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Shorter antibiotic regimens impact the control efforts in high tuberculosis burden regions of Taiwan

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ABSTRACT

Objectives: To assess the potential epidemiological impact and cost-effectiveness of shorter antibiotic regimens in high tuberculosis (TB) burden regions of Taiwan.
Methods: This study combined the TB population dynamic model and cost-effectiveness analysis with local data to simulate the disease burdens, effectiveness and costs of hypothetical 4-month, 2-month and 7-day regimens compared with the standard regimen.
Results: The main outcomes were the potential of shorter regimens for averted incidence, mortality and disability-adjusted life years, incremental cost-effectiveness ratio and net monetary benefit. Shorter regimens would lower incidence rates and mortality cases in a high TB burden region by an average of 19–33% and 27–41%, respectively, with the potential for cost-effectiveness or cost-saving. The 2-month and 7-day regimens would be more cost-effective than the 4-month regimen. The threshold daily drug prices for achieving cost-effectiveness and cost-saving for 4-month, 2-month and 7-day regimens were $US1, $US2 and $US70, respectively. Such cost-effectiveness would remain, even if the willingness-to-pay threshold was less than one gross domestic product per capita.
Conclusions: The findings support the inclusion of shorter regimens in global guidelines and regional-scale TB control strategies, which would improve disease control, particularly in settings with high rates of incidence and poor treatment outcomes.

1. Introduction

Over 60% of global tuberculosis (TB) incident cases are found in South-East Asian and Western Pacific regions (WHO, 2017). In Taiwan, TB has the highest incidence rate among all human communicable diseases. During 2005–2015 in Taiwan, TB incidence rates ranged from 45.7–72.5 per 100,000 population (Taiwan CDC, 2017). The TB burden in Taiwan varies geographically, with the highest rates being 73.0–137.8 and 69.8–115.2 per 100,000 population in two counties in the eastern region – Hualien and Taitung – respectively (Taiwan, 2017).

The current standard antibiotic treatment for TB is a first-line drug combination regimen (rifampin, isoniazid, pyrazinamide and ethambutol) for 6 months; however, the long duration of treatment with this regimen is a major barrier to adherence and has a significant negative impact on TB control (Silva et al., 2020). The development of shorter regimens is one of the pillars of the World Health Organization (WHO)'s End TB Strategy (WHO, 2015). It is widely recognized that shorter regimens have the potential to reduce costs incurred by patients and improve outcomes by increasing patient adherence to treatments and decreasing duration to cure (Gospodarevskaya et al., 2014; Silva et al., 2020). Several promising shorter regimens are under study by the TB Alliance and other research institutes (ClinicalTrials.gov, 2020; Silva et al., 2020; TB Alliance, 2020). For instance, a SimpliciTB trial (registration no. NCT03338621) has already been launched to evaluate the efficacy, safety and tolerability of a shorter 4-month regimen that combines bedaquiline with pretomanid, moxifloxacin and pyrazinamide. The RIFASHORT (NCT02581527) trial is currently evaluating whether two 4-month regimens with high-dose rifampicin will result in greater and faster killing of TB bacilli in the lungs. The S31/A5349 (NCT02410772) trial aims to determine whether one or two 4-month rifapentine-containing regimens for TB treatment are as effective as the standard regimen. The TRUNCATE-TB (NCT03474198) trial is currently underway to

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test the hypothesis that four novel 2-month regimens (containing new drugs and optimized doses of standard drugs) are non-inferior to the standard regimen.

Two key considerations for public health policy-making are assessing the impact of disease burden on the population and evaluating the cost-effectiveness of a particular intervention (Jamison and Mosley, 1991). Mathematical models can be used to address the infectious diseases of public concern, project the temporal dynamics of future disease burden, and predict the potential epidemiological consequences for identifying appropriate control strategies (Blower and Gerberding, 1998). Since 1993, the disability-adjusted life year (DALY) has become one of the most commonly used metric for both disease burden estimation and cost-effectiveness analysis (Fox-Rushby and Hanson, 2001). DALYs are favored and recommended by the WHO for use in cost-effectiveness analysis for comparability (Neumann et al., 2016; WHO, 2003).

Although previous models have explored the economic or epidemiological impacts of shorter regimens for TB treatment (Abu-Raddad et al., 2009; Fofana et al., 2014; Gomez et al., 2016; Owens et al., 2013; Salomon et al., 2006), there has been little simultaneous research into the population-level epidemiological impact and cost-effectiveness specifically focusing on high TB burden areas (Knight et al., 2014). Gomez et al. (2016) highlighted that more work is required to assess the cost-effectiveness of new TB regimens at a country level by parameterizing with locally-collected data, including sound clinical data on health service costs to reflect the influence of health system constraints.

Since novel regimens are not currently available, this study focused on assessing the impacts of hypothetical shorter regimens in high TB burden regions of Taiwan. Specifically, it aimed to develop a population model-based cost-effectiveness analysis with local epidemiological and cost data to: (i) understand the potential epidemiological benefits of shorter regimens in terms of population-level TB incidence and mortality and (ii) quantify the likely incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) with the calculation of DALY as an effectiveness indicator to evaluate whether shorter regimens could be cost-effective and analyze the threshold drug prices at which such regimens might achieve cost-saving.

