuberculosis Drug Resistance Surveillance [21]. The regimens for MDR-TB are listed in Table S1.

Table S1. Regimens proposed to treat TB according to drug resistance

Drug resistance	Treatment regimen
H+R; H+E	Z+S+Lfx+Eto+Cs+PAS
H+R+E+Z	S+Lfx+Eto+Cs+PAS
H+R+S; H+R+E+S; H+R+E+Z+S	Km+Lfx+Eto+Cs+PAS

Note: Each row illustrates the proposed regimen according to drug resistance. For example, resistance to H+R or H+E requires treatment with Z+S+Lfx+Eto+Cs+PAS. H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide; S = streptomycin; Lfx = levofloxacin; Eto = ethionamide; Cs = cycloserine; PAS = p-aminosalicylic acid; Km = kanamycin

The WHO maintains databases relating to the country-level percentage of drug resistance to DS-TB treatments. For example, the WHO estimates resistance to H + R in previously treated cases in the Dominican Republic to be 33.70% [19]. The resistance rate for H + R + E + streptomycin (S) is unavailable at the country level, so we use the regional resistance rate for the Americas: 3.81%. We use the global averages for resistance to H + R + E (3.3%), and H + R + S (11%) because no country- or region-level data are available [22]. Drug resistance rates in the Dominican Republic are illustrated in Table S2.

Table S2. Estimated TB drug resistance rates

Drug resistance	Previously treated	Newly treated
H+R	33.7%	50%
H+R+E	3.3%	3.3%
H+R+S	11%	11%
H+R+E+S	3.8%	0.5%

H = isoniazid; R = rifampicin; E = ethambutol; S = streptomycin

We must estimate MDR-TB resistance to regimens that include Z because the WHO database does not include resistance data concerning Z. Studies in South Africa indicate that 42.25% of MDR-TB cases are resistant to Z [23]. We use this value as a global estimate for resistance to Z due to the absence of data for resistance to Z as a part of a treatment regimen. Both H + R + E and H + R + E + S are taken with or without Z. We incorporate the resistance rate to Z by splitting the H + R + E and H + R + E + S rates into rates with and without Z. Take newly treated H + R + E as an example, this regimen has a resistance rate of 3.3%. Our goal is to split resistance rates to the original regimen between two new regimens: H + R + E (without Z) and H + R + E + Z. We can multiply 3.3%, the global average for resistance to H + R + E, by 42.25%, our estimate of resistance to Z, to get 1.39%, or the resistance rate of H + R + E + Z. We multiply 3.3% by 57.75% (1 – 42.25%) to get 1.9%, or the resistance rate of H + R + E (without Z). This is visualised in Table S3.

Table S3. Estimated TB drug resistance rates including treatments with Z

Drug resistance	Previously treated	Newly treated
H+R	33.7%	50%
H+R+E	1.9%	1.9%
H+R+E+Z	1.39%	1.39%
H+R+S	11%	11%
H+R+E+S	2.2%	0.28%
H+R+E+S+Z	1.61%	0.21%

H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide; S = streptomycin

Recall the three regimens proposed to treat TB according to drug resistance in Table S1. Ultimately, we want to estimate the impact of each of these three regimens on MDR-TB. In order to do so, we must first estimate the proportion of people receiving each of the MDR-TB treatments consumed in the Dominican Republic. Initially, we divide each regimen's resistance rates by the total sum of all drug resistance rates to find the proportion of resistance to each of the drug combinations (H + R, H + R + E, etc.). For example, the sum of all previously treated drug resistances is 51.8%: 33.7% + 1.9% + 1.39% + 11% + 2.2% + 1.61%. We can divide previously treated resistance to H + R, 33.7%, by 51.8%, giving us 65%, or, the estimated resistance rate of H + R as a proportion of the total previously treated drug resistance rate (call this its proportional resistance rate). We essentially adjusted the resistance rates from Table S3 to be out of 100%. The results of these calculations are seen in Table S4.

Table S4. Estimated TB drug resistance rates as a proportion of total drug resistance rate

Drug resistance	Previously treated	Newly treated
H+R	65%	77.16%
H+R+E	3.66%	2.93%
H+R+E+Z	2.68%	2.14%
H+R+S	21.23%	16.97%
H+R+E+S	4.24%	0.43%
H+R+E+S+Z	3.1%	0.32%

H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide; S = streptomycin

Next, we can sum the proportional resistance rates for each corresponding regimen for newly treated cases (and we then do the same for previously treated cases). For example, because people resistant to H + R and H + R + E are given the treatment regimen Z + S + Lfx + Eto + PAS, we can sum the proportional resistance rates of previously treated H + R, 65%, with previously treated H + R + E, 3%, to arrive at 68%. The results can be found in Table S5.

Table S5. Estimated distribution of treatment regimens used to treat MDR-TB

Drug resistance	Treatment regimen	Previously treated	Newly treated
H+R	Z+S+Lfx+Eto+Cs+PAS	68.72%	80.1%
H+R+E			
H+R+E+Z	S+Lfx+Eto+Cs+PAS	2.68%	2.14%
H+R+S	Km+Lfx+Eto+Cs+PAS	28.59%	17.75%
H+R+E+S			
H+R+E+S+Z			

H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide; S = streptomycin; Lfx = levofloxacin; Eto = ethionamide; Cs = cycloserine; PAS = p-aminosalicylic acid; Km = kanamycin

We now want to find the percentage of the population (whether newly or previously treated) in the Dominican Republic that should be treated with the three regimens. We know that of the MDR-TB cases in the Dominican Republic, 32.6% are new cases and 67.4% are previously treated cases. We multiply the percentage of new cases (32.6%) by the proportional resistance rate to Z + S + Lfx + Eto + Cs + PAS (regimen 1) for new cases (80.1%) [19]. The resulting value is 26.1%. We then multiply the percentage of new cases by the proportional resistance rate to S + Lfx + Eto + Cs + PAS (regimen 2) for new cases to get 0.70%. And again multiply the percentage of new cases by the proportional resistance rate to Km + Lfx + Eto + Cs + PAS (regimen 3) for new cases to get 5.79%. These three values (26.1%, 0.70% and 5.79%) can be thought of as the percentage of newly treated cases that should be treated with regimens 1, 2 and 3, respectively. The same process is done for previously treated cases: 46.32%, 1.81% and 28.59% are the percentages of previously treated cases that should be treated with regimens 1, 2 and 3, respectively. To arrive at the estimated percentage of people (of any case, whether newly or previously treated) who should be treated with regimen 1, we simply need to sum 26.1% (the percentage of newly treated cases that should be treated with regimen 1) and 46.32% (the percentage of previously treated cases that should be treated with regimen 1). The results of these calculations for regimen 1 and the other two regimens can be found in Table S6.

