TB TECHNICAL REPORT

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I. Data Dictionary

Column	Header Name	Description
A	Country	Name of country.
B	WHO Region	WHO-classified region (AMR, AFR, EUR, SEA, WPR).
D	DALYs	WHO age-weighted DALY estimates for all age groups.
J	Company	Companies manufacturing drugs targeting TB.
K	Drugs	List of drugs targeting TB.
L	Final Impact	Total impact of those drugs.
M	TB Prevalence	Newly diagnosed TB patients, plus patients who were diagnosed in the past. Collected from the WHO data dictionary.
N	TB Incidence	Number of people who are newly diagnosed with TB. Collected from the WHO data dictionary.
O	% TB Cases With Known HIV Status	% of TB cases in each country with a known HIV status (WHO).
P	TB Cases With Known HIV Status	Number of TB cases in each country with a known HIV status (WHO).
Q	TB/ HIV+	Number of TB cases with known HIV status who are HIV+ (WHO).
R	% TB Incidence With Known HIV Status	% of incident TB cases in each country with known HIV status (col L unless blank; if blank, then we calculate what the missing data would have to be in order to meet the glob- al average of 34%: 6.78%.
S	# TB Incidence With Known HIV Status	Number of Incident TB with known HIV status (Col O * Col

		K).
T	TB/HIV+ Among Incident Cases With Known HIV Status	Number of Incident TB with known HIV status that are HIV positive (Col N / Col M * Col P).
U	TB/HIV- Among Incident Cases With Known HIV Status	Number of Incident TB with known HIV status that are HIV negative (Col P - Col Q).
V	TB/HIV+ Proportion	Percent of Incident TB that are HIV+ (Col Q / Col P).
W	TB/HIV- Proportion	Percent of Incident TB that are HIV- (Col R / Col P).
X	Total Incident Drug Susceptible TB	Number of incident TB cases that are DS-TB.
Y	Incident cases that are TB/HIV+	Number of incident TB cases that are DS-TB and HIV+.
Z	Incident cases that are TB/HIV-	Number of incident TB cases that are DS-TB and HIV-.
AA	Total DALYS Lost to Drug Susceptible TB/HIV+	DALYs lost to DS-TB cases that are HIV+.
AB	Total DALYS Lost to Drug Susceptible TB/HIV-	DALYs lost to DS-TB cases that are HIV-.
AC	Treatment Coverage for TB / HIV+	Treatment Coverage for drug-susceptible TB/HIV+ cases (Cell I39)
AD	Treatment Coverage for TB / HIV-	Treatment Coverage for drug-susceptible TB/HIV- cases (Cell I39)
AE	Impact of Active TB/HIV+ Treatment Regimen	Impact of treatment for drug-susceptible TB/HIV+ (Col V * Col X * Cell I23)
AF	Impact of Active TB/HIV- Treatment Regimen	Impact of treatment for drug-susceptible TB/HIV- (Col W * Col Y * Cell I24)
AG	MDR-TB Incidence	Number of MDR-TB incident cases.
AH	New cases that have MDR-TB	Number of incident cases that have MDR-TB (from WHO)
AI	% of new cases that have MDR-TB	Percent of incident cases that have MDR-TB (from WHO)