2. Methods

2.1. Treatment-associated TB population dynamic model

The present treatment-associated TB population dynamic model was built upon previous models (Abu-Raddad et al., 2009; Dye et al., 1998; Fofana et al., 2014; Salomon et al., 2006) to explore the possible impact of shorter regimens on TB epidemics in Hualien and Taitung (Supplementary Figure S1; Tables S1–S3). Model performance was evaluated by comparing predicted county-specific incidence and mortality rates with the observed data (Supplementary Table S4), using the mean absolute percentage error (MAPE). The present model was used with discount rates of 0% and 3% over time to project county-specific TB dynamics, including new cases, mortality cases, incidence rates and mortality rates in the period 2006–2050 with different regimens. Details of the model structure, equations, parameterization and validation are provided in the Supplementary Materials.

2.2. Hypothetical shorter regimens

Novel regimens being studied by the TB Alliance and other research institutes are expected to shorten treatment duration from the current 6 months to 4 months, 2 months or 7 days (ClinicalTrials.gov, 2020; Silva et al., 2020; TB Alliance, 2014, 2020). Accordingly, three hypothetical shorter regimens – 4-month, 2-month and 7-day – were considered and modeled with a starting date of 2020. It was expected that these hypothetical shorter regimens would (i) increase the treatment success proportion, (ii) reduce treatment failure, and (iii) reduce the mortality of TB patients during treatment. According to the visions of Abu-Raddad et al. (2009) for shorter regimens, the expected treatment success proportions for hypothetical 4-month, 2-month and 7-day regimens were 89%, 96% and 99%, respectively. It was assumed that the treatment failure would consist of all unfavorable treatment outcomes, including failed, defaulted, transferred out and non-evaluated.

2.3. Economic evaluation

The survey data from Ma (2003) was used to calculate treatment cost per patient per day, including drug and other related costs, for outpatient and inpatient treatment under the standard 6-month regimen. All costs were converted to $US using a 2016 average exchange rate of 32.2 $NT/$US (http://www.x-rates.com). Detailed information and analysis of the cost data are provided in the Supplementary Materials.

Economic evaluations of hypothetical 4-month, 2-month and 7-day regimens were performed to evaluate whether they would be cost-effective or cost-saving, compared with the standard 6-month regimen, using both the ICER and NMB. The ICER was calculated as $\Delta C/\Delta E$ and the NMB was estimated as $(\Delta E \times \mathrm{WTP}) - \Delta C$ where ΔE is the incremental effectiveness (i.e. the number of DALYs a shorter regimen averts), ΔC is the incremental cost compared with the standard 6-month regimen, and WTP is the willingness-to-pay threshold per DALY averted, here given by $1 \times$ gross domestic product (GDP) per capita of Taiwan ($US22,561) in 2016 (National Development Council, 2018).

An ICER < 0 indicates that the regimen with such a daily drug price would be cost-saving, only if ΔC were negative (i.e. the shorter treatment has minor costs compared with the standard regimen) and the ΔE is positive (i.e. the shorter treatment is more effective than the standard regimen) (Gomez et al., 2016; Neumann et al., 2016; Owens et al., 2013). An NMB > 0 indicates that the regimen would be cost-effective at the given WTP threshold. The regimen with the highest NMB is considered the most cost-effective.

Since the drug prices of novel shorter regimens are highly uncertain, the treatment costs for hypothetical 4-month, 2-month and 7-day regimens were calculated using different assumptions of daily drug prices from $1, which was consistent with previous studies (Gomez et al., 2016; Owens et al., 2013) and assuming that other related costs would remain constant. DALYs were calculated by summing the number of years of life lost due to premature death (YLL) and years lost due to disability (YLD) (Diel and Lampenius, 2014; Fox-Rushby and Hanson, 2001) (Supplementary Table S1).

2.4. Sensitivity analysis

A sensitivity analysis was performed to assess how the NMB changes for different values of WTP thresholds. The WTP thresholds were set as a quarter, half, or one to three times GDP per capita based on the recommendations of Gomez et al. (2016) and the WHO (2002). A one-way sensitivity analysis was conducted to explore the impact of each parameter on cost-effectiveness analysis results. The input parameters in the sensitivity analysis were: (i) daily drug prices of shorter regimens, (ii) daily treatment costs under the standard regimen, (iii) the proportion of outpatients or outpatients in total new TB cases, and (iv) the number of TB cases under treatment. To calculate the percentage changes in NMB, the daily drug prices of shorter regimens varied within a specific range and each remaining parameter varied individually across the 95% confidence interval (CI) of its uncertainty

distribution. The ranges around daily drug prices of shorter regimens used in the sensitivity analysis were determined based on the cost-effectiveness analysis.

