South African National Essential Medicines List
South African National Essential Medicine List Primary Level Medication Review Process
Component: Respiratory conditions

Estimated budget impact of different TB preventive therapy options for reducing the incidence of TB in household contacts of people diagnosed with drug susceptible TB

21 June 2022

This analysis has been revised based on external stakeholder feedback received and further deliberation by the review team. Changes in the assumptions underlying the analysis led to changes in the results.

EXECUTIVE SUMMARY

Medicine: Isoniazid, rifapentine
Indication (ICD10 code): Z29.2
Research question: What is the potential budget impact of four TB preventive therapy (TPT) options for reducing the incidence of TB in household contacts of people diagnosed with drug susceptible TB?
Patient population: Household contacts of people diagnosed with drug-susceptible TB
Level of Care: Primary Health Care
Prescriber level: Nurse prescriber
Current Standard of Care/ Comparator(s): Household contacts of people diagnosed with drug-susceptible TB – only children aged <5 years (irrespective of HIV status)
Findings: The total estimated annual costs of providing TPT to the expanded populations are very uncertain due to significant uncertainty in model parameters – especially primary healthcare utilization and costs.

- The estimated ***pharmaceutical acquisition costs*** are less uncertain, with incremental costs (compared to current standard of care) calculated as:
  - *INH monotherapy for all ages – R18,265,490*
  - *3HP for >2y, INH monotherapy for <2y – R72,886,084*
  - *1HP for >13y, INH monotherapy for <13y – R111,735,429*
- The estimated *incremental costs (**total:** pharmaceutical, health resources, adverse events, costs averted)* of the expanded TPT options:
  - *INH monotherapy for all ages – R148,577,833*
  - *3HP for >2y, INH monotherapy for <2y – R136,418,923*
  - *1HP for >13y, INH monotherapy for <13y – R165,638,824*

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INTRODUCTION

Tuberculosis (TB) is a communicable disease and one of the top ten causes of death worldwide. Providing TB preventive therapy (TPT) to those at highest risk of developing active TB disease may decrease TB related morbidity and mortality.

The current South African Standard Treatment Guidelines and Essential Medicine List recommends that household contacts under the age of five (irrespective of HIV status) of people diagnosed with drug-susceptible (DS) TB receive isoniazid (INH) monotherapy for six months (1). Changes to national TPT guidelines in South Africa have been proposed. To inform consideration of changes in recommended options for TPT in household contacts of infectious DS TB cases, this budget impact analysis provides an estimate of the potential impact expansion of TPT to household contacts of all ages, and change in TPT regimen, will have on the healthcare budget.

METHODS

This analysis presents the potential budget impact of different TPT options for reducing the incidence of TB in household contacts of people diagnosed with DS TB. A review of clinical studies to assess the efficacy and safety of the TPT options for household contacts was conducted. The assumptions made in this budget impact analysis is based on the findings of that review, with additional references for South African-specific estimates to inform the budget impact analysis.

We included 4 TPT options (for household contacts):

- Standard of care: Daily INH for 6 months (children aged <5years),
- Daily INH for 6 months[1] (all ages),
- Weekly rifapentine plus INH for 3 months (3HP) (all ages covered[2]), and
- Daily rifapentine plus INH for 1 month (1HP) (all ages covered[2]).

All TPT populations include HIV positive and HIV negative household contacts.

The analysis was performed from the perspective of the National Department of Health of South Africa. The costs reflected in the analysis include the pharmaceutical acquisition costs, visits to primary healthcare (PHC) facilities, inpatient costs incurred as a result of severe adverse events (drug induced liver injury), and health system costs averted due to TB cases averted. It is assumed that people discontinuing TPT will incur 50% of medicine and clinic visit costs, but no adverse event costs and they will not contribute to the costs averted due to TB disease averted.

Costs are presented in nominal terms and undiscounted over time.

The costs represent complete (100%) adoption of the particular regimen for one course of TPT.

The assumptions and calculations that underpins the base-case analysis are presented in Appendix 1.

Univariate sensitivity analysis (varying one parameter at a time) was performed to assess the uncertainty of the model parameters. Parameters that were varied include inputs that changed population estimates (number of index cases, TB disease positivity rate amongst household contacts, discontinuation rates), the cost of INH monotherapy if 12 months of INH is given to HIV positive contacts weighing >25kg, cost and quantity of PHC clinic visits, length and risk of hospitalization due to adverse drug reactions, costs of DS TB treatment (representing healthcare cost averted), and the number needed to treat (NNT).

[1] Draft NDoH TPT guidelines recommends 12 months of INH monotherapy for HIV positive contacts who weigh more than 25kg, but this budget impact analysis assumed a TPT duration of 6 months for all patients irrespective of HIV status in line with WHO recommendation.

[2] Children not eligible to receive 3HP or 1HP will receive INH monotherapy for six months

RESULTS

The list of model parameters use in the base-case analysis is provided in Appendix 2.

The estimated size of the population likely to receive TPT will increase significantly (8 fold) compared to the population currently receiving TPT. The differences in the estimated size of the populations that will complete TPT options 1, 2 and 3 are due to variations in the number of people likely to discontinue TPT across the different regimens (see Table 1). The discontinuation rates used in the analysis are uncertain as real-world data is lacking. A sensitivity analysis was conducted to explore this uncertainty (see Table 3).

Table 1: Number of people likely to receive a course of TPT per year (by regimen)

	Estimated population size (n)		
TPT regimen	**Complete TPT course**	**Discontinue TPT course~**	**Total**
Standard of care: INH monotherapy (aged < 5 years)	17,301	8,953	26,254
TPT option 1: INH monotherapy (all ages included)	149,540	77,379	226,919
TPT option 2: 3HP for >2y, INH monotherapy for <2y (all ages included)	182,239	44,680	226,919
TPT option 3: 1HP for >13y, INH monotherapy for <13y (all ages included)	226,919	0	226,919

~Assumed that these people will incur half of medicine and clinic visit costs.

The estimated *incremental* (total) cost of expanding TPT to all household contacts of people diagnosed with PTB is R148.6 million for INH monotherapy, R136.4 million for 3HP regimen, and R165.6 million for the 1HP regimen (see Table 2).

The overall cost of TPT is largely driven by healthcare resource use costs (clinic visit costs) for INH monotherapy (see Figure 1). The parameters used to calculate the cost of clinic visits (the cost per visit and number of visits required) are highly uncertain. In addition, it is unclear if/to what extent additional clinic visits required for expansion of TPT can be absorbed by existing capacity within the health system and whether or not TPT can/will be provided using Chronic Medicines Dispensing (uncertainty is explored in sensitivity analysis - see Table 3). If clinic visit costs are not taken into account in the analysis, the estimated *incremental* cost of expanding TPT is R16 million for INH monotherapy, R68 million for the 3HP regimen, and R108 million for the 1HP regimen (see sensitivity analysis in Table 3).

