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MDR/RR-TB child household contact management: Estimates of impact & cost-effectiveness for 2019*

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* tinyurl.com/2hykpf82

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Background

- MDR/RR-TB is leading 'AMR' killer[1]
- ~40% receiving appropriate treatment[1]
- Children 0-14 years:
  - **Perhaps ~30K children with MDR-TB per year[2,3]**
  - **Appropriate treatment <20%**

⇒ Strategies to find & (appropriately) treat child MDR/RR-TB

1. World Health Organization. Global tuberculosis report 2021
2. Jenkins HE, et al. Lancet 2014
3. Dodd PJ, Sismanidis C, Seddon JA. LID 2016

Background

- In 2014 around 20 million people had MDR-LTBI[1]
  - **~ 1/10 recent & higher progression risk**
  - **Rate ~10x higher in children <15 years**
- Studies on TPT for MDR/RR-LTBI reporting soon
- Some regimens include fluoroquinolones (FQ), but some *M.tb* strains are FQR

⇒ Strategies to prevent child MDR/RR-TB in those at high risk

1. Knight GM, McQuaid CF, Dodd PJ, Houben RMGJ. LID 2019

Background

Household contact management (HHCM) can identify children with TB and at high risk of progression[1,2]

Coverage remains low;
previous work[3] ⇒ full coverage ≃ 100K deaths averted

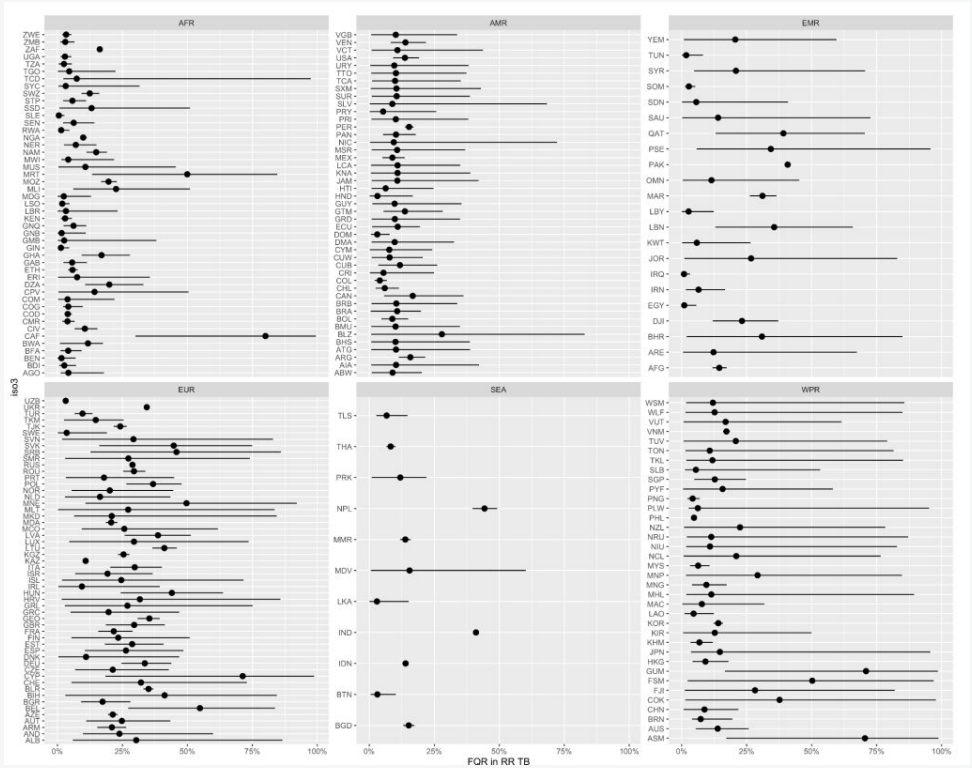
What impact could HHCM strategies for MDR/RR-TB achieve?
How would their cost-effectiveness compare?
How would these depend on FQR prevalence?