AK	% of retreatment cases that have MDR-TB	Percent of retreatment cases that have MDR-TB (from WHO)
AL	Estimated new cases (any type)	Estimated number of new cases of any type of TB (Col AB / Col AC)
AM	Estimated Retreatment Cases (any type)	Estimated number of retreatment cases of any type of TB (Col AD / Col AE)
AN	Weighted average of proportion of new and retreatment cases that have MDR-TB	Total proportion of cases (new and retreatment) that have MDR-TB [(Col AB + Col AD) / (Col AF + Col AG)]
AO	# MDR-TB Needing Treatment	Total number of MDR-TB cases needing treatment (Col J * Col AH)
AP	# MDR-TB Receiving Treatment	Total number of MDR-TB cases receiving Treatment (from WHO)
AQ	Treatment Coverage for MDR-TB	Treatment coverage for MDR-TB (Col AJ / Col AI)
AR	DALYs Lost to MDR-TB	Total DALYs lost to MDR-TB [(Col D * Col AH) - Col TB AQ]
AS	Impact of MDR-TB Treatment Regimen	Total impact of MDR-TB treatments respective to country.
AT:AV	Impact of MDR-TB Treatment Regimen	Impact of MDR-TB treatment credited to certain regimens.
AW	XDR-TB Incidence	Number of XDR-TB incident cases.
AX	# XDR-TB Needing Treatment	Number of XDR-TB cases needing treatment (Col AN * Col AP)
AY	# XDR-TB Receiving Treatment	Number of XDR-TB cases receiving treatment (Col AN * Col AP)
AZ	Treatment Coverage for XDR-TB	Treatment coverage for XDR-TB cases (Cell I38)

BA	DALYs lost to XDR-TB Impact of XDR-TB	Total DALYs lost to XDR-TB (Col D * Col AH * Cell I31)
BB	Impact of XDR-TB Treatment Regimen	Total impact of XDR-TB treatment respective to country. Divided by two because average length of XDR-Tb treatment is two years.
BC	Total TB Treatment Impact	Total DALYs alleviated by all TB treatment (Col Z + Col AA + Col AM + Col AR)
BD	Previously treated cases resistance rates (H+R)	Sourced from the Global Project on Anti-Tuberculosis Drug
BE	Previously treated cases resistance rates (H+R+E+S)	Sourced from the Global Project on Anti-Tuberculosis Drug Resistance Surveillance.
BF	Previously treated cases resistance rates (Multidrug)	Sourced from the Global Project on Anti-Tuberculosis Drug Resistance Surveillance.
BG	New MDR-TB cases resistance rates (H+R)	Sourced from the Global Project on Anti-Tuberculosis Drug Resistance Surveillance.
BH	New MDR-TB cases resistance rates (H+R+E+S)	Sourced from the Global Project on Anti-Tuberculosis Drug Resistance Surveillance.
BI	New MDR-TB cases resistance rates (Multidrug)	Sourced from the Global Project on Anti-Tuberculosis Drug Resistance Surveillance.
BJ	Previously treated cases resistance rates estimate (H+R)	Fallback data applied (regional or global averages).
BK	Previously treated cases resistance rates estimate (H+R+E+S)	Fallback data applied (regional or global averages).
BL	Previously treated cases resistance rates estimate (Multidrug)	Fallback data applied (regional or global averages).
BM	New MDR-TB cases resistance rates estimate (H+R)	Fallback data applied (regional or global averages).
BN	New MDR-TB cases resistance rates estimate (H+R+E+S)	Fallback data applied (regional or global averages).
BO	New MDR-TB cases resistance rates estimate (Multidrug)	Fallback data applied (regional or global averages).
CB	Previously treated cases portion of drug combination estimate (Z+S+Lfx+Eto+Cs+PAS)	Previously treated: H+R and H+R+E resistance proportion without resistance to Z

CC	Previously treated cases portion of drug combination estimate (S+Lfx+Eto+Cs+PAS)	Previously treated: H+R and H+R+E resistance proportion with resistance to Z
CD	Previously treated cases portion of drug combination estimate (Km+Lfx+Eto+Cs+PAS)	Previously treated: H+R+S and H+R+E+S resistance proportion
CE	New MDR-TB cases drug combination portion of total percent of MDR-TB cases of those with DST estimate (Z+S+Lfx+Eto+Cs+PAS)	Newly treated: H+R and H+R+E resistance proportion without resistance to Z
CF	New MDR-TB cases drug combination portion of total percent of MDR-TB cases of those with DST estimate (S+Lfx+Eto+Cs+PAS)	Newly treated: H+R and H+R+E resistance proportion with resistance to Z
CG	New MDR-TB cases drug combination portion of total percent of MDR-TB cases of those with DST estimate (Km+Lfx+Eto+Cs+PAS)	Newly treated: H+R+S and H+R+E+S resistance proportion
CH	Weighted average drug combination drug combination estimate (Z+S+Lfx+Eto+Cs+PAS)	(% retreatment cases * portion of previously treated cases respective to regimen) + (% new cases * portion of newly treated cases respective to regimen)
CI	Weighted average drug combination drug combination estimate (S+Lfx+Eto+Cs+PAS)	(% retreatment cases * portion of previously treated cases respective to regimen) + (% new cases * portion of newly treated cases respective to regimen)
CJ	Weighted average drug combination drug combination estimate (Km+Lfx+Eto+Cs+PAS)	(% retreatment cases * portion of previously treated cases respective to regimen) + (% new cases * portion of newly treated cases respective to regimen)