The *per patient* pharmaceutical acquisition costs for the TPT regimens are more certain, with confidence in the estimated pharmaceutical acquisition costs for the *expanded TPT population* only reduced due to uncertainty regarding the population size used in the analysis. The estimated *incremental* pharmaceutical acquisition cost is R18.3 million for INH monotherapy, R72.9 million for 3HP regimen, and R111.7 million for the 1HP regimen (see Table 2).

The cost of adverse events contributed the least of all the cost components to the total cost of TPT for all options considered (see Table 2). This is due to the low risk of hepatotoxicity severe enough to result in hospitalisation. The cost of adverse events may however be underestimated in this analysis as the cost of medicines and tests conducted during the inpatient stay for hepatotoxicity has not been captured.

The estimated cost per TB case (reflecting the 'costs averted') is uncertain as there is no current empirical data that reflects the mean cost of DS TB treatment across South Africa taking into account its variation and/or its distribution. A cost per TB case calculated in a South African TB costing study (increased by 50% to account for potential underestimation of the cost) was used as base-case estimate in the analysis.

Based on the findings from the budget impact analysis, the per patient cost of initiating a person on TPT will be 15-18% of the cost of treating an active DS TB case.

Table 2. Estimates of annual budget impact

	Standard of care (INH for <5Y)	**INH monotherapy for all ages**	**3HP for >2Y, INH monotherapy for <2Y**	**1HP for >13Y, INH monotherapy for <13Y**
Size of population that will receive TPT (n)	17,301	149,540	182,239	226,919
GROSS COST				
Pharmaceutical cost	R2,528,859	R20,794,349	R75,414,944	R114,264,289
Healthcare resource use cost	R17,338,767	R149,863,013	R85,308,096	R75,034,561
Adverse events cost	R0	R4,227,420	R3,595,107	R6,414,901
Savings due to TB cases averted	-R842,487	-R7,281,810	-R8,874,084	-R11,049,788
Gross total cost	**R19,025,140**	**R167,602,973**	**R155,444,062**	**R184,663,963**
NET BUDGET IMPACT *(other TPT regimens - standard of care)*				
Net pharmaceutical cost	-	R18,265,490	R72,886,084	R111,735,429
Net healthcare resource use cost	-	R132,524,246	R67,969,329	R57,695,794
Net adverse events cost	-	R4,227,420	R3,595,107	R6,414,901
Net savings due to TB cases averted	-	-R6,439,323	-R8,031,598	-R10,207,301
Net total cost	**-**	**R148,577,833**	**R136,418,923**	**R165,638,824**

SENSITIVITY ANALYSIS

A univariate sensitivity analysis was conducted where single model parameters were varied to assess uncertainty in these variables. The list of parameters used in the sensitivity analysis is provided in Appendix 3. The results of the sensivity analysis are presented in Table 3.

For all new TPT options, changing the cost of a clinic visit resulted in the most significant change in overall costs, followed by a change in the number of clinic visits, and changing the number of index cases.

Figure 1: Cost drivers for TPT options

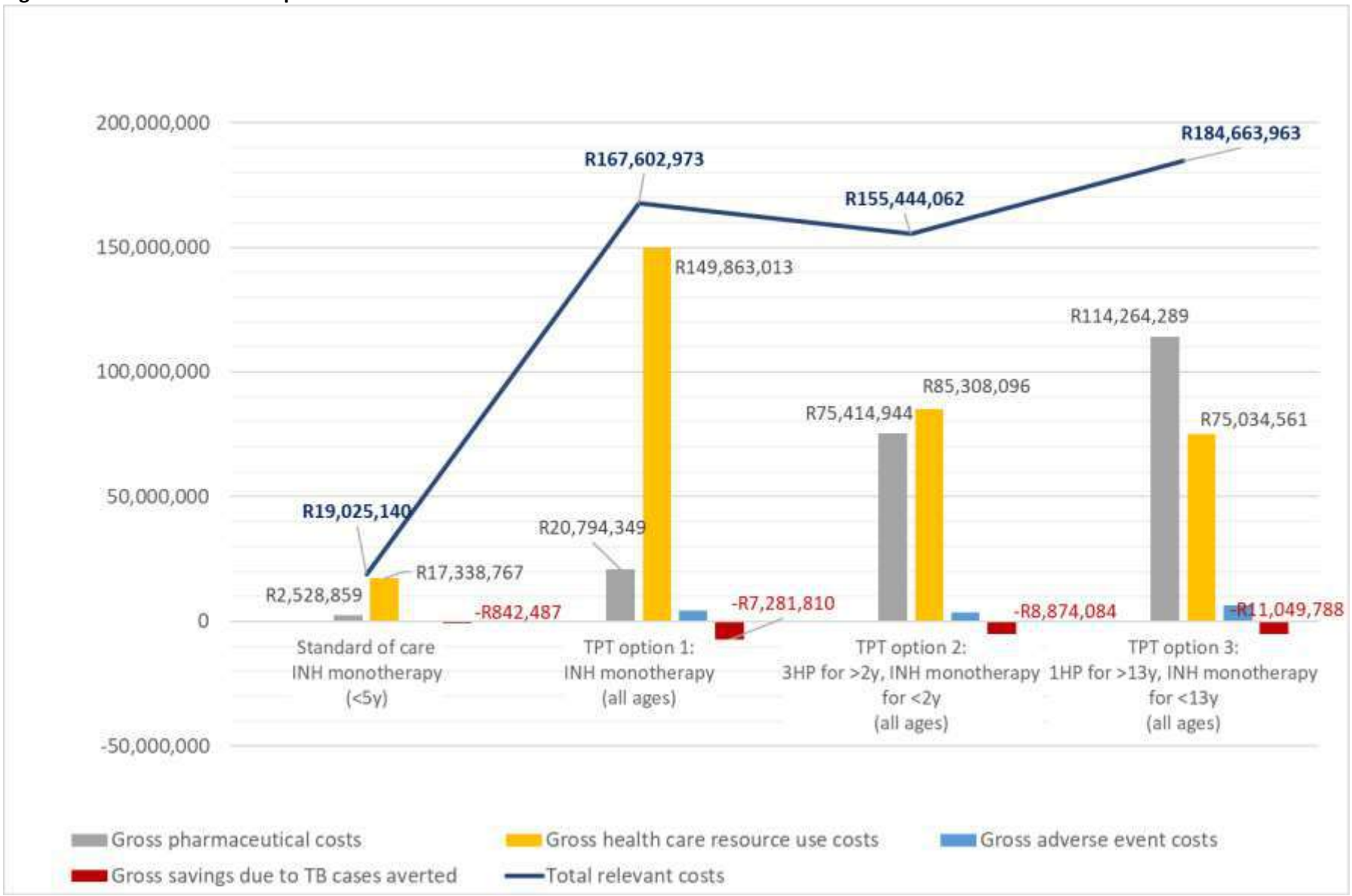

Table 3. Sensitivity analysis. Costs presented as NET COSTS (future - current treatment pathway costs)