1. Fox GJ, Barry SE, Britton WJ, Marks GB. ERJ 2013
2. Martinez L et al Lancet 2020
3. Dodd PJ, Yuen CM, Becerra MC, Revill P, Jenkins HE, Seddon JA. LGH 2018

Strategies

- Intervention:
  - **HHCM with no tuberculosis preventive therapy**
  - **TPT for children with HIV or <5 years**
  - **TPT for children with HIV, TST+ve, or <5 years**
  - **TPT for all children <15 years**
- TPT regimens:
  - **Fluoroquinolone (ie, levofloxacin or moxifloxacin)**
  - **Bedaquiline or delamanid**

Methods: index notifications



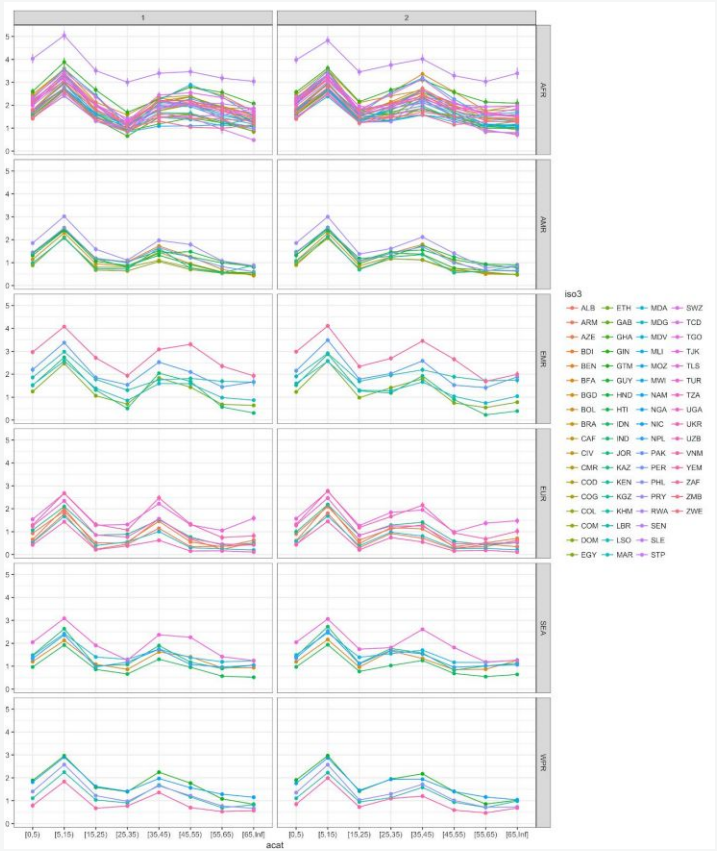
WHO data on MDR/RR-TB notifications

Need country estimates of FQR in MDR/RR-TB:

Low precision & high missingness

⇒ resampling estimation approach

Methods: contacts



WHO-collated notifications,
by country, age, sex

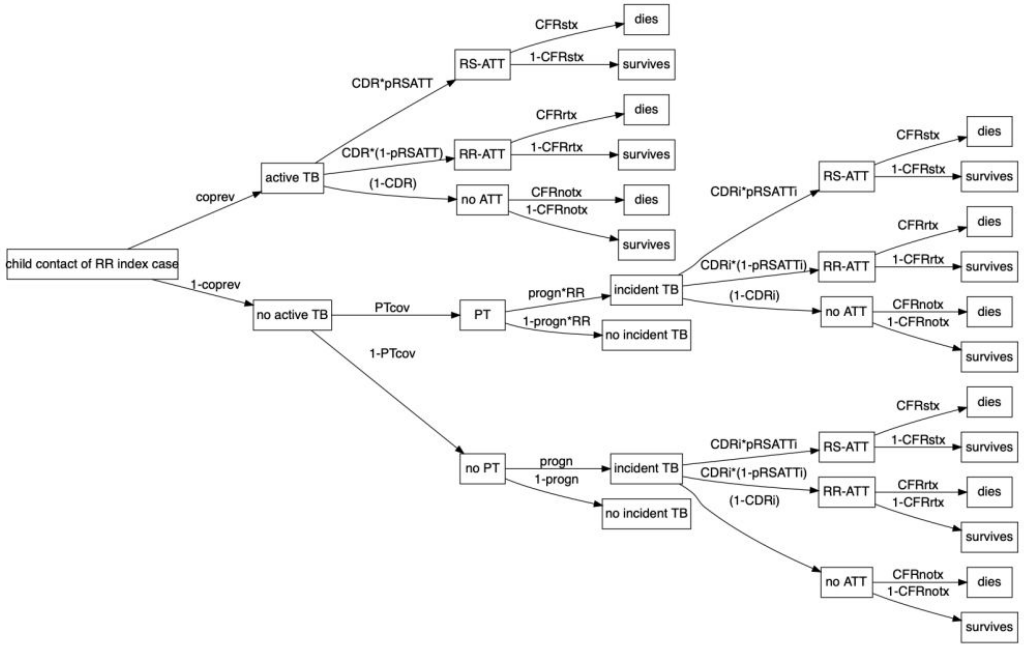
×

DHS data multivariate regression

⇒ **number child contacts**

given age, sex of index
(previous work)

Methods: outcomes

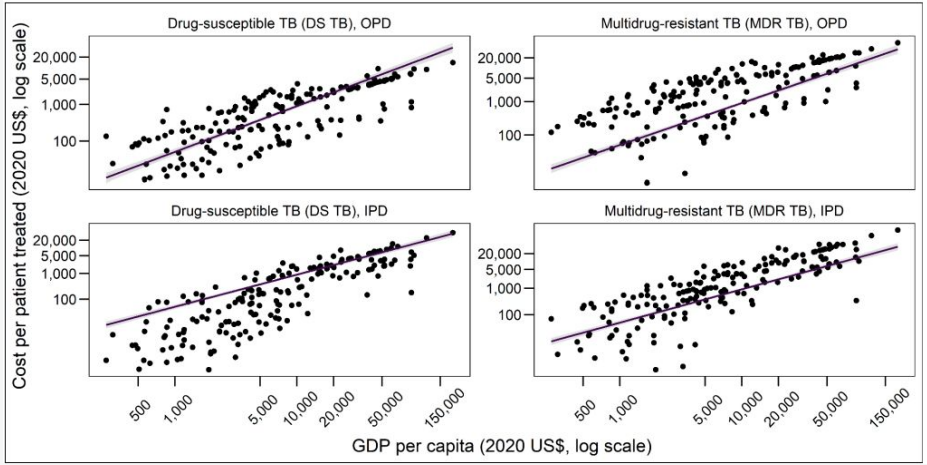


Review estimates of:

- Risk
  - **Co-prevalent TB**
  - **LTBI**
  - **DR-concordance**
- Progression
  - **LTBI → TB disease**
  - **Matched TPT efficacy**
- Outcomes
  - **CFR**