II. Missing Data

In order to find missing data we have sent multiple emails to country level TB research labs. We were able to find emails via StopTB and WHO TB Supranational Reference Laboratory Network (SRLN). So far in our efforts we have only received data from Australia, Denmark, Japan, and the United States. In place of country level data, we use regional and national data to create accurate estimates. The specific model columns that are missing data are:

1. BE - Previously Treated Resistance Rates; H+R+E+S
2. BF - Previously Treated Resistance Rates; Multidrug
3. BH - New MDR TB Cases; H+R+E+S
4. BI - New MDR TB Cases; Multidrug

III. Scoring Calculations

For each country (each row), treatment impact is computed using the general impact formula. This, however, is dependent upon the type of TB. DS-TB is calculated in this way but the final impacts of MDR-TB and XDR-TB are divided by two because the average length of treatment for these strains is two years.

$$\text{Impact} = \frac{D \cdot \theta \cdot e}{(1 - \theta \cdot e)}$$

The treatment impacts are then broken down in the following way:

For DS-TB, each of the drugs in the standard first-line regimen (H + R + E + Z) are given equal weight. Therefore, every component drug gets 25% of the total impact for DS-TB treatment impact.

For MDR-TB, each drug in the three regimens are given equal weight. Therefore, every component drug in the regimen Z+S+Lfx+Eto+Cs+PAS gets 17% credit.

For XDR-TB, the treatment regimen is the following: Cs + Km (or) Amk (or) Cm + Lfx (or) Mfx (or) Gfx (or) Ofx

Each drug is then given credit based on its proportion of the regimen. For example, Cs will always be one third of the regimen, so it receives 33.33% of the credit for XDR-TB impact. Km, on the other hand, is only one of three possible drugs that account for one third of the regimen. As such, Km receives one-third of one-third of the credit for XDR-TB impact, or 11.11%. Finally, the fluoroquinolones (Lfx, Mfx, Gfx, and Ofx) receive 8.33% of the credit for XDR-TB impact.

A major component of calculating the impact of MDR-TB is the inclusion of resistance rates to determine treatment proportions for the three possible regimens. We will cover MDR-TB in the example below to demonstrate this point. MDR-TB is treated with one of three regimens, based on what first-line drugs the individual demonstrates resistance to. Resistance to certain drugs is what determines the recommended treatment regimen, and can therefore be used to estimate the proportions of people that receive each regimen. These calculations are initially split into either new TB cases or retreatment cases, since there is unique resistance rate data for both. Once each category of MDR-TB drug resistance has a proportion calculated, the retreated and new cases are combined into the final section that determines the proportion of all MDR-TB cases that are receiving each treatment regimen.

IV. Example Scoring Calculation: Impact of Z in an MDR-TB regimen in Afghanistan

Let's derive the impact of Z in 2013. As a demonstration of how the model works we will first calculate Afghanistan's impact on DS-TB, MDR-TB and XDR-TB, then we will determine what drugs get credit for the treatment impact.

We first must estimate the proportion of the 448,000 DALYs lost to TB in Afghanistan in 2013 that were lost to DS-TB, MDR-TB, and XDR-TB. To do so, we assume that total MDR-TB cases are equal to:

Overall percentage of MDR-TB among TB cases * TB cases of any type

The WHO's TB database provides the number of MDR-TB cases among notified new pulmonary TB cases, the percentage of new TB cases that have MDR-TB, MDR-TB cases among notified previously treated pulmonary TB cases, and the percentage of previously treated TB cases that have MDR-TB.