Table S6. Weight of treatment regimens used to treat MDR-TB

Treatment regimen	Weight
Z+S+Lfx+Eto+Cs+PAS	72.43%
S+Lfx+Eto+Cs+PAS	2.52%
Km+Lfx+Eto+Cs+PAS	25.05%

Z = pyrazinamide; S = streptomycin; Lfx = levofloxacin; Eto = ethionamide; Cs = cycloserine; PAS = p-aminosalicylic acid; Km = kanamycin

The final step is to simply multiply the total MDR-TB impact score by the proportional use of each regimen to obtain individual regimen's scores. In the case of the Dominican Republic, we see that:

$$I_{Z+S+Lfx+Eto+Cs+PAS} = 62.16 * 72.43\% = 45.03$$

$$I_{S+Lfx+Eto+Cs+PAS} = 62.16 * 2.52\% = 1.56$$

$$I_{Km+Lfx+Eto+Cs+PAS} = 62.16 * 25.05\% = 15.57$$

We can estimate DALYs lost to XDR-TB by multiplying total TB DALYs lost, 18,000, by the overall percentage of MDR-TB among prevalent TB, 12%, and then multiplying the result by 9.6%—the percent of MDR-TB cases that are XDR-TB [19, 24]. Thus, we estimate that 15,184.71 DALYs were lost to XDR-TB. The WHO's Global Tuberculosis 2014 report states that there is a global average of 57% of treatment coverage for XDR-TB [19, 25].

The approximate global efficacy of XDR-TB treatment is 28% according to the WHO [19]. The data acquired can be inserted into the overall impact formula:

$$XDR - TB = \frac{15,184.7 * 28\% * 57\%}{1 - 28\% * 57\%} / 2 = 1,441.86$$

We can further separate the XDR-TB impact score into the regimens used to treat it. XDR-TB is categorised as TB resistant to H + R as well as a fluoroquinolone and a second-line injectable drug [26]. Successful treatment of XDR-TB always requires cycloserine, one injectable second-line agent and a fluoroquinolone. Possible second-line agents are kanamycin (Km), amikacin (Amk) and capreomycin (Cm). Possible fluoroquinolones are levofloxacin (Lfx), moxifloxacin (Mfx), gatifloxacin (Gfx) and ofloxacin (Ofx). Therefore, the combination used to treat XDR-TB is Cs + (Km or Amk or Cm) + (Lfx or Mfx or Gfx or Ofx). Each component of XDR-TB treatment is credited with one third of the XDR-TB impact score: Cs receives 33.3% of the credit, the second-line agents as a whole receive 33.3% of the credit and the fluoroquinolones as a whole receive 33.3% of the credit. We then break up credit within the second-line agents and the fluoroquinolones by individual drug. For example, Km receives 11% of the credit because we divide the credit we have assigned all second-line agents, 33.3%, by three, the possible number of second-line agents. The same holds true for the fluoroquinolones. We then calculate the impact of an individual drug by multiplying the total impact of the regimen by the credit given to the individual drug.

HIV/AIDS model

To understand the HIV/AIDS model, we will walk through the process of determining the impact of the antiretroviral drug zidovudine (AZT) in Benin in 2013. The HIV/AIDS model uses data collected from the WHO AIDS Medicines and Diagnostics Service survey that splits countries into two groups: Groups A and B. Group A countries are defined as low- and middle-income countries excluding the region of the Americas. Group B countries are low- and middle-income countries in the Americas. We then extrapolated this methodology to include high-income countries as well.

To start determining impact we must first gather DALY data. The WHO produces statistics for adults (15 years old and above) and children (below 15 years old); therefore, the model starts by calculating impact for these patient groups. The Global Health Data Exchange provides country-specific DALY data according to these age groups. In 2013, Benin lost 106,998.33 adult DALYs and 40,703.47 child DALYs to HIV/AIDS [15].

Next, we estimate treatment coverage. The WHO estimates the number of individuals in all age groups that need treatment as well as the number of individuals in all age groups who are receiving treatment. These data allow us to

determine treatment percentages, or the proportion of people who receive needed treatment, split by age group. In 2013, Benin had a treatment coverage of 38.82% and 21.0% for adults and children, respectively [12].

Efficacy is the last variable to calculate. We utilise treatment use proportions and efficacy information for adults and children using first- or second-line antiretroviral regimens [27, 28]. Each unique grouping of age and regimen can be considered a quadrant. An example of a quadrant is “second-line regimens for adults” or “first-line regimens for children.” If we lack regimen-specific efficacy or proportion of use data, we take the average of all original data points of that regimen, no matter what quadrant it is in. If this estimate does not yield results, we average all original data points in that quadrant. The instances in which there are missing data represent cases where we cannot make an accurate estimate due to a lack of original data points. These quadrants are further separated by Groups A and B countries in the 2010 and 2013 models to reflect variations in access to medicines. Because we lack treatment percentage data separated by country grouping in 2015 we cannot employ this aspect of the methodology for the 2015 model: we use average efficacy data across all groups. The full list of the proportions of antiretroviral treatment use and efficacies for Groups A and B countries can be found in Tables S7 and S8.