			TPT option 1: INH monotherapy	TPT option 2: 3HP for >2y, INH for <2y	TPT option 3: 1HP for >13y, INH for <13y
Base case analysis	*Base case assumptions*	Population increase from standard of care (SoC)	132,238	164,938	209,618
		Net total costs	R148,577,833	R136,418,923	R165,638,824
		Net pharmaceutical costs	R18,265,490	R72,886,084	R111,735,429
SENSITIVITY ANALYSIS					
1. Changes to population parameters					
NUMBER OF INDEX CASES	175,530 Number of patients diagnosed and started on treatment in 2020 (2)	Population increase from SoC (n)	119,015	148,444	188,656
		Net total costs	R133,720,050	R122,777,031	R149,074,941
		Net pharmaceutical costs	R16,438,941	R65,597,476	R100,561,886
DIAGNOSED WITH TB DISEASE PRIOR TO TPT INITIATION	7.50% Proportion from Targeted Universal Testing for TB (TUTT) study (3)	Population increase from SoC (n)	126,234	157,448	200,100
		Net total costs	R141,831,265	R130,224,462	R158,117,556
		Net pharmaceutical costs	R17,436,097	R69,576,499	R106,661,788
DISCONTINUATION RATES	INH monotherapy: 31.0% 3HP: 17.9% Discontinuation rates reported by Stirling et 2011 (4)	Population increase from SoC (n)	138,459	168,186	208,804
		Net total costs	R151,291,433	R137,565,201	R165,307,209
		Net pharmaceutical costs	R18,606,798	R73,587,500	R111,688,175
	INH monotherapy: 37.51% 3HP: 21.66% 10% increase from base-case analysis	Population increase from SoC (n)	125,396	161,365	210,513
		Net total costs	R145,592,873	R135,158,017	R166,003,599
		Net pharmaceutical costs	R17,890,051	R72,114,526	R111,787,409

Table 3. Sensitivity analysis (continued)			TPT option 1: INH monotherapy	TPT option 2: 3HP for >2y, INH for <2y	TPT option 3: 1HP for >13y, INH for <13y
Base case analysis	*Base case assumptions*	Net total costs	R148,577,833	R136,418,923	R165,638,824
		Net pharmaceutical costs	R18,265,490	R72,886,084	R111,735,429
		Net healthcare resource use costs	R132,524,246	R67,969,329	R57,695,794
SENSITIVITY ANALYSIS					
2. Changes to cost of TPT					
AVG MEDICINE COST FOR TPT OPTION 1 and 3	TPT Option 1: R122.59 TPT Option 3: R506.44 HIV+ contacts: >25kg - 12 months INH TPT <25kg - 6 months INH TPT	Net total costs	R150,857,628	R136,418,923	R166,296,509
		Net pharmaceutical costs	R20,545,285	R72,886,084	R112,393,115
3. Changes to healthcare resource use and cost parameters					
NUMBER OF CLINIC VISITS	<u>Standard of care and TPT Option 1: all receive INH monotherapy</u> HIV- or not on ARVs - 6 visits, HIV+ and on ARTs - 0 visits <u>TPT Option 2: 3HP and INH</u> *3HP* >2y, HIV- or not on ARVs: 3 visits >2y, HIV+ and on ARVs: 0 visits *INH monotherapy:* <2y: 6 visits <u>TPT Option 3: 1HP and INH</u> *1HP* >13y, HIV- or not on ARVs: 1 visit >13y, HIV+ and on ARVs: 0 visits *INH monotherapy:* <13y: 6 visits	Net total costs	R136,211,826	R130,076,618	R160,255,155
		Net healthcare resource use costs	R120,158,239	R61,627,024	R52,312,125
	<u>Standard of care and TPT Option 1: all receive INH monotherapy</u> 1 screening visit + 6 visits <u>TPT Option 2: 3HP and INH</u> 3HP for >2y: 1 screening visit + 3 visits INH for <2y: 1 screening visit + 6 visits <u>TPT Option 3: 1HP and INH</u> 1HP for >13y: 1 screening visit + 1 visit INH for <13y: 1 screening visit + 6 visits	Net total costs	R170,665,207	R160,675,803	R192,860,143
		Net healthcare resource use costs	R154,611,621	R92,226,209	R84,917,113

Table 3. Sensitivity analysis (continued)			TPT option 1: INH monotherapy	TPT option 2: 3HP for >2y, INH for <2y	TPT option 3: 1HP for >13y, INH for <13y
Base case analysis	*Base case assumptions*	Net total costs	R148,577,833	R136,418,923	R165,638,824
		Net healthcare resource use costs	R132,524,246	R67,969,329	R57,695,794
		Net adverse event costs	R4,227,420	R3,595,107	R6,414,901
		Net cost averted	-R6,439,323	-R8,031,598	-R10,207,301
SENSITIVITY ANALYSIS					
3. Changes to healthcare resource use and cost parameters (continued)					
MIX OF CLINIC VISITS AND MEDICINE COLLECTION VISITS	People receiving INH monotherapy 2 clinic visits + 4 medicine collection visits People on 3HP regimen 1 clinic visit + 2 medicine collection visits People on 1HP regimen 1 clinic visit	Net total costs	R107,976,731	R115,595,340	R154,435,163
		Net healthcare resource use costs	R91,923,144	R47,145,746	R46,492,133
COST OF CLINIC VISITS	R0	Net total costs	R16,053,587	R68,449,594	R107,943,030
		Net healthcare resource use costs	R0	R0	R0
	R279	Net total costs	R294,424,436	R211,221,052	R229,134,642
		Net healthcare resource use costs	R278,370,849	R142,771,458	R121,191,612
4. Changes to adverse events parameters					
INPATIENT - LENGTH OF STAY	7 days	Net total costs	R146,464,123	R134,621,369	R162,431,373
		Net adverse event costs	R2,113,710	R1,797,554	R3,207,451
SEVERE HEPATOTOXICITY	TPT option 1 (INH monotherapy): 0.11% TPT option 2 (3HP for >2y, INH for <2y): 0.07% TPT option 3 (1HP for >13y, INH for <13y): 0.11%	Net total costs	R145,834,044	R134,085,534	R161,475,259
		Net adverse event costs	R1,483,631	R1,261,718	R2,251,336
	TPT option 1 (INH monotherapy): 0.50% TPT option 2 (3HP for >2y, INH for <2y): 0.35% TPT option 3 (1HP for >13y, INH for <13y): 0.50%	Net total costs	R151,321,622	R138,752,312	R169,802,389
		Net adverse event costs	R6,971,209	R5,928,496	R10,578,467