Using this information we can obtain the estimated new cases of any type in Afghanistan by dividing MDR-TB cases among new cases of TB (4) by the percentage of new TB cases that were MDR-TB (3.7%).

4 / 3.7% = **108.11 new cases**

We estimate the estimated retreatment cases of any type using the same logic.

15 / 20% = **75 retreatment cases**

Having obtained this we can determine the percentage of MDR-TB cases in Afghanistan:

(4 + 15) / (108.11 + 75) = **10.38% of prevalent TB cases in Afghanistan in 2013 are MDR-TB**

Note that 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 this fallback data will maintain

a total MDR-TB impact score but will lack the further disaggregation of impact among treatment regimens. This is due to the absence of resistance rate data for new and retreated MDR-TB cases at the country-level.

The overall percentage of MDR-TB cases, 10.38%, is assumed to extend to the percentage of total DALYs attributed to TB that are attributable to MDR-TB and XDR-TB. Thus, of the 448,000 DALYs in Afghanistan, those attributable to XDR-TB are 9.6% of 10.38% of 448,000, or 4,462.68. 10.38% of the 448,000 DALYs subtracted by the number of XDR-TB DALYs, 42,023.52, are assumed to be MDR-TB. The remainder of the DALYs attributed to TB are attributed to DS-TB, 401,513.80 in Afghanistan.

However, this drug-susceptible number must be split into TB/HIV+ and TB/HIV-, as the treatment efficacy differs based on HIV status. The WHO states that there were 58,000 TB incidence cases and 26% of those cases were tested for HIV status. Out of those tested, 16 were HIV+ and 15,064 were HIV-, or .11% and 99.89% respectively.

TB/HIV+: 401,513.8 * .11% = **438.17 DALYs**
TB/HIV-: 4015,513.8 * 99.89% = **401,075.63 DALYs**

Thus, the following numbers have been obtained for Afghanistan in 2013:

$_{D}$TB/HIV+ = 438.17
$_{D}$TB/HIV- = 401,075.63
$_{D}$MDR = 42,023.52
$_{D}$XDR = 4,462.68

We know that Afghanistan had 100,000 prevalent cases of TB, so we can estimate that there were 10,380 prevalent MDR-TB cases (100,000 * 10.38%). This number is used to estimate MDR-TB treatment coverage. The WHO states that 48 Afghani nationals received treatment for MDR-TB. Therefore we can estimate MDR-TB treatment coverage to be .46%, or (48 / 10,380).

The final data point we need is the efficacy of MDR-TB treatment. This number, 52%, was found in the WHO"s Global Tuberculosis Report. At this point we have enough data to use the general impact formula to calculate the final impact of MDR-TB treatment in Afghanistan:

$$\frac{DALYs\ lost\ to\ MDR-TB\ *\ MDR-TB\ treatment\ coverage\ *\ efficacy\ of\ MDR-TB\ treatment}{1\ -\ MDR-TB\ treatment\ coverage\ *\ efficacy\ of\ MDR-TB\ treatment}\ /\ 2$$

$$\frac{42{,}023.52\ *\ .46\%\ *\ 52\%}{1\ -\ .46\%\ *\ 52\%}\ /\ 2$$

50.66

Similar steps are taken to compute the impact of XDR-TB drugs. We already know that there were 4,462.68 DALYs lost to XDR-TB. The WHO's GLobal Tuberculosis Report states that there is a global average of 57% of treatment coverage for XDR-TB. The WHO also approximates that the efficacy of XDR-TB treatment is 28%. Thus the impact of XDR-TB medicines in Afghanistan in 2013 is:

$$\frac{4{,}462.68\ *\ 28\%\ *\ 57\%}{1\ -\ 28\%\ *\ 57\%}\ /\ 2$$

423.75

The impact of DS-TB can be easily calculated as well. Country level treatment coverage data for Afghanistan in 2013 is unable to be found so for now we use the WHO's estimate of directly observed treatment coverage of 58% for every case. We use estimates in the WHO's Global Tuberculosis Report in 2015 to determine an efficacy of 73% for HIV+ cases and an efficacy of 88% for HIV- cases. We can use this data to calculate the final impact score for the TB/HIV+ and TB/HIV- treatment regimens:

TB/HIV+: (438.17 * 58% * 73%) / (1 - 58% * 73%) **= 321.75**
TB/HIV-: (401,075.63 * 58% * 88%) / (1 - 58% * 88%) **= 418,114.79**

By now we have calculated the impact of MDR-TB, XDR-TB, and DS-TB. The next step is to determine what drugs get credit for the treatment impact. Most anti-TB treatment is a combination therapy. The contribution of each drug should sum to the overall impact of the therapy. However, determining what proportion of the overall impact each drug gets differs depending on the type of TB.

A difficulty that arises with MDR-TB treatment is that patients are oftentimes resistant to different drugs. The treatment regimen used varies depending upon which drugs the patient is resistant to. The following regimens for MDR-TB are listed below:

MDR-TB Treatment Regimen

Drug Resistance	Treatment Regimen
Isoniazid (H) + Rifampicin (R) or R + Ethambutol (E)	Z+S+Lfx+Eto+Cs+ PAS
H + R + E + Pyrazinamide (Z)	S+Lfx+Eto+Cs+PAS
H+R+Streptomycin (S); H+R+E+S; H+R+E +Z+S	Km+Lfx+Eto+Cs+PAS

The percentage of treatment that each regimen comprises is then based on proportions of drug resistances. To calculate the weight of each drug combination relative to the other MDR-TB regimens, we need to refer to the percentage of drug resistance to drug-susceptible TB treatments, since the resistance an affected person has is what determines the MDR-TB treatment that they receive. According to the WHO, the estimated resistance to H+R in previously treated cases in Afghanistan is 88.24% while the resistance rate for newly treated cases is 100%. The resistance rates for H+R+E+S are unavailable at the country level for previously treated cases and new cases, so the respective regional averages of 23.28% and 1.24% respectively are used. We use the global averages for resistance to H+R+E (3.3%), and H+R+S (11%). Unfortunately, this data does not include pyrazinamide. The drug resistance rates in Afghanistan are illustrated in the table below:

MDR-TB Resistance Rates

Drug	Previously treated	Newly treated
H+R	88.24%	100%
H+R+E	3.3%	3.3%
H+R+S	11%	11%
H+R+E+S	23.28%	1.24%

Given the values above, we can calculate the estimated MDR-TB treatment resistances to treatments that include pyrazinamide. According to studies conducted in South Africa, the resistance to pyrazinamide (Z) is 42.25%. We use this value as a global

estimate for the resistance of Z due to the absence of data for the resistance of Z as a part of a treatment regimen. Both H+R+E and H+R+E+S can be taken with or without Z. We calculate their estimated resistance rates (previously treated cases only) as follows:

MDR-TB Resistance Rates (includes treatments with Z)

Drug	Previously treated	Newly treated
H+R	88.24%	100%
H+R+E without Z	3.3% * *(1-42.25%)* = 1.9%	3.3% * *(1-42.25%)* = 1.9%
H+R+E+Z	3.3% * *42.25%* = 1.39%	3.3% * *42.25%* = 1.39%
H+R+S	11%	11%
H+R+E+S without Z	23.28% * *(1-42.25%)* = 13.44%	1.24% * *(1-42.25%)* =0.72%
H+R+E+S+Z	23.28% * *42.25%* = 9.83%	1.24% * *42.25%* = .52%

We use these values to calculate the proportion of each resistance rate out of the total resistance rates of all drugs.