Table S7. Antiretroviral treatment regimen proportions and efficacies for Group A countries

First line regimens	Adult proportion	Adult efficacy	Child proportion	Child efficacy
AZT + 3TC + NVP	32.00%	81.93%	48.80%	81.93%
d4T + 3TC + NVP	26.00%	84.30%	23.80%	84.30%
AZT + 3TC + EFV	11.40%	75.75%	10.40%	70.67%
TDF + 3TC + NVP	6.50%	75.00%		65.50%
TDF + 3TC + EFV	6.50%	78.00%		78.83%
TDF + FTC + EFV	6.60%	77.50%		77.40%
TDF + FTC + NVP	4.50%	71.03%		69.02%
d4T + 3TC + EFV	4.90%	84.00%	4.60%	78.00%
Others	1.50%	75.07%	4.80%	50.00%
ABC + 3TC + NVP		75.07%	6.00%	50.00%
ABC + 3TC + EFV		70.63%	1.60%	72.98%
Second line regimens	Adult proportion	Adult efficacy	Child proportion	Child efficacy
ABC + 3TC + LPV/r	2.70%	63.00%	35.60%	63.00%
AZT + 3TC + LPV/r	19.40%	50.00%	18.30%	50.00%
ABC + ddl LPV/r	4.90%	74.18%	10.70%	83.40%
AZT + ABC + 3TC + LPV/r	25.50%	83.00%	3.90%	83.40%
TDF + 3TC + LPV/r		74.18%	4%	83.00%
AZT + ddl + LPV/r	16.50%	74.18%	3.70%	83.40%
Others	5.80%	74.18%	24.20%	83.40%
AZT + 3TC + TDF + LPV/r	4.40%	78.83%		78.83%
TDF + 3TC + EFV	3%	74.18%		83.40%
d4T + 3TC + LPV/r	2.30%	74.18%		83.40%
TDF + AZT + LPV/r	15.50%	65.20%		71.25%
TDF + FTC + LPV/r				

AZT = zidovudine; 3TC = lamivudine; NVP = nevirapine; d4t = stavudine; EFV = efavirenz; TDF = tenofovir; FTC = emtricitabine; ABC = abacavir; LPV/r = lopinavir/ritonavir; ddl = didanosine

Table S8. Antiretroviral treatment regimen proportions and efficacies for Group B countries

First line regimens	Adult proportion	Adult efficacy	Child proportion	Child efficacy
AZT + 3TC + NVP	9.90%	81.93%	9.90%	81.93%
ABC + 3TC + LPV/r	6.40%	63.00%	6.40%	63.00%
AZT + 3TC + EFV	35.00%	73.00%	35.00%	70.67%
TDF + 3TC + NVP	2.70%	65.50%	2.70%	65.50%
TDF + 3TC + EFV	18.20%	78.00%	18.20%	78.83%
TDF + FTC + EFV	12.40%	75.11%	12.40%	77.40%
TDF + FTC + NVP	1.00%	63.90%	1.00%	69.02%
TDF + 3TC + LPV/r	1.40%	83.00%	1.40%	83.00%
TDF + FTC + LPV/r	1.40%	67.50%	1.40%	71.25%
TDF + FTC + ATV/r	2.90%	78.58%	2.90%	79.42%
ABC + 3TC + EFV	3.60%	66.00%	3.60%	72.98%
AZT + 3TC + ATV/r	2.30%	75.70%	2.30%	75.70%
TDF + 3TC + ATV/r	1.40%	65.00%	1.40%	65.00%

Second line regimens	Adult proportion	Adult efficacy	Child proportion	Child efficacy
TDF + 3TC + ATV/r	21.00%	65.00%	21.00%	65.00%
AZT + 3TC + LPV/r	25.00%	50.00%	25.00%	50.00%
ABC + ddl + LPV/r	1.00%	65.20%	1.00%	65.20%
ABC + 3TC + LPV/r	3.00%	63.00%	3.00%	63.00%
TDF + 3TC + LPV/r	21.00%	83.00%	21.00%	83.00%
ABC + 3TC + ATV/r	2.00%		2.00%	
TDF + FTC + ATV/r	3.00%	79.42%	3.00%	79.42%
TDF + FTC + LPV/r	2.00%	71.25%	2.00%	71.25%
AZT + 3TC + ATV/r	19.00%	75.70%	19.00%	75.70%
3TC + TDF + FPV/r	3.00%		3.00%	

AZT = zidovudine; 3TC = lamivudine; NVP = nevirapine; EFV = efavirenz; TDF = tenofovir; FTC = emtricitabine; ABC = abacavir; LPV/r = lopinavir/ritonavir; ddl = didanosine; ATV/r = atazanavir/ritonavir; FPV/r = fosamprenavir/ritonavir

The WHO produces information concerning the percentage of adults and children that are receiving first- and second-line regimens by country Groups A and B [28]. We assume that the DALYs each regimen can avert are proportionate to their use in each population. The data can be found in Table S9.

Table S9. Antiretroviral treatment breakdown in 2013

Group	Treatment type	Number of adults receiving ART	Number of children receiving ART
A	First-line	9,958,772	881,335
A	Second-line	388,630	31,525
B	First-line	772,553	19,624
B	Second-line	131,780	4,279

The percentage of adults and children using first- or second-line treatments in Group A or B can be derived using the data in Table S9. For instance, the percentage of adults receiving first-line regimens in Group A is the number of adults receiving first-line regimens in Group A divided by the total number of adults using either first-line or second-line treatment in Group A = $9,958,772/(9,958,772 + 388,630) = 96.24\%$ [28]. Consider how we calculate AZT's score in Benin, a Group A country. First, we estimate AZT's impact for the adult first-line treatment regimen AZT + lamivudine (3TC) + nevirapine (NVP). Recall that, in 2013, Benin lost 106,998.33 adult DALYs to HIV/AIDS [15]. It is also important to remember that, in 2013, Benin had a treatment coverage of 38.82% for adults [12, 15]. We multiply these two data points by three variables: the percent of adults that receive first-line treatment (96.24%), the proportion of those adult first-line treatments that receive AZT + 3TC + NVP in Group A (32%) and the efficacy of this particular treatment (81.93%) [27]. Now, it is possible to plug these data points into the overall impact formula to derive impact:

$$I_{AZT+3TC+NVP} = \frac{106,998.33 * 81.93\% * 96.24\% * 32\% * 38.82\%}{1 - 81.93\% * 96.24\% * 32\% * 38.82\%} = 11,618.49$$

Because AZT is one of the three drugs in this regimen, we divide the impact score by three to get 3,872.83 DALYs averted. A similar calculation is repeated for each regimen that includes AZT and that is classified as a regimen used in Group A countries. This includes all subgroups such as first- or second-line treatments that are used to treat adults or used to treat children. This leaves four categories of regimens that could contain AZT. Group B countries undergo the same process but use data specific to that group of countries. The impact of AZT in each regimen for all patient and country groups is 6,554.89 DALYs averted. The full list of impact scores for regimens containing AZT in Benin in 2013 can be seen in Table S10; note that regimens lacking efficacy data have been excluded from this section.