Table 3. Sensitivity analysis (continued)

			TPT option 1: INH monotherapy	TPT option 2: 3HP for >2y, INH for <2y	TPT option 3: 1HP for >13y, INH for <13y
Base case analysis	*Base case assumptions*	Net total costs	R148,577,833	R136,418,923	R165,638,824
		Net healthcare resource use costs	R132,524,246	R67,969,329	R57,695,794
		Net adverse event costs	R4,227,420	R3,595,107	R6,414,901
		Net cost averted	-R6,439,323	-R8,031,598	-R10,207,301
5. Changes to healthcare costs averted					
COST DIAGNOSIS & TREATMENT OF DS-TB	R14,025	Net total costs	R134,636,447	R119,030,201	R143,539,619
		Net costs averted	-R20,380,709	-R25,420,320	-R32,306,505
NUMBER NEEDED TO TREAT (NNT)	NNT 33	Net total costs	R137,260,235	R122,302,782	R147,698,719
		Net costs averted	-R17,756,922	-R22,147,739	-R28,147,405
	NNT 83	Net total costs	R147,957,175	R135,644,793	R164,654,987
		Net costs averted	-R7,059,981	-R8,805,727	-R11,191,137
	NNT 167	Net total costs	R151,508,303	R140,074,021	R170,284,062
		Net costs averted	-R3,508,853	-R4,376,499	-R5,562,062

LIMITATIONS OF THE ANALYSIS

The budget impact analysis has been strengthened by feedback received from stakeholders and further deliberations by the review team[3]. Reducing the number of index cases (from estimated incidence to recorded incidence) and the unit cost of a PHC clinic visit were the main drivers for the reduction in total budget impact.

Population size calculation

The number of children aged <5 years who received TPT in 2020 was 22,689, which is lower than the estimated 'standard of care' population likely to start TPT calculated in budget impact analysis (26,254). In addition, real-world discontinuation rate data for the different TPT regimens are lacking, so the estimations of the number of people that will complete a course of TPT per year is less certain. Sensitivity analyses was conducted to explore this uncertainty (see Table 3).

Healthcare resource use costs

There is significant uncertainty in regards to the estimated healthcare resource use costs (clinic visit costs). The cost of clinic visits per TPT course is a major component of the total costs of INH monotherapy, and an area of potential efficiency savings for short-term TPT regimens (3HT and 1HT) which have higher drug acquisition costs but require less clinic visits. The inability to reliably predict the impact that implementation of the TPT options will have on healthcare resource use costs is a significant weakness of the analysis. Sensitivity analyses were conducted to explore this uncertainty.

The following costs have not been included in this analysis which adds to the uncertainty of the real healthcare resource use cost: 1) cost of following up people who default on TPT and restarting TPT when possible, 2) training required for implementation of the expanded TPT options, 3) monitoring and evaluation costs and 4) laboratory costs for tests to monitor for adverse drug events (e.g. liver function tests).

An ongoing TPT feasibility study may provide some insight into the healthcare resources required for implementation of the different TPT options as well as real-world discontinuation rates. These findings will hopefully inform future analyses in this area.

Healthcare costs averted

The costs averted due to DS PTB cases averted does not take population-level benefits of TPT into account. Costs averted relating to the transmission of TB to secondary cases (including costs for further contact tracing, diagnosis, and providing TPT or active treatment for secondary cases identified) are not included.

Lastly, some people eligible to receive TPT as a household contact might already be receiving TPT as part of comprehensive package of care, but this has not been adjusted for in the analysis.

[3] Across TPT regimens, the eligible population size reduced by more than 50%, pharmaceutical costs per patient changed slightly (less than 5%), healthcare resource use cost per patient reduced by around 50% (mainly due to change in cost of clinic visit used), adverse event costs per patient reduced by more than 50%, and healthcare costs averted due to TB cases averted has been added to the analysis.

APPENDIX 1: ASSUMPTIONS AND CALCULATIONS

1. ELIGIBLE POPULATION

The following assumptions were made in the calculation of the population eligible to receive TPT.

1.1. Population currently eligible for TPT (standard of care)

- INH TPT (duration: 6 months) is currently offered to all children <5 years (irrespective of HIV status) who have been exposed to a close/household contact diagnosed with PTB.
- People living with HIV (PLHIV) are offered TPT as part of a comprehensive package of care at the time of diagnosis, but PLHIV who have been exposed to a household contact diagnosed with PTB are not currently eligible to receive TPT (for 'household contact' indication) according to the Standard Treatment Guidelines.

1.2. Population that will be eligible for new TPT options proposed (INH monotherapy, 3HP, 1HP)

- TPT (one of 3 options) will be offered to people of all ages (irrespective of HIV status) who have been exposed to a household contact diagnosed with PTB.
- For TPT options 2 and 3, people not eligible to receive 3HP or 1HP due to age (aged <2y and <13y, respectively) will receive INH monotherapy.
- People will not receive more than one course of TPT per year and all people exposed to a patient newly diagnosed with PTB will be eligible to receive treatment.

1.3. Number of index cases

- The reported number of bacteriologically and clinically confirmed PTB cases[4] diagnosed and treated in 2020 (175,530 cases) (2) was adapted to reflect the number of diagnosed PTB cases for whom household contacts could be reached.
    - Initial loss to follow up of patients between diagnosis and treatment: 20% (Osman et al 2021 (6))
    - Adjusted down to 10% to account for lower likelihood that household contacts of PTB patients lost to follow up will be reached successfully
    - 195,033 index cases used as base-case estimate

  [A sensitivity analysis was conducted to estimate the budget impact if the number of patients diagnosed and started on treatment (175,530 cases) for PTB is used.]

1.4. Household contacts

- Used estimation of population at high risk for TB through household exposure in high-incidence countries reported by Ross et al 2021 (7) to inform:
    - Average household size: 3.5 people per household
      Assumed only one index case per household, so 2.5 people exposed per household
    - Proportion of population with household exposure to PTB aged <5 years: 11.74%

- Costs relating to contact tracing were not taken into account in the analysis, as it was assumed contact tracing activities will be conducted irrespective of whether TPT is available in order to rule out TB disease in close contacts.