Table IIE: Proportion of MDR-TB Cases

Drug	Previously treated	Newly treated
H+R	88.24% / 125.81% = 70.13%	100% / 115.53% = 86.57%
H+R+E without Z	1.9% / 125.81% = 1.51%	1.9% / 115.53% = 1.64%
H+R+E+Z	1.39% / 125.81% = 1.1%	1.39% / 115.53% = 1.2%
H+R+S	11% / 125.81% = 8.74%	11% / 115.53% = 9.52%
H+R+E+S without Z	13.44% / 125.81% = 10.68%	0.72% / 115.53% = 0.62%
H+R+E+S+Z	9.83% / 125.81% = 7.81%	0.52% / 115.53% = 0.45%

Given the estimated resistance rates for these MDR-TB treatments, we can calculate the portion of each MDR-TB treatment used. Recall that:

1. Those with resistance to H+R and H+R+E without Z are treated by the Z+S+Lfx+Eto+Cs+PAS MDR-TB treatment regimen.
2. Those with resistance H+R+E+Z are treated by the S+Lfx+Eto+Cs+PAS MDR-TB treatment regimen.
3. Those with resistance H+R+S, H+R+E+S without Z, and H+R+E+S+Z are treated by the Km+Lfx+Eto+Cs+PAS MDR-TB treatment regimen.

Therefore, the weights for treatment regimens for the previously and newly treated can be calculated in the following way:

Proportion of MDR-TB Treatment Based on Resistance Rates (previously treated cases)

Drug resistance	Treatment regimen	Proportion of treatment (previously treated cases)	Proportion of treatment (newly treated cases)
H+R only	Z+S+Lfx+Eto+Cs+PAS	70.13% + 1.51% = 71.65%	86.57% + 1.64% = 88.21%
H+R+E without Z			
H+R+E+Z	S+Lfx+Eto+Cs+PAS	1.1%	1.2%
H+R+S	Km+Lfx+Eto+Cs+PAS	8.74% + 10.68% + 7.81% = 27.23%	9.52% + 0.62% + 0.45% = 10.59%
H+R+E+S without Z			
H+R+E+Z+S			

With the proportion of MDR-TB treatment for each regimen calculated for both newly and previously treated cases we can calculate the weight of each MDR-TB regimen.

For Afghanistan, we have 4 new cases and 15 retreatment cases of MDR-TB. There are a total of 19 MDR-TB cases in Afghanistan: 21.25% are new cases and 78.95% are retreatment cases. We calculate the weight of each treatment as follows:

Weight of MDR-TB Treatment Based on Regimen

Regimen	Weight of MDR-TB treatment
Z+S+Lfx+Eto+Cs+PAS	(21.25%*71.64%) + (78.95%*88.19%) = 75.13%
S+Lfx+Eto+Cs+PAS	(21.25%*1.1%) + (78.95%*2.14%) = 1.13%
Km+Lfx+Eto+Cs+PAS	(21.25%*21.59%) + (78.95%*10.59%) = 23.74%

The final step is to simply multiply the total MDR-TB impact score for Afghanistan by the weight of each treatment. In the case of Afghanistan, we see that:

$I_{Z+S+Lfx+Eto+Cs+PAS}$ = 50.66 * 75.13% = 40

$I_{S+Lfx+Eto+Cs+PAS}$ = 50.66 * 1.2% = .57

$I_{Km+Lfx+Eto+Cs+PAS}$ = 50.66 * 23.74% = 12.03

Recall that our goal is to calculate the impact of Z in an MDR-TB regimen Afghanistan. Additionally, recall that every component drug in the MDR-TB regimen Z+S+Lfx+Eto+Cs+PAS gets 17% credit. We simply need to multiply the impact of the regimen Z+S+Lfx+Eto+Cs+PAS by 17% to derive the impact of Z:

I_Z = 40 * 17% = 6.8

V. Assumptions

Data	Value Assumed	Column/Range
Efficacy of treatment for HIV+ TB	73%	I23
Efficacy of treatment for HIV- TB	87%	I24
Efficacy of MDR-TB treatment	48%	I25
Efficacy of treatment for HIV+ TB	20%	I26
% of MDR-TB that is XDR-TB	9%	I31
XDR-TB Treatment Coverage	43%	I38
Drug-Susceptible-TB Treatment Coverage	65.9%	I39