Table S10. Impact of regimens containing AZT in Benin

Adult regimen	Adult regimen impact
AZT + 3TC + NVP	3,873
AZT + 3TC + EFV	1,189
AZT + 3TC + LPV/r	50.6
AZT + ABC + 3TC + LPV/r	0
AZT + 3TC + TDF + LPV/r	16.8
Child regimen	Child regimen impact
AZT + 3TC + NVP	1,197
AZT + 3TC + EFV	205.2
AZT + 3TC + LPV/r	9
AZT + ABC + 3TC + LPV/r	2.4
AZT + ddl + LPV/r	3.03

AZT = zidovudine; 3TC = lamivudine; NVP = nevirapine; EFV = efavirenz; ABC = abacavir; LPV/r = lopinavir/ritonavir; ddl = didanosine

We now divide the 6,554.89 DALYs averted by the average treatment period in order to split up the impact of a treatment that is carried out over a course of several years. We do so using retention rate data. Retention rate is a measure of the percentage of patients that have begun treatment and remain in treatment [29]. We can use resistance rates to estimate the average period of treatment that patients will complete with this formula:

$100\%/(100\% - \text{retention rate})$. Take a retention rate of 80%, for example, the formula will tell us that the average treatment period is 5 years. We would then take the total impact that the drug had for the given year and divide it by 5, because the full impact of treatment would not be completed in that year, but rather over the 5 years that the average patient would be treated. Antiretrovirals are calculated to extend life expectancy by 35 years, so we arrive at a maximum retention rate of 97.14 when solving for retention rate using the formula shown previously. Given the assigned maximum retention rate of 97.14 instituted, the model will choose the number that is smaller between any country-level data and 97.14; if no data are available for that country, it uses 97.14 as the default retention rate. Sensitivity analysis on this variable yields no significant change in ranking when increased or decreased. Benin's retention rate is 97.14, or 35 years. We divide the total impact of AZT in each regimen for all patient and country groups (6554.89) by 35 to arrive at the overall impact for AZT in Benin in 2013 (187.47). We calculate other drug scores in Benin (and other countries) in a similar way.

Malaria model

Our model estimates the impact of medicines on Plasmodium falciparum (P. falc.) and Plasmodium vivax (P. vivax) malaria. Consider an example of how we calculate the impact of the first-line P. falc. treatment, artesunate-amodiaquine (AS + AQ), in Burundi during the year 2013. In 2013, 934,300 DALYs were lost to malaria; 100% of this can be attributed to P. falc. [30]. Treatment coverage, or the percentage of febrile children receiving artemisinin-based combination therapy (ACT) treatment, is taken from the UNICEF database “Malaria mortality as a cause of death in children under 5” [31]. This percentage, 22.64%, is an average of treatment coverage in the Africa region because no country-specific data are available in Burundi [32]. Finally, regional-level efficacy data for AS + AQ in Burundi are 86.08% [27, 33]. So, using the overall impact formula, the impact due to AS + AQ treatments is equal to:

$$I_{AS+AQ} = \frac{934,300 * 22.64\% * 86.08\%}{1 - 22.64\% * 86.08\%} = 226,221.54$$

This same process is repeated for every country in which AS + AQ was administered. In countries where multiple regimens were utilized, the impact score for a given treatment is divided by the number of separate regimens. For example, Burkina Faso recommended administering either AS + AQ or artemether-lumefantrine (AL), so we assume that half of the patients were administered AS + AQ, and half AL. In this manner, we calculated every country's impact score for each regimen. In summary, we estimated that the global impact for the *P. falc* drug AS + AQ in 2013 was 7,960,542.06. Finally, the aforementioned method to derive impact is used for *P. vivax* drugs as well.

NTD model

The general impact formula is used to calculate the impact of treatment for several NTDs; however, there are a number of modifications to the original methodology to account for differences in the available data and for the general nature of the treatment for NTDs—MDA. The most significant change is that we reduce MDA impact scores by estimated prevalence as only a percentage of the treated population will be infected with a given NTD [37]. This reduces the final impact score to account for the difference between the population requiring preventive chemotherapy and the actual number of people with the NTD as the model intends to measure only the direct impact of treatment. Additionally, we divide the impact score for onchocerciasis by 30 because treatment is required twice a year for the 15-year lifespan of the adult worm [34].

To determine which MDA was initiated in each country, we applied two algorithms provided by the WHO's guidance for preventive chemotherapy in human helminthiasis (PCHH). There are instances in which a targeted treatment is to be administered along with the MDA. The PCHH defines a targeted treatment as the group-level application of drugs irrespective of infection status; therefore, we model these treatments the same as we do MDAs [37].

We gather data on endemicity from the WHO's PCT database [35]. The decision trees rely on endemicity data that are not publicly available, leaving us to estimate a country's disease endemicity level. We assume that a disease is endemic to a country if it has a population requiring treatment as stated in the WHO's PCT database.

Consider how we estimate drugs' impacts for Ghana. The WHO's PCT database tells us that Ghana is endemic for LF, onchocerciasis and schistosomiasis. Using our algorithm, we can see the corresponding treatment recommendation is ivermectin (IVM) + albendazole (ALB) and praziquantel (PZQ). IVM + ALB is used to treat LF, and PZQ is used to treat schistosomiasis. We will first calculate the impact score for IVM + ALB. The first step is to locate DALYs lost for LF in the year 2010. Through the IHME's database, we find this to be 21,374.72 DALYs lost [15]. The next step is to calculate efficacy data for LF in 2010. We do so by averaging the efficacy data of IVM + ALB on LF from multiple sources [27, 35]. We found this number to be 39.46%. Next, we estimate treatment coverage by dividing reported prevalence by the reported number of people treated. Both of these data points are national and were taken from the WHO's PCT database. Estimated treatment coverage was 62.82% [35]. Finally, IHME estimates LF prevalence at 1.8% [15]. We are now able to enter these values into our overall impact formula for NTDs to derive IVM + ALB's DALYs averted:

$$I_{IVM+ALB} = \frac{21,374.72 * 39.46\% * 62.82\%}{1 - 39.46\% * 62.82\%} * 1.8\% = 126.82$$