1.5. Mortality rate in eligible population

Used 2019 mortality rates (8) due to significant impact COVID 19 had on death rates in 2020/21:

- Age under-five mortality rate (U5MR): 34.1 child deaths per1 000 live births
- Crude death rate (overall population): 8.7 deaths per 1000 population

[4] Excludes patients with extra pulmonary TB [EPTB]

1.6. Eligibility to be treated in public health sector

- The majority of the eligible population will be accessing public sector services: 95%

1.7. Ruling out active TB disease

- Assumed that 3.1% of contacts will be diagnosed with TB disease prior to initiation of TPT (9).

  [A sensitivity analysis was conducted to estimate the budget impact if the positivity rate recorded in the Targeted Universal Testing for TB (TUTT) study (3) *the is used. The TUTT study has not been published yet, so only limited details of study design and findings are available.]*

- Costs associated with ruling out TB disease (e.g. diagnostic tests, clinical evaluation) in household contacts were not taken into account in the analysis, as it was assumed that these investigations will be performed irrespective of whether TPT is available.

1.8. Eligible population likely to be started on TPT

- In 2020, 51% of children <5 years eligible for TPT accessed treatment (10).
- Assume % coverage will be the same for the extended population (same for all TPT options).
- People living with HIV receiving TPT as part of comprehensive package of care (not as an household contact) not adjusted for in the analysis.

1.9. Discontinuation rates

- Discontinuation rates reported by Stirling et al 2011 (4) were achieved under study conditions, with INH monotherapy TPT duration of 9 months, and the 3HP regimen administered as directly observed treatment.
- Increased Stirling et al 2011 discontinuation rates by 10% for base-case analysis to be more reflective of real-world scenario. Discontinuation rates used in base-case analysis:
  - INH monotherapy: 34.1%
  - 3HP: 19.7%

  [A sensitivity analysis was conducted to explore the impact of using the discontinuation rates reported by Stirling et al 2011 (4) *(as lower bound estimate) and using 10% higher discontinuation rates than those used in the base-case analysis (upper bound estimate)]*

- People who discontinue TPT will incur some health system costs. Therefore, the following is assumed in the analysis for people who discontinue TPT:
  - Will incur half of medicine and clinic visit costs (assumption aligned with Pooran et al 2013 (5) who assumed people who default on DS-TB treatment only incur half the costs)
  - Will incur no adverse event costs
  - No cost savings to the health system due to TB cases averted is expected
- For the one month regimen (1HP), the discontinuation rate is not relevant seeing that the medication would have been issued in its entirety at the start of treatment.

2. ACQUISITION COSTS OF TPT REGIMENS

The following assumptions were made in the calculation of the dosages and costs of TPT medicines.

2.1. Dose calculation

- Proportion of population exposed (as household contact of patients diagnosed with PTB) by age group obtained from Ross et al 2021 (7), in which estimates were provided in age groupings (0-4y, 5-14y, 15-49y and over 50y).
- To calculate the average doses (based on weight), disaggregated data on ages was required for children (aged < 16y) to estimate the relative cost contribution of an age group to the average cost of TPT for the relevant population. As this disaggregated data is not provided in Ross et al 2021, the proportion of the population in the grouped age

categories were evenly divided by the number of life years represented in that category, e.g. the 0-4y proportion of the population exposed was divided by 5 to estimate the proportion of children aged 0, 1, 2, 3, and 4 that will be exposed (relative to the total exposed population).

- Average weight for children aged up to 12 years were derived from a 2008 study validating weight measurement techniques in the Western Cape (11). The estimated weights are in line with the weight estimates for boys and girls in the World Health Organization (WHO) and Road to Health growth charts. The weight of children aged 12-16y were estimated.
- Assumed that people aged >16y all receive an adult dose.
- INH monotherapy dosing (168 doses required for 6 month's treatment) based on weight-based dosing recommended in the PHC STGs and EML, 2020 (1)
- 3HP dosing (12 doses required for 3 month's treatment) and 1HP dosing (28 doses required for 1 month's treatment) based on WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment (12).

2.2. Drug costs

- Cost per unit for TPT options based on average prices on contract circular (HP01-2021TB) on 4 March 2022.
- Average cost of a TPT regimen for the whole patient population indicated was calculated under assumption that people requiring TPT will be distributed across population in quantities relative to the size of that age group to the full exposed population

2.3. Frequency of treatment

- Assumed people will not receive more than one course of TPT per year

[Sensitivity analysis: Draft NDoH TPT guidelines include a recommendation for 12 months of INH TPT for household contacts who are HIV positive and weigh over 25kg (HIV positive children weighing <25kg will receive 6 months of INH TPT). A sensitivity analysis was conducted to explore the potential impact of this recommendation under the following assumptions:

- *HIV positive prevalence rate of 13.68%* (13)
- *Children <7y assumed to weigh <25kg* (11)*, which make up 16.37% of the eligible (extended) population (calculation based on Ross et al 2021* (7)*).*
- *Assumed no children aged <5y weighed >25kg, so no change in TPT duration for standard of care population*
- *TPT Option 1: INH medicine cost per patient for HIV negative population remains unchanged (R110), but INH cost for HIV positive population will increase - calculated as R199 per person. Average INH medicine costs for TPT option 1 (per person) calculated as R123.*
- *TPT Option 3: Medicine cost per patient for HIV negative population remains unchanged (R504), but cost for HIV positive population will increase - calculated as R525 per person. Average medicine costs for TPT option 3 (per person) calculated as R506.*
- *Number of clinic visits costed remains unchanged (6 clinic visits for INH monotherapy population)*
    - *For 12 month INH TPT regimen, HIV+ contacts would have required clinic visits for double the duration of a 6 month regimen. However, only 6 clinic visits were costed, under assumption that TPT will be provided as part of chronic dispensing services (TPT duration >6 months), and therefore clinic visits every second month will be required.*
    - *Assumed that TPT with duration of 6 months or less not eligible for chronic dispensing services.]*

3. HEALTHCARE RESOURCE USE COSTS

The following assumptions were made in the calculation of the primary health care (PHC) clinic visit costs associated with a course of TPT.