Detection & life-expectancy: country-specific estimates

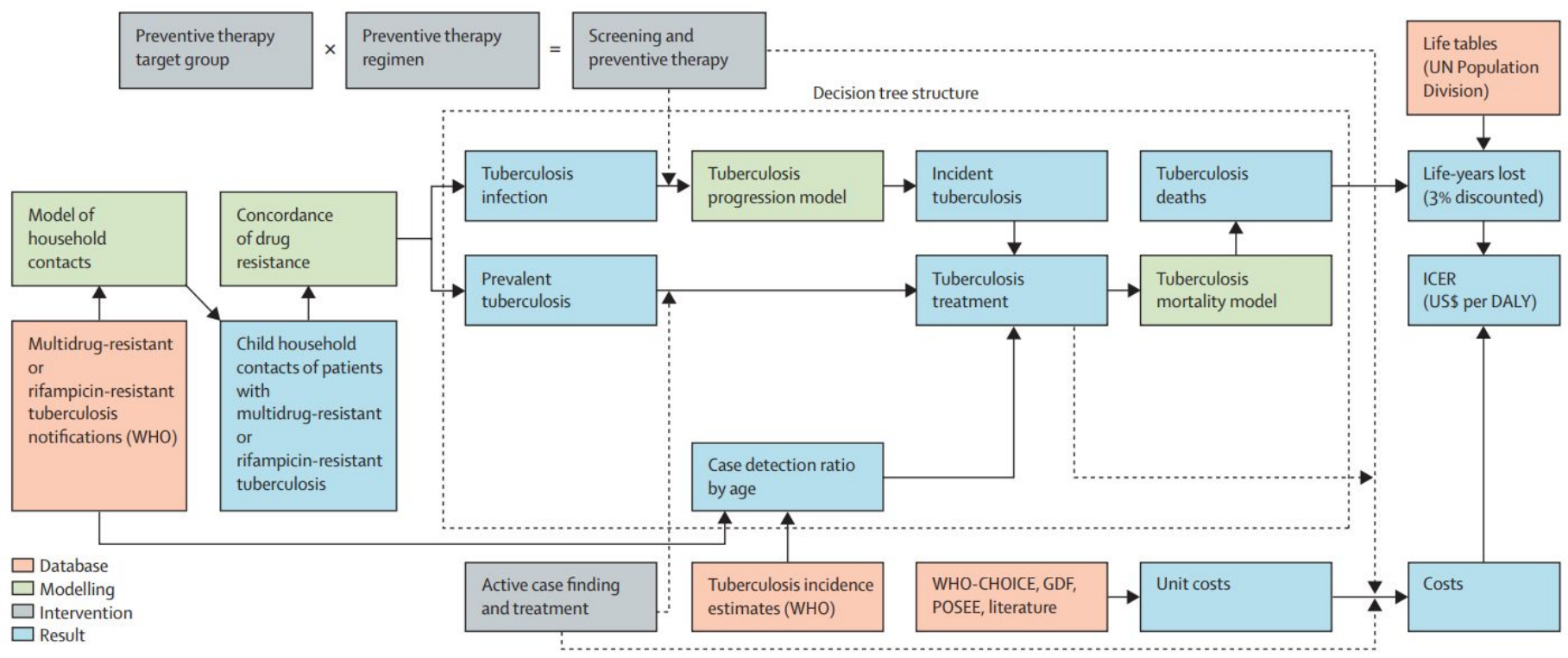
Methods: costs



Unit costs based on:

- Literature
  (eg tests, visits)
- Global drug facility
  (cost of drugs)
- Regression models
  (eg inpatient treatment