We calculate PZQ's DALYs averted in the same way. Because of the lack of available data, there is a critical difference in the way we calculate efficacy and treatment coverage for PZQ. While we were able to find studies containing relevant efficacy and treatment coverage information for IVM + ALB, we were unable to do the same for PZQ. For both variables, we average available data in the same WHO region as Ghana. We employ a similar methodology to derive impact scores for targeted NTD drugs in endemic countries. Here is our overall impact formula for PZQ's DALYs averted:

$$I_{PZQ} = \frac{50,239.32 * 64.44\% * 25.2\%}{1 - 4.44\% * 25.2\%} * 20\% = 1,984$$

Aggregation and company attribution

Once we obtain individual drug scores for each individual disease, we can aggregate them in several ways: by drug, disease, country, and companies originating and manufacturing the treatments. We aggregate drug scores by summing individual drug scores across disease (sub-) types where individual drugs are used to treat multiple conditions. We aggregate disease scores by taking the sum of the drug impact scores for each disease. We aggregate country score by summing all drugs' impacts within a given country. The same concept is used to aggregate drug scores across companies: we sum the impact of all drugs distributed by each manufacturing company, and separately we sum the impact of all drugs patented by each originating company. Next, we explain the company component of our model.

Originator companies were located via a patent search confirmed by Cornell Law School [27]. We searched only for the original patent holder or licensee as opposed to companies or organisations that have acquired the technology in the interim as we now evaluate company contributions post-development separately. We show results for originator companies by patent date and impact/revenue.

Our impact scores can be used to assess the performance of companies involved in drug development and the manufacturing sector of the pharmaceutical industry for malaria, TB and HIV/AIDS. We use manufacturing and distribution data provided by the WHO Global Price Reporting Mechanism to evaluate company contributions post-development [36]. The database provides important information such as cost, drug strength and the total number of units (TNU) of each drug that are involved in shipments of a variety of medicines. These data can be used to determine the proportion of certain classes of drugs that each manufacturer in the database is responsible for shipping. This can help highlight which manufacturers are doing the most to extend access to essential medicines to the countries that would benefit from the medicine. However, the Global Price Reporting Mechanism does not provide data on the health impact one shipment provides compared with another. The following formula estimates the proportional years of treatment provided by each shipment of drugs (and subsequently, we estimate the DALYS averted by manufacturer).

$$\text{Number of Treatment Years Provided} = \frac{\text{TNU}}{365 \times \text{DD}}$$

In this formula, TNU stands for total number of units and is the quantity per package times the number of packages in the shipment. For example, if the drug comes in tablet form, and there are 20 tablets per package and 1,050 packages per shipment, the TNU is 21,000. DD represents the daily dosage (the quantity of medication at the strength of that shipment given per day of treatment), and 365 represents the number of days in a year. In other words, the calculation provides an estimate of how many years of treatment a particular shipment could potentially provide for one person.

This formula allows us to estimate the DALYs averted by any given manufacturer for a particular drug. First, we use the formula to calculate the number of treatment years a drug has provided as an individual drug as well as part of a combination within all shipments that contain that drug. We know the manufacturer of the drugs contained in each shipment, so can therefore estimate the treatment years that a manufacturer provided within all shipments.

We also know the number of DALYs that the drug has averted, so we can simply multiply the DALYs averted by that drug by the percentage of treatment years provided by the manufacturer. For instance, the sum of all shipments of Ethambutol (both as an individual drug and as part of a combination) is found to potentially provide 7,322 treatment years, and Lupin Ltd. is responsible for potentially providing 46 of those. So, it is responsible for 0.63% of the total DALYs averted by Ethambutol. Ethambutol has averted the loss of 8,470,126 DALYs. So, we can estimate that Lupin Ltd. has averted the loss of 53,686 DALYs (or $8,470,126 \times 0.63\%$).

There are slight differences in the way that the various components of the formula are calculated, based on disease type. For example, to calculate daily dose for the malaria model, we use guidelines that are based on the weight of the patient. We first obtain average weights for three age groups from the WHO: children 0–4, children 5–14 and adults 14+ [27]. Then, we obtain malaria incident cases within these age groups from the GHDx. We use the following formula to calculate the weighted average of body weight for all malaria incident cases:

$(AX + BY + CZ)/(A + B + C)$. Variables A, B and C represent the incidence of malaria for the 0–4 age group, the 5–14 age group and the 14+ age group, respectively. Variables X, Y and Z represent the average weight of the 0–4 age group, the 5–14 age group and the 14+ age group, respectively. Having calculated the average body weight for all malaria incident cases, we look at dosage guidelines to arrive at the number of milligrams the average person should receive per day. We then divide the number of milligrams in each shipment's formulation by the number of milligrams the average person should receive each day to see what the daily dose is for that formulation. For instance, if the average adult who weighs 45 kg is prescribed Dihydroartemisinin + Piperaquine (40 + 320 mg), she should get a dose of 120 mg of Dihydroartemisinin per day [27]. So we divide 120 mg by 40 mg in the formulation to arrive at a daily dose of 3 for the average adult. The daily dosage for HIV/AIDS drugs was estimated by the WHO [27]. We use published estimates for daily doses for TB drugs [27].

Using the data that are available from the Global Price Reporting Mechanism on the price of shipments and data that were generated in the previous section regarding each manufacturer's DALYs averted, it was possible to generate a cost-effective analysis model that evaluates the cost for a manufacturer to avert the loss of one DALY. Take Micro Labs Ltd. as an example in 2013: this company manufactures Primaquine. We take the total DALYs averted by Primaquine and multiply this by the percentage of the global supply that Micro Labs Ltd. manufactured, giving us 12,415 DALYs. In 2013, Micro Labs Ltd. manufactured \$21,662 worth of Primaquine [27]. So, it averted the loss of 12,415 DALYs at a price point of \$21,662 and receives a cost effectiveness value of 0.57 DALYs/\$. That is, one dollar spent on its shipments averted the loss of a little more than half a DALY. This calculation allows us to compare different manufacturing companies' drugs' cost effectiveness.