3.1. Number of clinic visits

- TPT initiated at first consultation, with monthly follow-up visits for monitoring and medicine collection.
- Number of visits = number of months on treatment

[A sensitivity analysis was conducted to explore the impact of varying the number of clinic visits:

- *Lower bound estimate – assumed that many HIV positive patients eligible to receive TPT due to household exposure will already be accessing health services on a monthly basis to collect ARVs/monitoring (68% of HIV+ population), so no additional clinic appointment will be required for these patients.*
- *Upper bound estimate - assumed patients will require an additional clinic visit for screening before TPT is initiated.]*

[A sensitivity analysis was conducted to explore the impact if TPT was provided through the Chronic Medicines Dispensing Programme. Assumed that patients receiving INH monotherapy will require 2 clinic visits at the start, followed by 4 medicine collection visits to complete treatment; patients on the 3HP regimen will require 1 clinic visit followed by 2 medicine collection visits, and patients on 1HP regimen will only require 1 clinic visit]

3.2. Cost per clinic visit

- Calculated average clinic visit cost based on clinic costs cited in TB publications (5,14–16): R.132.70
- Costs were converted to ZAR at rate noted in publication or average conversion rate for the year of analysis, and then adjusted for inflation using the South African Consumer Price Index.
- Applied same per-visit cost estimate to all age groups and regimens

[A sensitivity analysis was conducted to estimate the budget impact if the cost per clinic visit was changed:

- *Lower bound estimate - assumed that there is staff capacity within the health system to accommodate the additional clinic visits required, so all clinic costs excluded from analysis (clinic cost = R0.00)*
- *Upper bound estimate - clinic cost used in original analysis (R279) which has been used in previous EML analyses. Based on top-down costing using provincial and local government PHC expenditure]*

3.3. Costs not taken into account in analysis

- Diagnostic tests to screen for TB disease before initiation of TPT not included in analysis as assumed these costs would be incurred irrespective of TPT policy.
- Laboratory tests to screen for adverse drug events (e.g. liver function tests)
- Assumed that tuberculin skin test (TST) or Interferon Gamma Release Assay (IGRA) testing prior to initiation of TPT will not be a requirement.
- Following up patients who default on TPT
- Training requirements for implementation of one or more of the treatment options have not been included in the analysis.

4. ADVERSE EVENT COSTS

4.1. Probability of people experiencing severe hepatotoxicity (Grade3/4) over course of TPT

- Risk of hepatotoxicity in patients under the age of 18 years was considered negligible (17)
- Assumed people over the age of 18 years initiated on TPT had a defined risk of severe hepatoxicity resulting in hospitalization.
- Risk of severe hepatotoxicity resulting in hospitalization: Base-case
    - Used value midway between lower and upper bound estimates calculated (see below).
        - INH monotherapy: 0.30%
        - 3HP: 0.21%

- 1HP: 0.30%

- Risk of severe hepatotoxicity resulting in hospitalization: Lower bound
  - According to data reported by Stirling et al 2011, the risk of severe (Grade 3 or 4) hepatotoxicity was 0.11% for patients on INH monotherapy and 0.07% for patients on the 3HP regimen (18).
  - Assumed 1HP TPT pose no lesser nor greater risk for hepatotoxicity than INH monotherapy (19).

  [Explored in sensitivity analysis]

- Risk of severe hepatotoxicity: Upper bound
  - Probability of drug-induced liver injury (DILI) due to INH reported as 0.5% (compared to placebo) (19)
  - Applied same reduction in risk of severe hepatotoxicity used in calculation of lower bound estimate for calculation of upper bound estimates of risk for 3HP (relative to INH risk of DILI).
  - Assumed 1HP TPT pose no lesser nor greater risk for hepatotoxicity than INH monotherapy (19).

  [Explored in sensitivity analysis]

4.2. Number of inpatient days to treat severe hepatotoxicity

- Assumption that INH associated adverse drug reactions result in 2 weeks in hospital (20,21).

[A sensitivity analysis was conducted to estimate the budget impact if the duration of inpatient stay to manage severe hepatotoxicity is reduced to 7 days]

4.3. Cost of inpatient stay

- Assumed patients with severe hepatotoxicity are admitted for inpatient care at a Level 1 facility for an average of 2 weeks where they are under the care of a general medical practitioner.
- The UPFS Fee Schedule for Full Paying Patients: 1 APRIL 2021 was used to determine the unit costs for the inpatient care.

4.4. Costs not taken into account in analysis

- Tests to monitor hepatotoxicity not included.
- Additional costs not included in UPFS fee schedule incurred in and out of hospital to manage severe hepatotoxicity (e.g. medicines, follow-up visits).

5. SAVINGS TO THE HEALTH SYSTEM

- Calculation of number of cases of PTB averted based on needed to treat (NNT) calculated in Medicine Review and number of people who completed a TPT course.
- NNT to avert one PTB case assumed to be the same for all TPT options assessed (NNT=91).

[A sensitivity analysis was conducted to explore the impact if the NNT was adjusted for low (1%), moderate (2%) and high (5%) prevalence of TB in the comparison group. Anticipated NNT values: low TB prevalence: 167, moderate TB prevalence: 83, high TB prevalence: 33]

- Healthcare cost per TB case averted is derived from a reported estimate of 'Cost of diagnosis and management of DS-TB' by Pooran et al 2013 (5). The reported cost included PHC visits, TB drugs, diagnostic and monitoring tests, and adverse drug reactions, and the costs estimated for each of these cost categories were reported. To account for the uncertainty regarding the current cost of a TB case in South Africa and the potential that Pooran et al's estimate is an underestimation of the actual cost, a 50% increase on the Pooran et al estimate has been incorporated as the cost per TB case base-case estimate in the budget impact analysis (increased from R2,954 to R4,431).
- Expected cost savings due to PTB cases averted will (in practice) be achieved over two years (time horizon for study that informed NNT estimate), but all potential cost savings presented in analysis over one year.

[A sensitivity analysis was conducted to explore an extreme cost scenario in which the WHO estimate of R14,025 was used as the cost per DS TB case. This cost was not used for the base-case analysis as the estimate does not include estimates of unit costs, so it isn't possible to judge the extent to which the resource use and costs reflected items of most relevance to this review]

APPENDIX 2: MODEL PARAMETERS FOR BASE-CASE ANALYSIS

Parameter	Value	Source/justification
ANNUAL TREATED NUMBERS		
Number of PTB cases diagnosed in 2020 - EPTB not included in this number	195,033	WHO DSTB data 2020 report (unpublished) (2) *- PTB cases (excluding EPTB) diagnosed and started on treatment in 2020 (all ages): 175,530* Osman et al 2021 (6) *- Initial loss to follow up of patients between diagnosis and treatment: 20%* *- Adjusted to 10% to account for lower likelihood that household contacts of PTB patients lost to follow up will be reached successfully*
Percentage of exposed population aged <5y	11.87%	Ross et al 2021 (7) *- Percentage of exposed population aged <5y: 11.87%*
Average number of household contacts of TB patients in South Africa	2.5	Ross et al 2021 (7) *- Average household size of people at high risk for TB through household exposure in SA: 3.5 people* *- Average number of household contacts: 2.5 people*
Under-five mortality rate (U5MR)	3.41%	StatsSA mid-year population estimates 2019 (8) *- Under-five mortality rate (U5MR): 34.1 child deaths per 1 000 live births* *- Used 2019 mortality rates due to significant impact COVID 19 had on death rates in 2020/21.*
Crude death rate	0.87%	StatsSA mid-year population estimates 2019 (8) *- Crude death rate: 8.7 deaths per 1000 population* *- Used 2019 mortality rates due to significant impact COVID 19 had on death rates in 2020/21.*
Percentage of eligible people treated in the public health sector	95.00%	Estimate *- Assumption that majority of the eligible population will be accessing public sector services*
Percentage of eligible patients likely to be diagnosed with active TB prior to initiation of TPT	3.10%	Fox et al 2013 (9) *- Prevalence of TB disease in household contacts* *- Studies from low- and middle-income settings included, including South Africa*
Proportion of eligible patients likely to be started on TPT (%)	51.00%	WHO TB profile for South Africa (10) *- Eligible household contacts aged <5y started on TPT in 2020* *- Assume similar uptake by expanded population*
Discontinuation rate INH monotherapy	34.10%	Estimate *- Increased discontinuation rate reported by Stirling et al 2011* (4) *by 10% as this was achieved under study conditions and participants were given 9 months of INH monotherapy TPT*
Discontinuation rate 3HP monotherapy	19.69%	Estimate *- Increased discontinuation rate reported by Stirling et al 2011* (4) *by 10% as this was achieved under study conditions and 3HP as administered as directly observed therapy*
Discontinuation rate 1HP	0.00%	N/A - receive full month's treatment at first appointment
HIV positive prevalence rate	13.68%	StatsSA mid-year population estimates 2021 (13)