Methods: summary



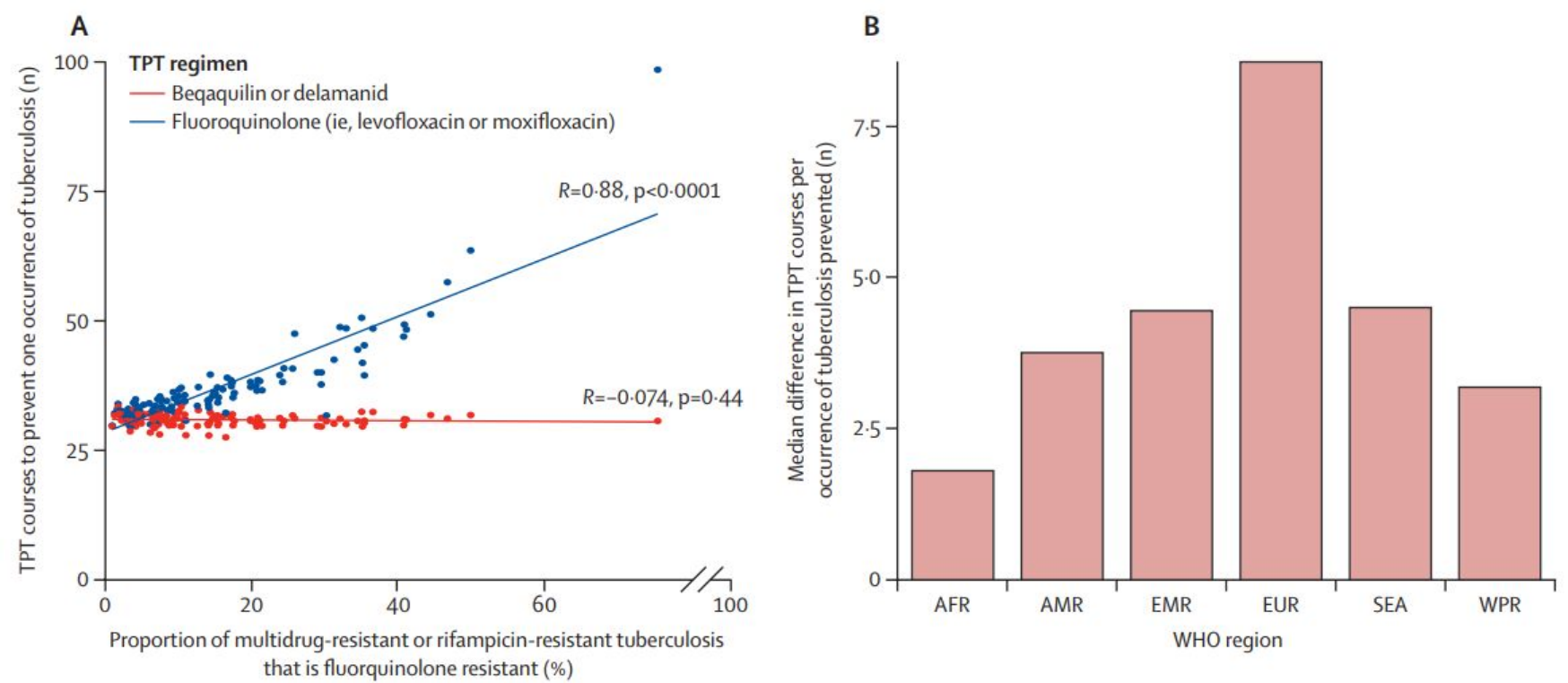
Results

	No intervention	HCM only	HCM and TPT for all children aged <5 years or <15 years living with HIV		HCM and TPT for all children aged <5 years or <15 years living with HIV or with positive tuberculin skin test		HCM and TPT for all children aged <15 years	
			Fluoroquinolone*	Bedaquiline or delamanid	Fluoroquinolone*	Bedaquiline or delamanid	Fluoroquinolone*	Bedaquiline or delamanid
Total resources								
Household contacts screened	0	227 000 (205 000 to 252 000)	227 000 (205 000 to 252 000)	227 000 (205 000 to 252 000)	227 000 (205 000 to 252 000)	227 000 (205 000 to 252 000)	227 000 (205 000 to 252 000)	227 000 (205 000 to 252 000)
TPT courses	0	0	71 200 (63 400 to 79 100)	71 200 (63 400 to 79 100)	144 000 (129 000 to 160 000)	144 000 (129 000 to 160 000)	209 000 (189 000 to 232 000)	209 000 (189 000 to 232 000)
Rifampicin-susceptible tuberculosis treatments	12 700 (10 100 to 15 600)	7930 (6310 to 9890)	7010 (5480 to 8870)	6830 (5310 to 8720)	5770 (4570 to 7160)	5340 (4270 to 6570)	5410 (4290 to 6740)	4910 (3930 to 5970)
Multidrug-resistant or rifampicin-resistant tuberculosis treatments	5170 (3570 to 7240)	16 700 (14 500 to 19 100)	16 400 (14 300 to 18 800)	16 300 (14 200 to 18 700)	16 000 (14 100 to 18 200)	15 700 (13 700 to 17 800)	15 900 (14 000 to 18 100)	15 500 (13 500 to 17 600)
Incremental resources								
Household contacts screened	Reference	227 000 (205 000 to 252 000)	227 000 (205 000 to 252 000)	227 000 (205 000 to 252 000)	227 000 (205 000 to 252 000)	227 000 (205 000 to 252 000)	227 000 (205 000 to 252 000)	227 000 (205 000 to 252 000)
TPT courses	Reference	0	71 200 (63 400 to 79 100)	71 200 (63 400 to 79 100)	144 000 (129 000 to 160 000)	144 000 (129 000 to 160 000)	209 000 (189 000 to 232 000)	209 000 (189 000 to 232 000)
Rifampicin-susceptible tuberculosis treatments	Reference	−4770 (−6980 to −2900)	−5690 (−8010 to −3800)	−5870 (−8220 to −3980)	−6930 (−9390 to −4940)	−7360 (−9820 to −5290)	−7290 (−9780 to −5250)	−7800 (−10 300 to −5670)