2. MONTE CARLO SENSITIVITY ANALYSES

We conducted a sensitivity analysis (SA) in order to study how various sources of uncertainty in our model (e.g. regarding drug efficacy, treatment percentage and DALY estimates) should affect our confidence in the model overall (see below for a description of each individual test). We utilised the Monte Carlo (MC) method to conduct the SA by randomly choosing values from a preassigned distribution for each test. For each individual test, we ran the MC 100 times to study the average effect of each variable (e.g. drug efficacy and treatment coverage). For the overall test, we randomly picked values from a preassigned distribution for each test simultaneously to obtain 1,000 new companies' ranks to create a boxplot for each company. Maximum likelihood estimation (MLE) has been used to estimate unknown parameters in the preassigned distribution if the variable is not a fixed number; otherwise, we choose a mean based on the fixed number with small variance (0.05). We say that an individual company's rank is stable if the interquartile range of its boxplot is between 2 and -2 and say that a model ranking is stable overall (in a given year) if >16 companies' ranks are stable. The following are the individual tests, and the models for all years were stable overall.

Individual tests of assumptions

Test 1

Assumption tested: The model assumes that the proportion of DALYs lost to MDR-TB relative to all DALYs lost to TB is equal to the percent of MDR-TB cases out of all TB cases.

Distribution and parameters: We assumed that the percentage of MDR-TB cases follows a beta distribution, which picks a random variable that is between 0% and 100%. We used MLE to do the estimation by replacing the original percentage with new values that are randomly generated from that distribution.

Test 2

Assumption tested: The model divides the country-level impact of HIV by the country's respective treatment length. The model uses regional and global treatment length as fall-back data if data for a given country are unavailable.

Distribution and parameters: We assumed that treatment length follows a beta distribution and used MLE to derive estimates. We replaced fall-back values for countries missing treatment length data with new values drawn from that distribution.

Test 3

Assumption tested: Research indicates that overall treatment efficacy for XDR-TB is 20%, 28% and 30% for the years 2010, 2013 and 2015, respectively.

Distribution and parameters: We assumed that the overall treatment efficacy for XDR-TB is drawn from a beta distribution with a mean equal to 20%, 28% and 30% in 2010, 2013 and 2015, respectively, and 0.05 variation.

Test 4

Assumption tested: Our model uses the regional and global treatment coverage for an HIV/AIDS drug as fall-back data if that drug's treatment coverage data are not available for a given country.

Distribution and parameters: When treatment coverage data are not available for a country, we assume that it is drawn from a beta distribution, with a mean equal to global average and 0.05 variation.

Test 5

Assumption tested: Our model assumes that the proportion of XDR-TB among MDR-TB cases is equal to the proportion of XDR-TB DALYs lost to MDR-TB.

Distribution and parameters: We assumed that the proportion of MDR-TB cases that were classified as XDR-TB is drawn from a beta distribution, with mean equal to 9.5% and 0.05 variation.

Test 6

Assumption tested: Research indicates that drug-susceptible TB both with and without comorbid HIV has a treatment coverage of 65.9%, 58% and 59% in 2010, 2013 and 2015, respectively.

Distribution and parameters: We assume that the treatment coverage for drug-susceptible TB both with and without comorbid HIV draws from a beta distribution, with a mean equal to 65.9%, 58% and 59% in 2010, 2013 and 2015, respectively, and 0.05 variation.

Test 7

Assumption tested: In the absence of country-specific treatment coverage data, our model uses regional or global data as a fall-back for the percentage of febrile children under 5 receiving antimalarial treatment.

Distribution and parameters: When treatment coverage data are absent, we assume that the treatment coverage follows a beta distribution, with a mean equal to the global average and 0.05 variation.

Test 8

Assumption tested: We estimate the treatment efficacy for TB with comorbid HIV to be 72%, 73% and 78% for the years 2010, 2013 and 2015, respectively.

Distribution and parameters: We assume that the treatment efficacy for TB with comorbid HIV follows a beta distribution, with a mean equal to 72%, 73% and 78% in 2010, 2013 and 2015, respectively, and 0.05 variation.

Test 9

Assumption tested: We estimate the treatment efficacy for TB without comorbid HIV to be 88% in 2010 and 2013 and 83% in 2015.

Distribution and parameters: We assume that the treatment efficacy for TB without comorbid HIV follows a beta distribution, with a mean equal to 88% in 2010 and 2013 and 95% in 2015 and 0.05 variation.

Test 10

Assumption tested: The components of XDR-TB treatment is credited with one third of the XDR-TB impact score: Cs receives 33.3% of the credit, the second-line agents as a whole receive 33.3% of the credit and the fluoroquinolones as a whole receive 33.3% of the credit.

Distribution and parameters: For the three treatment regimens, we assume that it follows a Dirichlet distribution dimension 3, and a mean equal to 33% for all treatment regimens, with variation 0.05 in each.

Test 11

Assumption tested: In the absence of drug-specific efficacy data for malaria, our model uses regional and then global data as a fall-back.

Distribution and parameters: When efficacy data are unavailable for a country, for each drug we assume that it follows a beta distribution with a mean equal to the regional or global efficacy of that malaria drug and 0.05 variation.

Test 12

Assumption tested: The model determines treatment efficacy for malaria drugs that target *P. falc* and *P. vivax* using data collected from the World Malaria Report. If there are no data present for a specific country, the model uses data from our own review of the published data on efficacy. When data are unavailable for a country, the model uses regional and then global averages.

Distribution and parameters: Here, when efficacy data are unavailable for a country, we assume that it follows a beta distribution with a mean equal to the estimated regional or global value and 0.05 variation.

Test 13

Assumption tested: Our model constrains the fall-back data used to estimate treatment efficacy for NTDs to studies that took place before or during our model year. We tested different time constraints by removing all time constraints.

Distribution and parameters: No distribution used.

Test 14

Assumption tested: Research indicates that MDR-TB has a treatment efficacy of 48%, 52% and 54% for the years 2010, 2013 and 2015, respectively.

Distribution and parameters: We assume that the treatment efficacy follows a beta distribution, with a mean equal to 48%, 52% and 54% in 2010, 2013 and 2015, respectively, and 0.05 variation.

Test 15

Assumption tested: Research indicates that XDR-TB has a treatment coverage of 38%, 57% and 95% for the years 2010, 2013 and 2015, respectively.