Parameter		Value	Source/justification
MEDICINE ACQUISITION COSTS			
Average cost for a course of TPT (ZAR)	Standard of care: INH mono <5y	116.12	Calculation based on the following: - *Proportion of exposed population estimates from Ross et al 2021* (7) - *INH dosing weight-based dosing from PHC STGs and EML, 2020* (1) - *3HP and 1HP dosing based on WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment* (12) - *Drug prices: Average prices on contract circular (HP01-2021TB) on 4 Mar 2022*
	TPT option 1: INH monotherapy all ages	110.47	
	TPT option 2: 3HP >2y, INH <2y	368.63	
	TPT option 3: 1HP >13y, INH <13y	503.55	
Proportion of cost expected to be incurred by people who discontinue TPT		0.5	Estimate - *Pooran et al 2013* (5) *assumed that DS TB patients who default from treatment incur only half of the cost of a treatment regimen.* - *Same proportion applied to all TPT options*
HEALTHCARE RESOURCE USE AND COSTS			
Average number of visits per person on TPT course	Standard of care: INH monotherapy <5y	6	TPT initiated at first consultation (visit 1), with monthly follow-up visits for monitoring and medicine collection (visits 2-6).
	TPT option 1: INH monotherapy all ages	6	TPT initiated at first consultation (visit 1), with monthly follow-up visits for monitoring and medicine collection (visits 2-6).
	TPT option 2: 3HP >2y – 3 visits INH monotherapy <2y – 6 visits	3.1	Aged >2y: 3HP TPT initiated at first consultation (visit 1), with monthly follow-up visits for monitoring and medicine collection (visits 2 & 3). Aged <2y: INH TPT initiated at first consultation (visit 1), with monthly follow-up visits for monitoring and medicine collection (visits 2-6).
	TPT option 3: 1HP >13y – 1 visit INH monotherapy <13y – 6 visits	2.5	Aged >13y: 1HP TPT initiated at first consultation (visit 1). Aged <13y: INH TPT initiated at first consultation (visit 1), with monthly follow-up visits for monitoring and medicine collection (visits 2-6).
Cost of PHC clinic visit (ZAR)		132.70	Estimate - *Published clinic visit costs in reported for South Africa vary significantly.* - *Reviewed clinic cost estimates from 4 TB costing studies in South Africa* (5,14–16)*. Converted estimates from US$ to ZAR for year of analysis, and adjusted for inflation using the South African Inflation rate (StatsSA).* - *Costs ranged from R72 to R193. Calculated average between 4 studies.*
Proportion of cost expected to be incurred by people who discontinue TPT		0.5	Estimate - *Pooran et al 2013* (5) *assumed that DS TB patients who default from treatment incur only half of the cost of a treatment regimen.* - *Same proportion applied to all TPT options*

Parameter		Value	Source/justification
ADVERSE EVENTS			
Inpatient facility fee - level 1 facility (12 hours)		R439	UPFS Fee Schedule for Full Paying Patients: 1 APRIL 2021
Professional fee: general medical practitioner		R91	UPFS Fee Schedule for Full Paying Patients: 1 APRIL 2021
Number of inpatient days		14	Moosa et al 2020 (21) and Schultz et al 2012 (20) *- Assumption that adverse drug reactions due to DS-TB treatment will require 2 weeks of hospitalization*
Percentage of people experiencing severe hepatotoxicity (Grade 3/4) or DILI over course of TPT	Standard of care: INH mono <5y	0.00%	Villarino 2015 (17) *- For children aged <18y, assumed negligible severe drug-induced hepatotoxicity*
	TPT option 1: INH monotherapy all ages	0.30%	Estimate - midway between lower and upper bound estimates
	TPT option 2: 3HP >2y, INH <2y	0.21%	Estimate - midway between lower and upper bound estimates
	TPT option 3: 1HP >13y, INH <13y	0.30%	Estimate - midway between lower and upper bound estimates
COSTS AVERTED			
Cost of diagnosis and management of DS-TB		4431.23	Pooran et al 2013 (5) *- Converted estimates to ZAR and adjusted for inflation using the South African Consumer Price Index.* *- The cost include PHC visits, TB drugs, diagnostic and monitoring tests, adverse drug reactions.* *- Patient population: DS TB patients* *- 50% increase to account to potential underestimation of costs*
Number needed to treat to avert one PTB case		91	See Medicine Review *- Assumed same NNT to prevent one PTB case for all TPT options*