3. Results

3.1. Epidemiological impact of shorter regimens

When assuming a 3% discount rate, the predicted incidence rates with 95% CI were consistent with the observed data in Hualien (MAPE = 7.07%) and Taitung (MAPE = 13.03%) (Fig. 1a and b). The model was able to describe the trend of mortality rates in Hualien (MAPE = 14.55%) and Taitung (MAPE = 42.61%) (Fig. 1c and d). The model with a 0% discount rate was also able to capture the trend of incidence rates (MAPE range 6.76–9.88%) and mortality rates (15.93–46.02%) (Supplementary Figure S2). All MAPE values were <50%, indicating that the developed model was predictably robust.

Fig. 2 illustrates the effect by year up to 2050 of hypothetical shorter regimens on TB incidence rates and mortality cases, with a

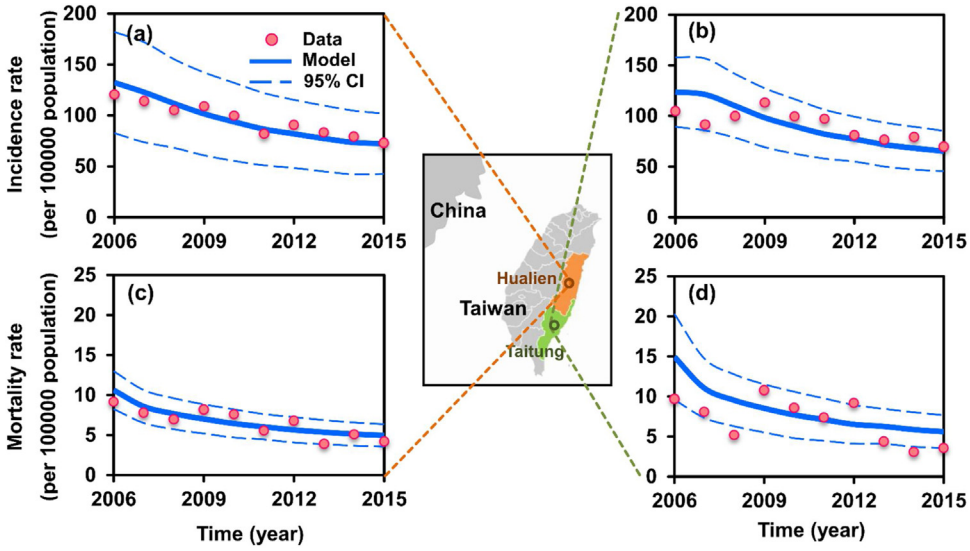

Fig. 1. Comparisons of TB incidence and mortality rates between model predictions and observed data during 2006–2015, with a discount rate of 3%. (a) Incidence rates and (c) mortality rates in Hualien. (b) Incidence rates and (d) mortality rates in Taitung.

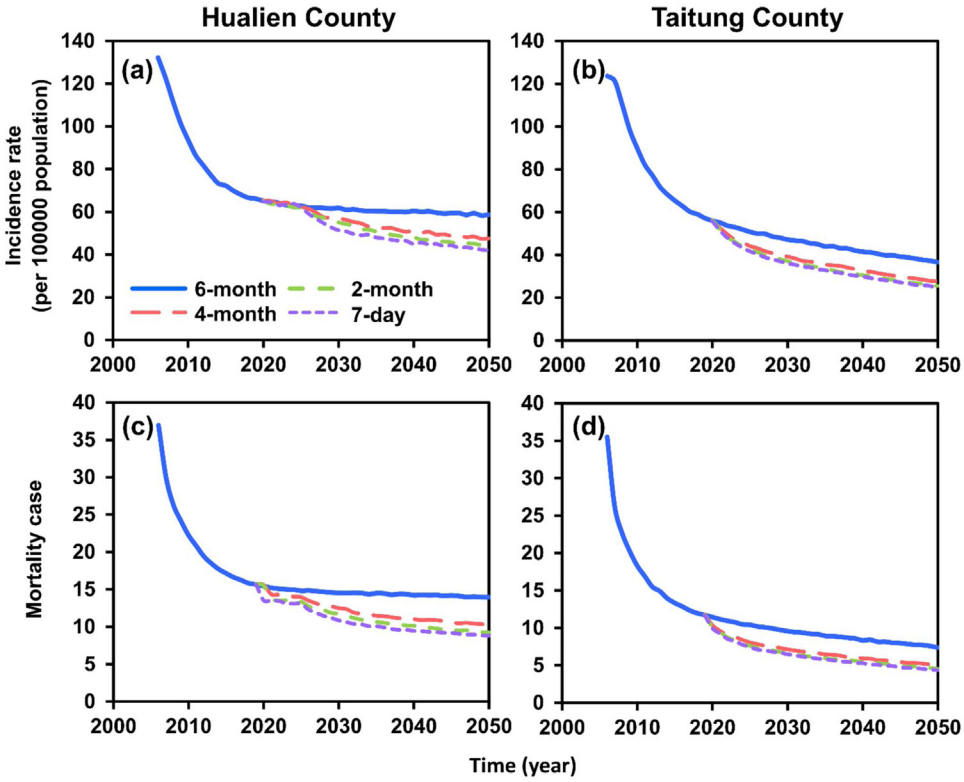

Fig. 2. Epidemiological impact by year up to 2050 of hypothetical shorter regimens on TB incidence rates and mortality cases, with a discount rate of 3%. Incidence rates in (a) Hualien and (b) Taitung. Mortality cases in (c) Hualien and (d) Taitung.