Multidrug-resistant or rifampicin-resistant tuberculosis treatments	Reference	11 600 (9360 to 13 800)	11 300 (9100 to 13 500)	11 100 (8980 to 13 400)	10 900 (8600 to 13 100)	10 500 (8200 to 12 800)	10 700 (8460 to 13 000)	10 300 (8010 to 12 700)
Total outcomes								
Incident tuberculosis	11 300 (9200 to 13 600)	11 300 (9200 to 13 600)	8860 (7060 to 11 000)	8210 (6530 to 10 200)	6390 (5150 to 7820)	5090 (4150 to 6200)	5680 (4600 to 7000)	4180 (3400 to 5090)
Incident rifampicin-susceptible tuberculosis	1980 (1400 to 2810)	1980 (1400 to 2810)	1440 (984 to 2160)	1440 (984 to 2160)	893 (624 to 1270)	893 (624 to 1270)	733 (514 to 1040)	733 (514 to 1040)
Incident multidrug-resistant or rifampicin-resistant tuberculosis	9310 (7400 to 11 500)	9310 (7400 to 11 500)	7410 (5730 to 9490)	6760 (5200 to 8780)	5500 (4260 to 6840)	4200 (3320 to 5260)	4940 (3820 to 6240)	3450 (2700 to 4290)
Incident tuberculosis deaths	2530 (2020 to 3120)	2530 (2020 to 3120)	1660 (1310 to 2070)	1420 (1130 to 1760)	1370 (1070 to 1720)	1040 (834 to 1280)	1290 (1010 to 1630)	936 (747 to 1160)
Prevalent tuberculosis deaths	3580 (3040 to 4130)	1230 (1020 to 1470)	1230 (1020 to 1470)	1230 (1020 to 1470)	1230 (1020 to 1470)	1230 (1020 to 1470)	1230 (1020 to 1470)	1230 (1020 to 1470)
Incremental outcomes								
Incident tuberculosis	Reference	0	−2440 (−3060 to −1900)	−3090 (−3880 to −2440)	−4900 (−6000 to −3950)	−6210 (−7500 to −5070)	−5620 (−6890 to −4540)	−7120 (−8610 to −5800)
Incident rifampicin-susceptible tuberculosis	Reference	0	−539 (−824 to −375)	−539 (−824 to −375)	−1090 (−1550 to −775)	−1090 (−1550 to −775)	−1250 (−1780 to −893)	−1250 (−1780 to −893)
Incident multidrug-resistant or rifampicin-resistant tuberculosis	Reference	0	−1900 (−2510 to −1410)	−2550 (−3290 to −1940)	−3810 (−4830 to −2960)	−5120 (−6360 to −4060)	−4370 (−5530 to −3370)	−5870 (−7280 to −4620)
Incident tuberculosis deaths	Reference	0	−871 (−1130 to −652)	−1110 (−1420 to −852)	−1160 (−1450 to −907)	−1490 (−1870 to −1180)	−1240 (−1540 to −970)	−1590 (−1980 to −1270)
Prevalent tuberculosis deaths	Reference	−2350 (−2790 to −1940)	−2350 (−2790 to −1940)	−2350 (−2790 to −1940)	−2350 (−2790 to −1940)	−2350 (−2790 to −1940)	−2350 (−2790 to −1940)	−2350 (−2790 to −1940)