Distribution and parameters: We assume that the treatment coverage follows a beta distribution, with a mean equal to 38%, 57% and 95% in 2010, 2013 and 2015, respectively, and 0.05 variation.

Test 16

Assumption tested: In our TB model, for countries lacking data on HIV status, we use the global average to estimate the percentage of people with known HIV status. Research indicates that the global average was 34%, 46% and 55% for the years 2010, 2013 and 2015, respectively.

Distribution and parameters: For countries lacking data on the percentage of people with known HIV status, we assume that it follows a beta distribution, with a mean equal to 34%, 46% and 55% in 2010, 2013 and 2015, respectively, and 0.05 variation.

Test 17

Assumption tested: The model estimates that the percentage of TB cases that have comorbid HIV is 23%, 13% and 15% for the years 2010, 2013 and 2015, respectively.

Distribution and parameters: We assume that the percentage of TB cases that have comorbid HIV follows a beta distribution, with a mean equal to 23%, 13% and 15% in 2010, 2013 and 2015, respectively, and 0.05 variation.

Test 18

Assumption tested: In calculating LF's impact score, the average regional treatment coverage of a drug is used as fall-back data for that drug if treatment coverage data are not available for a country.

Distribution and parameters: When treatment coverage is not available for a given country, we assume that it follows a beta distribution, with a mean equal to global average and 0.05 variation.

Test 19

Assumption tested: In calculating schistosomiasis' impact score, the average regional treatment coverage of a drug is used as fall-back data for that drug if treatment coverage data are not available for a country.

Distribution and parameters: When treatment coverage is not available for a given country, we assume that it follows a beta distribution, with a mean equal to the global average and 0.05 variation.

Test 20

Assumption tested: In calculating LF's impact score, the average regional or global efficacy of a drug is used as fall-back data for that drug if efficacy data are not available for a country.

Distribution and parameters: When efficacy data are not available for a given country, we assume that it follows a beta distribution, with a mean equal to regional or global average and 0.05 variation.

Test 21

Assumption tested: In calculating schistosomiasis' impact score, the average regional or global efficacy of a drug is used as fall-back data for that drug if efficacy data are not available for a country.

Distribution and parameters: When efficacy data are not available for a given country, we assume that it follows a beta distribution, with a mean equal to the regional or global average and 0.05 variation.

Test 22

Assumption tested: In calculating whipworm's impact score, the average regional or global efficacy of a drug is used as fall-back data for that drug if efficacy data are not available for a country.

Distribution and parameters: When efficacy data are not available for a given country, we assume that it follows a beta distribution, with a mean equal to the regional or global average and 0.05 variation.

Test 23

Assumption tested: In calculating roundworm's impact score, the average regional or global efficacy of a drug is used as fall-back data for that drug if efficacy data are not available for a country.

Distribution and parameters: When efficacy data are not available for a given country, we assume that it follows a beta distribution, with a mean equal to the regional or global average and 0.05 variation.

Test 24

Assumption tested: In calculating hookworm's impact score, the average regional or global efficacy of a drug is used as fall-back data for that drug if efficacy data are not available for a country.

Distribution and parameters: When efficacy data are not available for a given country, we assume that it follows a beta distribution, with a mean equal to the regional or global average and 0.05 variation.

Test 25

Assumption tested: Our model uses the average regional and then global treatment coverage for an onchocerciasis drug as fall-back data if that drug's treatment coverage data are not available for a given country.

Distribution and parameters: When treatment coverage is not available for a given country, we assume that it follows a beta distribution, with a mean equal to regional or global average and 0.05 variation.

Test 26

Assumption tested: Our model uses the average regional and then global treatment efficacy for an onchocerciasis drug as fall-back data if that drug's efficacy data are not available for a given country.

Distribution and parameters: When a drug's efficacy is not available for a given country, we assume that the drug's efficacy follows a beta distribution, with a mean equal to the regional or global average and 0.05 variation.

MONTE CARLO SIMULATION RESULTS

Next, we provide the results of our overall analysis for all tests for each year. Each boxplot visualises the change in rank for each company within each test. The y-axis indicates the change in company rank: a 1 stands for a decrease in rank by one, a -1 stands for an increase in rank by one and 0 indicates no change occurred. The x-axis lists each

company's assigned number—the numbers assigned to each company can be found in Table S11. Again, we say that an individual company's rank is stable if the interquartile range of its boxplot is between 2 and -2 and say that a model year's ranking is stable overall if >16 companies' ranks are stable.

Table S11. Company Index Across Years 2010, 2013, and 2015

Index	Company (2010)	Company (2013)	Company (2015)
1	Kyorin Pharmaceutical	Kyorin Pharmaceutical	Kyorin Pharmaceutical
2	F. Hoffmann-La Roche	F. Hoffmann-La Roche	F. Hoffmann-La Roche
3	Merck	Merck	Merck
4	Bayer Healthcare	Bayer Healthcare	Bayer Healthcare
5	Sanofi	Sanofi	Sanofi
6	Daiichi Sankyo	Daiichi Sankyo	Daiichi Sankyo
7	Bristol-Myers	Bristol-Myers	Bristol-Myers
8	Pfizer Inc.	Pfizer Inc.	Pfizer Inc.
9	Shire Pharmaceuticals	Shire Pharmaceuticals	Shire Pharmaceuticals
10	Boehringer Ingelheim	Boehringer Ingelheim	Boehringer Ingelheim
11	Gilead Sciences	Gilead Sciences	Gilead Sciences
12	Eli Lilly	Eli Lilly	Eli Lilly
13	Abbott Laboratories	Abbott Laboratories	Abbott Laboratories
14	Novartis	Novartis	Novartis
15	Chongqing Holley	Chongqing Holley	Chongqing Holley
16	GlaxoSmithKline	GlaxoSmithKline	GlaxoSmithKline
17	Johnson and Johnson	Johnson and Johnson	Johnson and Johnson
18	Taisho Pharmaceuticals	Guilin Pharmaceutical	Guilin Pharmaceutical
19	Artepharm	Artepharm	Artepharm
20	Imperial Chemical Industries	Imperial Chemical Industries	Imperial Chemical Industries

The boxplot for each company provides information on average rank changes for each company in the MC analysis. For each boxplot, the bold line in the middle stands for the median (second quartile), and the box stands for first

quartile to third quartile. The upper whisker stands for [third quartile + 1.5*(third quartile – first quartile)]. Similarly, the lower whisker stands for [first quartile – 1.5*(third quartile – first quartile)]. Any points beyond or below whisker are outliers. So, if 0 is inside the box, then 50% of the time the middle contains value 0. If the height of the box is between 2 and –2, that means that 50% of the time, the changed rank will be no higher than 2. There are few outliers, so we focus on the main portion of the following boxplots for 2010, 2013 and 2015. As we do not consider outliers, we can consider the upper whisker and lower whisker to be the maximum and minimum changed rank in the 1,000 trials.