3% discount rate. The results indicated that by 2050, incidence rates in Hualien and Taitung could be reduced from 58.69 (95% CI 33.58–83.81) and 36.62 (25.28–47.97) per 100,000 population under the standard regimen to 41.97 (24.19–59.74) and 24.61 (17.01–32.21) per 100,000 population under the 7-day regimen, respectively (Fig. 2a and b; Supplementary Table S5). Average reductions in incidence for Hualien for 4-month, 2-month and 7-day regimens were predicted to be 19%, 25% and 28%, respectively, compared with the standard 6-month regimen (Fig. 2a). For Taitung, average reductions in incidence for 4-month, 2-month and 7-day regimens were predicted to be 24%, 30% and 33%, respectively (Fig. 2b).

By 2050, mortality cases could also be lowered from 14 (95% CI 10–18) and 7 (5–10) by the standard regimen to 9 (6–11) and 4 (2–6) by the 7-day regimen in Hualien and Taitung, respectively (Fig. 2c and d; Supplementary Table S5). Average reductions in mortality cases for 4-month, 2-month and 7-day regimens were predicted to be 27%, 34% and 37%, as well as 31%, 39% and 41%, respectively, in Hualien and Taitung, compared with the standard regimen. Moreover, shorter regimens had a similar effect on the incidence and mortality when assuming a discount rate of 0% (Supplementary Figure S3, Table S5).

3.2. Effectiveness

The essential parameter values used to estimate DALYs are given in Supplementary Tables S6 and S7. Fig. 3 shows that DALYs were significantly decreased by shorter regimens compared with the standard regimen. When assuming a 3% discount rate, DALYs for Hualien could be reduced from 123.52 (95% CI 36.25–340.45) by the standard regimen to 90.22 (26.17–255.44) by the 4-month regimen, 81.36 (23.58–232.80) by the 2-month regimen, and 77.92 (22.81–213.31) by the 7-day regimen (Fig. 3a). In Taitung, DALYs could be reduced from 55.89 (13.58–168.54) by the standard regimen to 33.06 (8.02–102.38) by the 7-day regimen (Fig. 3a). Under the model with a 0% discount rate, DALYs could also be reduced from 139.26 (39.61–383.89) and 61.39 (12.07–213.40) by the standard regimen to 86.51 (25.27–242.75) and 27.72 (6.63–85.93) by the 7-day regimen in Hualien and Taitung, respectively (Fig. 3b).

3.3. Treatment costs

Daily costs per patient for outpatient and inpatient treatment under the standard 6-month regimen are provided in Supplementary Table S8. The results indicated that daily drug costs and other related costs for outpatient and inpatient treatment were \$US0.428 ± 0.742 (mean ± sd) and \$US0.353 ± 0.176 as well as \$US3.042 ± 5.550 and \$US21.045 ± 10.123, respectively. The median value of daily drug costs for outpatient treatment (\$US0.308) was similar to that of inpatient treatment (\$US0.313). Inpatient programs (\$US21.398 ± 10.257) cost more than outpatient treatment (\$US3.470 ± 6.201) due to the additional costs of hospitalization, productivity loss and government allowances.

3.4. Cost-effectiveness of shorter regimens

Given the incremental costs of shorter regimens (ΔC) calculated from the total treatment costs (Supplementary Table S9) and the DALYs averted (ΔE, Fig. 3a) with a discount rate of 3%, the ICERs and NMBs, which varied with different daily drug prices, were estimated and presented in Table 1. The results showed that the 4-month regimen with a daily drug price of \$US1 could be both cost-effective and cost-saving for Taitung, but only cost-effective for Hualien. Therefore, an additional daily drug price of \$US0.3, the same as the median price of the standard regime, was used to perform cost-effectiveness analysis. However, in Hualien, the 4-month regimen still could not be cost-saving at a drug price of \$US0.3 but could be cost-effective at drug prices ranging from \$US0.3 to 10. Moreover, the results revealed that 2-month and 7-day regimens were potentially either cost-effective or cost-saving for both counties (Table 1). The threshold daily drug prices, at which 2-month and 7-day regimens would be cost-effective and cost-saving, were \$US2 and \$US70, respectively. The same findings could be drawn when considering a discount rate of 0% (Supplementary Table S11). As a result, the threshold drug prices were \$US1, \$US2 and \$US70 for 4-month, 2-month and 7-day regimens, respectively.