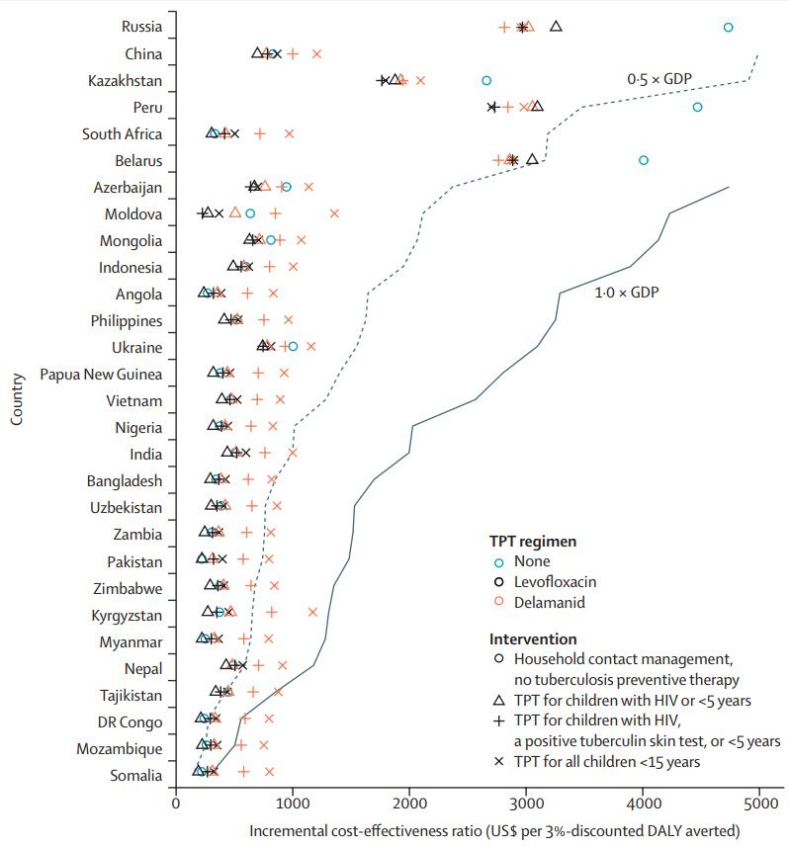
Results

	No intervention	HCM only	HCM and TPT for all children aged <5 years or <15 years living with HIV				HCM and TPT for all children aged <5 years or <15 years living with HIV or with a positive tuberculin skin test				HCM and TPT for all children aged <15 years			
			Levofloxacin	Moxifloxacin	Delamanid	Bedaquiline	Levofloxacin	Moxifloxacin	Delamanid	Bedaquiline	Levofloxacin	Moxifloxacin	Delamanid	Bedaquiline
Cost, US$ million	51 (31 to 80)	114 (86 to 151)	117 (90 to 153)	119 (91 to 154)	128 (100 to 164)	119 (92 to 154)	127 (100 to 162)	130 (103 to 166)	157 (128 to 194)	130 (103 to 164)	135 (108 to 171)	140 (113 to 177)	184 (152 to 223)	141 (112 to 174)
Deaths	6110 (5230 to 7100)	3760 (3130 to 4440)	2890 (2420 to3410)	2890 (2420 to 3410)	2650 (2230 to 3100)	2650 (2230 to 3100)	2600 (2180 to 3080)	2600 (2180 to 3080)	2280 (1920 to 2660)	2280 (1920 to 2660)	2520 (2110 to 2980)	2520 (2110 to 2980)	2170 (1830–2530)	2170 (1830 to 2530)
Life-years lost, 3% discounted	171 000 (145 000 to 199 000)	105 000 (86 900 to 124 000)	80 600 (67 300 to95 200)	80 600 (67 300 to 95 200)	73 800 (61 700 to 86 400)	73 800 (61 700 to 86 400)	72 600 (60 700 to 86 000)	72 600 (60 700 to 86 000)	63 500 (53 500 to 74 300)	63 500 (53 500 to 74 300)	70 300 (58 800 to 83 400)	70 300 (58 800 to 83 400)	60 400 (50 900–70 700)	60 400 (50 900 to 70 700)
Incremental cost, US$ million	Reference	63 (40 to 95)	66 (43 to 97)	68 (44 to 99)	77 (53 to 108)	68 (45 to 99)	76 (52 to 108)	79 (55 to 111)	106 (79 to 141)	79 (54 to 110)	84 (59 to 116)	89 (64 to 122)	133 (102 to 171)	90 (63 to 122)