The results in Figures S1–S3 show that all model years are stable. In 2010, most companies are stable, except company 14 (Novartis)—in more than 50% of the cases, its rank has a tendency to move up by 1 or move down by 3. In 2013, there are some small changes, but all of them are within 2 and –2. In 2015, company 2 (F. Hoffmann–La Roche) is not stable. Its rank has a tendency to move down by 3 most of the time. The rest of the companies are stable.

Result 2010

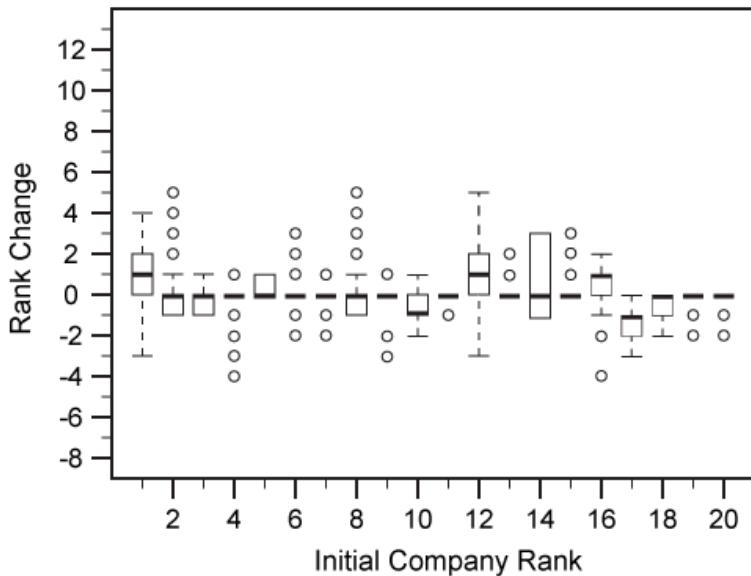


Figure S1: Box plot showing change in company rank in 2010 from 1,000 monte carlo simulations using the criteria from all 26 tests. The dark lines indicate median change in rank. The boxes represent the 25th and 75th percentiles. T-bars represent extremes and outliers are marked with an (o) icon.

Result 2013

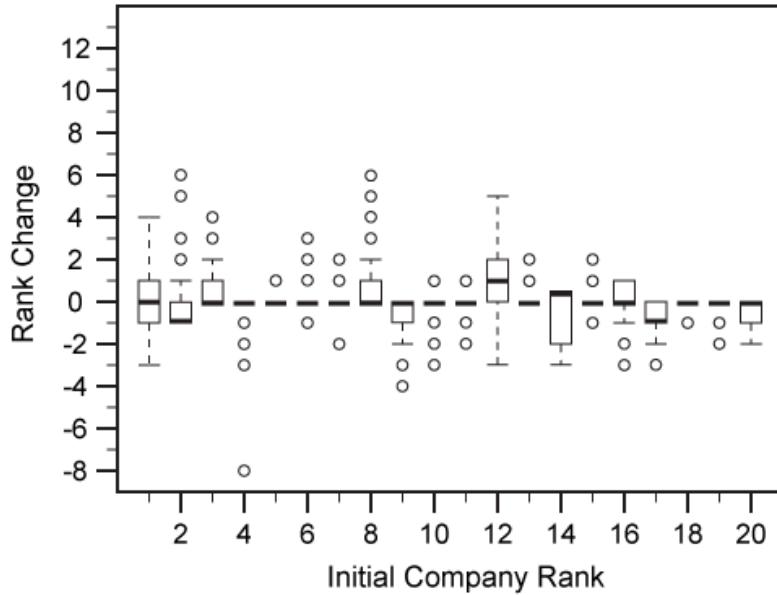


Figure S2: Box plot showing change in company rank in 2013 from 1,000 monte carlo simulations using the criteria from all 26 tests. The dark lines indicate median change in rank. The boxes represent the 25th and 75th percentiles. T-bars represent extremes and outliers are marked with an (o) icon.

Result 2015

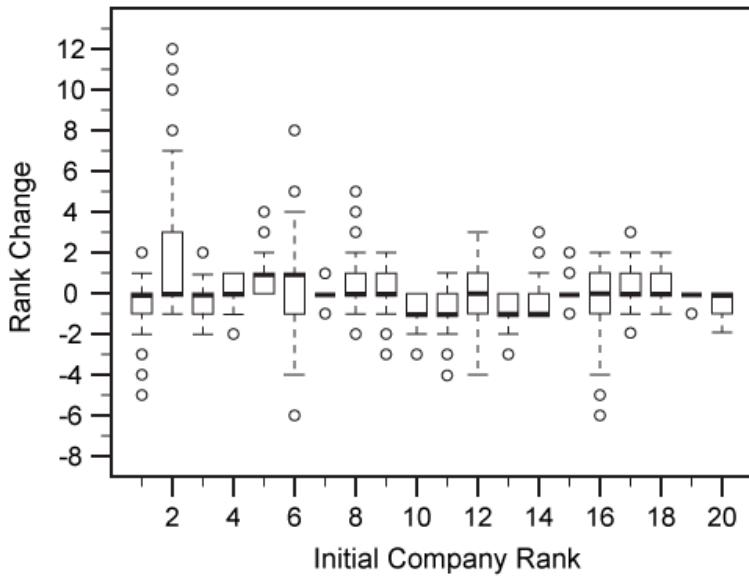


Figure S3: Box plot showing change in company rank in 2015 from 1,000 monte carlo simulations using the criteria from all 26 tests. The dark lines indicate median change in rank. The boxes represent the 25th and 75th percentiles. T-bars represent extremes and outliers are marked with an (o) icon.

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