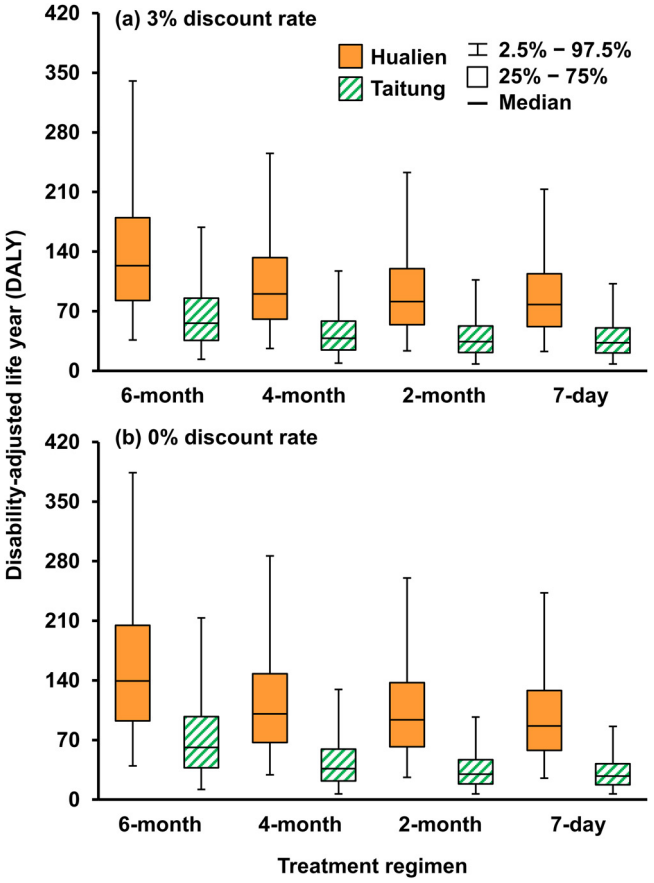

Fig. 3. Box and whisker plots of DALYs for the standard 6-month regimen and hypothetical 4-month, 2-month and 7-day regimens by 2050. (a) 3% discount rate. (b) 0% discount rate.

Furthermore, shortening treatment durations to 2-month and 7-day was predicted to be more cost-effective than to 4-month, in terms of NMB. When assuming a 3% discount rate, the 7-day regimen with a daily drug price of \$US70 would be the most cost-effective, with NMB values of \$US1010 (95% CI \$US325–3585) and \$US492 (\$US143–1912) for Hualien and Taitung, respectively (Table 1). The same conclusions could be obtained when assuming a discount rate of 0% (Supplementary Table S11).

3.5. Sensitivity analysis for NMB

Fig. 4 demonstrates that, at both discount rates of 0% and 3%, shorter regimens at their threshold daily drug prices would remain cost-effectiveness in Hualien and Taitung, even if the WTP threshold was less than 1 × GDP per capita. The results of one-way sensitivity analyses showed that when assuming a 3% discount rate, the most critical parameter for NMB was the daily drug price

Table 1
Cost-effectiveness analysis of hypothetical shorter regimens, with a discount rate of 3%.

Daily drug price ($US)	Hualien County		Taitung County	
	ICER	NMB[a]	ICER	NMB
4-month regimen				
0.3	CS[b] (CS–1524)	635 (159–2984)[c]	CS	342 (87–1676)[c]
1	**CS (CS–2250)**	**628 (150–2979)**[c]	**CS**	**338 (84–1673)c**
2	CS (CS–3470)	616 (138–2971)[c]	CS (CS–372)	334 (80–1669)[c]
10	1027 (CS–18,050)	535 (28–2882)[c]	817 (CS–9000)	298 (43–1633)[c]
15	2892 (CS–29,462)	482 (−44–2837)	2337 (CS–16,613)	276 (18–1614)[c]
20	4897 (CS–41,328)	431 (−121–2790)	3958 (227–24,566)	254 (−7–1596)
30	8935 (CS–65,267)	330 (−277–2677)	7177 (997–41,561)	209 (−59–1543)
2-month regimen				
1	CS	904 (282–3485)[c]	CS	463 (138–1923)[c]
2	**CS**	**898 (276–3480)**[c]	**CS**	**460 (136–1920)**[c]
8	CS (CS–1239)	869 (243–3450)[c]	CS	448 (123–1970)[c]
20	CS (CS–6281)	808 (174–3373)[c]	CS (CS–2504)	423 (97–1888)[c]
30	982 (CS–11,881)	757 (111–3306)[c]	809 (CS–6399)	402 (75–1864)[c]
40	2240 (CS–18,058)	704 (50–3267)[c]	1885 (CS–11,039)	381 (53–1844)[c]
80	7585 (CS–43,953)	516 (−232–3098)	6349 (1194–31,247)	297 (−39–1770)
7-day regimen				
70	**CS**	**1010 (325–3585)**[c]	**CS**	**492 (143–1912)**[c]
80	CS (CS–146)	1004 (320–3578)[c]	CS	490 (141–1910)[c]
100	CS (CS–527)	993 (307–3564)[c]	CS	485 (136–1906)[c]
120	CS (CS–967)	981 (294–3555)[c]	CS	480 (131–1901)[c]
150	CS (CS–1832)	966 (277–3539)[c]	CS (CS–309)	473 (124–1896)[c]
300	617 (CS–8318)	885 (183–3446)[c]	589 (CS–5518)	438 (88–1862)[c]
600	4366 (CS–24,253)	721 (−24–3272)	3995 (637–20,436)	369 (11–1788)[c]