APPENDIX 3: MODEL PARAMETERS USED IN SENSITIVITY ANALYSIS

Parameter (sensitivity analysis)	Value	Source/justification
ANNUAL TREATED NUMBERS		
Number of PTB cases bacteriologically and clinically confirmed in 2020 and started on treatment (all ages) - EPTB not included in this number	175,530	WHO DSTB data 2020 report (unpublished) (2) - PTB cases (excluding EPTB) confirmed and started on treatment in 2020 (all ages) - More restrictive population than the population under review (patients diagnosed)
Percentage of eligible patients likely to be diagnosed with active TB prior to initiation of TPT	7.50%	Lebina et al 2021 (3) *- Results from TUTT study: TB positivity rate of 7.5% of TB contacts tested (part of screening process)* *- Detailed description of study design and results not available (not yet published in peer reviewed journal).*
Discontinuation rate INH monotherapy (lower bound)	31.00%	Stirling 2011 (4) *- Under study conditions - self-administered, 9 months of INH TPT*
Discontinuation rate INH monotherapy (upper bound)	37.51%	Estimate *- 10% increase from base-case value*
Discontinuation rate 3HP monotherapy (lower bound)	17.90%	Stirling 2011 (4) *- Under study conditions - self-administered, directly observed therapy*
Discontinuation rate 3HP monotherapy (upper bound)	21.66%	Estimate *- 10% increase from base-case value*
MEDICINE ACQUISITION COSTS		
Average medicine cost for TPT Option 1 and 3	TPT Option 1: R122.59 TPT Option 3: R506	Draft NDoH TPT guidelines include a recommendation that HIV positive household contacts that weigh over 25kg should receive 12 months of INH TPT (HIV positive children weighing <25kg will receive 6 months of INH TPT). *- TPT Option 1: INH medicine cost per patient for HIV negative population remains unchanged (R110), but INH cost for HIV positive population will increase - calculated as R199 per person. Average INH medicine costs for TPT option 1 (per person) calculated as R123.* *- TPT Option 3: Medicine cost per patient for HIV negative population remains unchanged (R504), but cost for HIV positive population will increase - calculated as R525 per person. Average medicine costs for TPT option 3 (per person) calculated as R506.* *- Number of clinic visits costed remains unchanged (6 clinic visits for INH monotherapy population)* o *For 12 month INH TPT regimen, HIV positive contacts would have required clinic visits for double the duration of a 6 month regimen. However, only 6 clinic visits were costed under assumption that TPT will be provided as part of chronic dispensing services (TPT duration >6 months), and therefore clinic visits every second month will be required.* o *Assumed that TPT with duration of 6 months or less not eligible for chronic dispensing services.*

MODEL PARAMETERS USED IN SENSITIVITY ANALYSIS (continued)			
Parameter (sensitivity analysis)		**Value**	**Source/justification**
HEALTHCARE RESOURCE USE AND COSTS			
Average number of visits per patient per TPT course (lower bound)	Standard of care: INH mono <5y	5.4	Estimate: *- Under assumption that many HIV positive patients eligible to receive TPT as a household contact will already be accessing health services on a monthly basis for ARVs/monitoring, so no additional clinic appointment will be required for these patients.* *- HIV positive prevalence rate of 13.68% used (StatsSA mid-year population estimates 2020* (13)*)* *- 68.21% ART coverage assumed (UNAIDS key population atlas 2019* (22)*)* *- Average number of clinic visits calculated for people of all ages eligible under described scenario*
	TPT option 1: INH monotherapy all ages	5.4	
	TPT option 2: 3HP >2y, INH <2y	2.8	
	TPT option 3: 1HP >13y, INH <13y	2.3	
Average number of visits per patient per TPT course (upper bound)	Standard of care: INH mono <5y	7.0	Estimate *- Under assumption that patients will require an additional clinic visit for screening before TPT is initiated.* *- Average number of clinic visits calculated for people of all ages eligible under described scenario*
	TPT option 1: INH monotherapy all ages	7.0	
	TPT option 2: 3HP >2y, INH <2y	4.1	
	TPT option 3: 1HP >13y, INH <13y	3.5	
Mix of clinic visits and medicine collection visits	Standard of care: INH mono <5y AND TPT option 1: INH monotherapy all ages	2 clinic visits + 4 medicine collection visits	Estimate *- Under assumption that patients will only attend one or two clinic visits at start of TPT (depending on regimen), followed by medicine collection visits only*
	TPT option 2: 3HP >2y (INH <2y same as above)	1 clinic visit + 2 medicine collection visits	
	TPT option 3: 1HP >13y (INH monotherapy <13y same as above)	1 clinic visit	
Cost of PHC clinic visit (ZAR) (lower bound)		0	Estimate *- Assumption that there is staff capacity within the health system to accommodate the additional clinic visits required, so all clinic costs excluded from analysis*
Cost of PHC clinic visit (ZAR) (upper bound)		278.73	Estimate from original analysis (Nov 2021) *- Top-down costing based on provincial and local government PHC expenditure* *- Value has been used in previous EML analyses*

MODEL PARAMETERS USED IN SENSITIVITY ANALYSIS (continued)			
Parameter (sensitivity analysis)		**Value**	**Source/justification**
ADVERSE EVENTS			
Number of inpatient days (lower bound)		7	Pooran et al 2013 (5) *- Assumption used in costing analysis*
Percentage of people experiencing severe hepatotoxicity (Grade 3/4) over course of TPT (lower bound)	Standard of care: INH mono <5y	0.00%	Villarino 2015 (17) *- For children aged <18y, assumed negligible severe drug-induced hepatotoxicity*
	TPT option 1: INH monotherapy all ages	0.11%	Supplement to Stirling 2011 (18) *- Severe hepatotoxicity (Grade 3/4) over course of TPT*
	TPT option 2: 3HP >2y, INH <2y	0.07%	Supplement to Stirling 2011 (18) *- Severe hepatotoxicity (Grade 3/4) over course of TPT*
	TPT option 3: 1HP >13y, INH <13y	0.11%	WHO Grade tables (Annex 3) 2020 (19) *- Assumed 1HP TPT pose no lesser nor greater risk for hepatotoxicity than INH monotherapy*
Percentage of people experiencing severe hepatotoxicity (Grade 3/4) over course of TPT (upper bound)	Standard of care: INH mono <5y	0.00%	Villarino 2015 (17) *- For children aged <18y, assumed negligible severe drug-induced hepatotoxicity*
	TPT option 1: INH monotherapy all ages	0.50%	WHO Grade tables (Annex 3) 2020 (19) *- Relative risk: INH monotherapy vs placebo*
	TPT option 2: 3HP >2y, INH <2y	0.35%	Applied same reduction in risk of severe hepatotoxicity (compared to INH monotherapy) as for lower bound
	TPT option 3: 1HP >13y, INH <13y	0.50%	WHO Grade tables (Annex 3) 2020 (19) *- Assumed 1HP TPT pose no lesser nor greater risk for hepatotoxicity than INH monotherapy*
COSTS AVERTED			
Cost of diagnosis and management of DS-TB (upper bound)(ZAR)		14,025	WHO estimate for cost per TB case *- Extreme cost scenario based on global, generalised analysis by WHO*
Number needed to treat to avert one PTB case (high TB prevalence)		33	NNT estimate anticipated for high (5%) TB prevalence of TB in comparison group
Number needed to treat to avert one PTB case (moderate TB prevalence)		83	NNT estimate anticipated for moderate (2%) TB prevalence of TB in comparison group
Number needed to treat to avert one PTB case (low TB prevalence)		167	NNT estimate anticipated for low (1%) TB prevalence of TB in comparison group

NEMLC MEETING OF 23 JUNE 2022:
NEMLC accepted the updated report.

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