Incremental deaths	Reference	–2350 (–2790 to –1940)	–3220 (–3840 to –2690)	–3220 (–3840 to –2690)	–3470 (–4150 to –2880)	–3470 (–4150 to –2880)	–3510 (–4170 to –2930)	–3510 (–4170 to –2930)	–3840 (–4550 to –3220)	–3840 (–4550 to –3220)	–3590 (–4250 to –3010)	–3590 (–4250 to –3010)	–3950 (–4660 to –3330)	–3950 (–4660 to –3330)
Incremental life-years saved, 3% discounted	Reference	65 700 (54 100 to 78 100)	90 100 (74 600 to 108 000)	90 100 (74 600 to 108 000)	96 900 (80 300 to 116 000)	96 900 (80 300 to 116 000)	98 000 (81 700 to 117 000)	98 000 (81 700 to 117 000)	107 000 (89 600–128 000)	107 000 (89 600 to 128 000)	100 000 (83 800 to 119 000)	100 000 (83 800 to 119 000)	110 000 (92 600 to 131 000)	110 000 (92 600 to 131 000)
ICER, US$ per DALY	--	960	738	754	799	703	773	807	992	737	838	890	1208	814

Results


A
TPT regimen
Beqaquilin or delamanid
Fluoroquinolone (ie, levofloxacin or moxifloxacin)
R=0·88, p<0·0001
R=−0·074, p=0·44
TPT courses to prevent one occurrence of tuberculosis (n)
100
75
50
25
0
0
20
40
60
100
Proportion of multidrug-resistant or rifampicin-resistant tuberculosis that is fluorquinolone resistant (%)
B
Median difference in TPT courses per occurrence of tuberculosis prevented (n)
7·5
5·0
2·5
0
AFR
AMR
EMR
EUR
SEA
WPR
WHO region

Results



- Whether ICERs are considered cost-effective is for decision makers
- ICERs typically below US$1K for WHO DRTB watchlist countries
- Better ICERs (but smaller impact):
  - More focussed targeting
  - FQ-containing TPT

Summary

- Widespread use of HHCM for MDR/RR-TB could avert ~ 6K child MDR/RR-TB per year
- Even without the TPT, ~ 2400 child deaths averted
- With TPT +1600 deaths averted
- Resources ~US$ 60 million (though not designed as budget impact analysis)
- Cost-effective in most settings at <$1K per DALY averted
- Better cost-effectiveness (but less impact) with FQ-TPT & more focussed use