Note: Values of ICERs and NMBs are presented as median (95% CI). Value in bold indicates the threshold daily drug price. ICER, incremental cost-effectiveness ratio; NMB, net monetary benefits.
[a] In thousand $US.
[b] CS: cost-saving (ICER < 0).
[c] Cost-effective (NMB > 0) under the WTP threshold of US$22,S561.

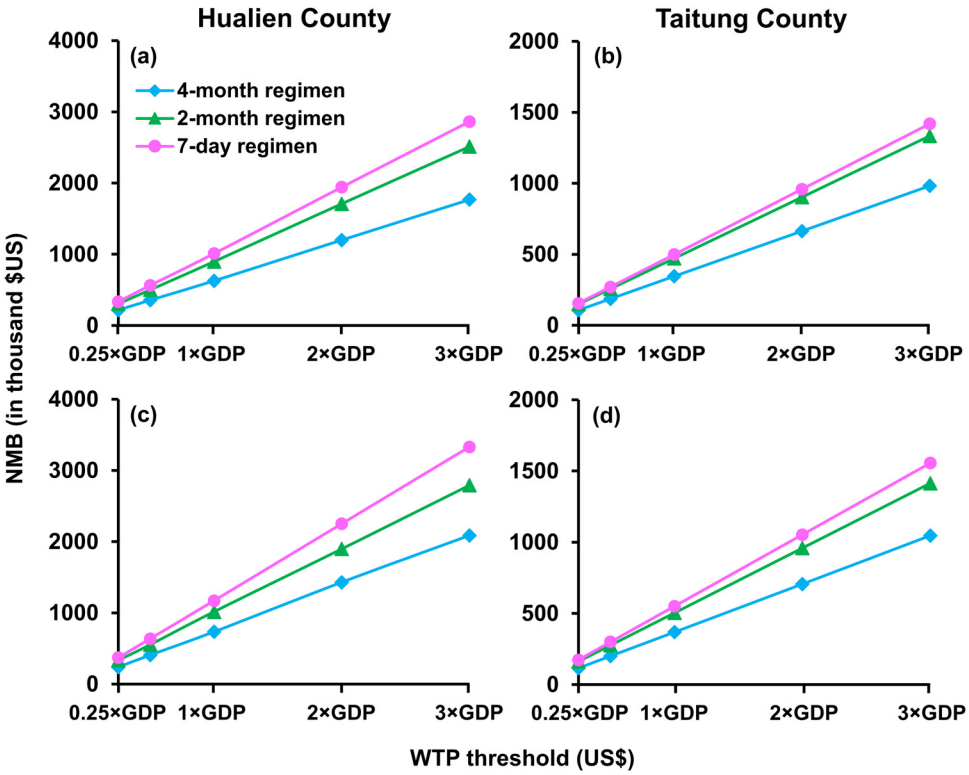

Fig. 4. Net monetary benefits (NMBs) for hypothetical shorter regimens under their threshold daily drug prices and different willingness-to-pay thresholds (WTPs). (a, b) 3% discount rate. (c, d) 0% discount rate. The threshold daily drug prices for 4-month, 2-month and 7-day regimens were $US1, $US2 and $US70, respectively (Table 1).

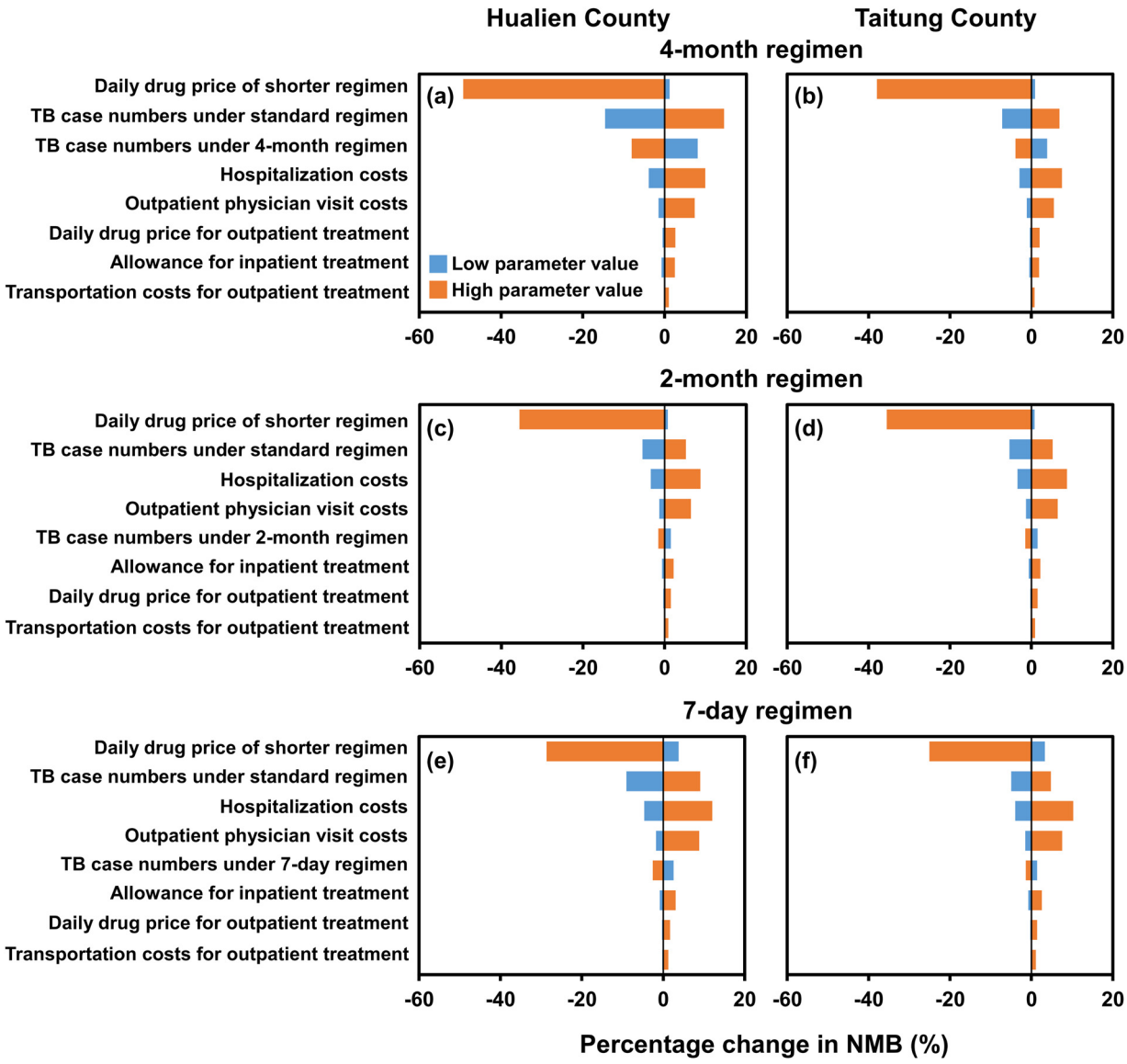

Fig. 5. One-way sensitivity analysis of net monetary benefit (NMB) for hypothetical shorter regimens. (a, b) 4-month regimen; (c, d) 2-month regimen; (e, f) 7-day regimen. For this sensitivity analysis, a discount rate of 3% and a WTP threshold of $US22,561 were used. The ranges around the daily drug prices of 4-month, 2-month and 7-day regimens used in this analysis were $US0.3–30, $US1–80 and $US70–600, respectively (Table 1). Meanwhile, each remaining parameter (including daily treatment costs, the proportion of outpatients or outpatients in total new TB cases, and the number of TB cases under treatment) individually varied across the 95% CI of its uncertainty distribution.

of shorter regimens of 4 months, 2 months and 7 days (Fig. 5). An increase in any one of the following two parameters corresponds with a decrease in NMB: (i) daily drug price of shorter regimens and (ii) TB case numbers under shorter regimens. In contrast, an increase in any of the following six parameters corresponds to an increase in NMB: (i) TB case numbers under the standard regimen, (ii) hospitalization costs, (iii) outpatient physician visit costs, (iv) daily drug price for outpatient treatment, (v) allowance for inpatient treatment, and (vi) transportation costs for outpatient treatment. The same conclusions could be drawn when considering a discount rate of 0% (Supplementary Figure S4).

4. Discussion

This study developed a population model-based cost-effectiveness analysis to assess the epidemiological impact and cost-effectiveness of the introduction of hypothetical 4-month, 2-month and 7-day regimens in high TB burden regions of Taiwan. The results showed that the epidemiological benefits and cost-effectiveness of shorter regimens were similar at both discount rates of 0% and 3%. When assuming a 3% discount rate and a WTP threshold of $US22,561, this study found that (i) shorter regimens would lower incidence rates and mortality cases in 2050, respectively, by 19–28% and 27–37% in Hualien and by 24–33% and 31–41% in Taitung; (ii) 4-month regimen costing $US1 per day could be both cost-effective and cost-saving in Taitung, but only be cost-effective in Hualien; and (iii) 2-month and 7-day regimens would be more cost-effective than a 4-month regimen. Overall, the threshold daily drug prices for achieving cost-effectiveness and cost-saving for 4-month, 2-month and 7-day regimens were $US1, $US2 and $US70, respectively.

The expected impacts of shorter regimens on TB in a specific country are rarely explored; however, those have been evaluated for the WHO's South-East Asian region (Abu-Raddad et al., 2009; Salomon et al., 2006). Salomon et al. (2006) indicated that the 2-month regimen prevented 22–51% of incidences and 32–54% of

mortalities. Abu-Raddad et al. (2009) showed that 4-month, 2-month and 10-day regimens produced 10–27% reductions in incidences and prevented 11–30% of deaths. The differences between their results and the results of this study could be partly due to different model methodologies, parametrizations and scenario assumptions. Salomon et al. (2006) developed a model specific to directly observed short-course therapy (DOTS) and non-DOTS programs, whereas Abu-Raddad et al. (2009) used an age-structured model. For the 2-month regimen, the cure probabilities in DOTS and non-DOTS programs assumed by Salomon et al. (2006) were 93% and 80%, respectively. By contrast, Abu-Raddad et al. (2009) and the current study both assumed a treatment success proportion of 96% for the 2-month regimen. The reduction in the incidence of Abu-Raddad et al. (2009) was less than that of this study, which may be due to a higher proportion of treatment success of the current regimen in their study, leaving little room for improvement with a new regimen.

This study also found that the epidemiological benefits of shorter regimens were higher in Taitung than in Hualien, which may have been due to the higher transmission rate, higher treatment failure rate, higher TB-related mortality rate, and lower treatment success proportion in Taitung. Thus, shorter regimens are likely to have greater epidemiological impacts in settings with high rates of incidences and poor treatment outcomes, which is similar to the finding by Fofana et al. (2014). The benefits of shorter regimens appear to be attributable to the direct impacts on improved treatment outcomes due to accelerated treatment completion and the indirect impacts of reducing transmission due to shortened duration of infectiousness for treated patients (Salomon et al., 2006).

The WHO (2002) suggested that cost-effective interventions are those where each DALY averted costs between one and three times GDP per capita. The universal WTP thresholds used in Taiwan ranged from 0.5 to three times GDP per capita (Chan et al., 2017; Koh et al., 2016; Yang et al., 2018). Although no WTP threshold is universally accepted in Taiwan, the current sensitivity analysis demonstrated that the cost-effectiveness of shorter regimens would remain, even if the WTP threshold was less than 1 × GDP per capita. These potential benefits are important in light of the End TB Strategy's target of no affected families facing catastrophic costs due to TB (WHO, 2015). The shorter regimen could reduce out-of-pocket expenses for patients and allow earlier return to productive activities (Gospodarevskaya et al., 2014).

Owens et al. (2013) estimated that 4-month and 2-month regimens became cost-saving at daily drug prices of <$US0.48–2.38 and $US1.37–9.17 for scenarios of low, moderate and high treatment costs. They also found that cost-effectiveness is primarily driven by the balance struck between drug price, delivery costs and the ability of shorter regimens to avert mortality. In the current analysis, 2-month and 7-day regimens showed higher cost-effectiveness than the 4-month regimen, which may be attributed to greater reductions in incidences and mortalities by such regimens. Gomez et al. (2016) indicated that the cost-effectiveness of shorter regimens substantially varied by setting and current treatment practice and that 4-month regimen costing $US1 a day showed cost-saving in Brazil, South Africa and Tanzania, but not in Bangladesh. Drug price is likely to be critical for cost-effectiveness (Gomez et al., 2016). In Bangladesh, where existing treatment cost was low ($US1.27 per day), the shorter regimen assumed daily drug price of $US1 increased overall health service costs (Gomez et al., 2016). In contrast, where existing treatment cost was higher (e.g. $US22.57 per day in Brazil), the shorter regimen was cost-saving. The current study also demonstrated that drug price is the most important factor for cost-effectiveness.

The present study had several limitations. First, a key weakness of the cost-effectiveness analysis was the uncertainties surrounding future costs and prices, which will depend on future socio-economic developments. Second, this study did not account for the impacts of program costs, age and indigenous subpopulation on the cost-effectiveness of shorter regimens. Third, the exclusion of the cost of DOTS implementation may have overestimated cost-effectiveness. More than 90% of TB cases in Taiwan were found in adults and elderly persons, with the largest fraction of cases among ≥65 years (50%) (Liao et al., 2012). It implies that transmission rates, connected to the incidence, vary among different age populations. We thus suggests that the age-structured contact pattern is one of the critical elements for quantifying the uncertainty in transmission rates for a more accurate prediction of TB population dynamics. Moreover, older TB patients in Taiwan have a much lower cure rate compared with younger patients (Li et al., 2010), in which case, clinical trials for different age groups are warranted to assess the potential epidemiological benefits of more effective TB drugs. Despite these limitations, the results support the inclusion of shorter regimens in global guidelines and regional-scale TB control strategies, which would improve TB control, especially in areas with high rates of incidence and poor treatment outcomes.

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Patient consent for publication

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Ethical approval

Not required.

Author contributions

YJL and CML conceived, initiated and led the study. YJL, HCL, YFY, CYC, and THL collected and analyzed the data with input from all the authors. YJL and CML wrote the manuscript. All authors reviewed and approved the manuscript.

Conflict of interest

The authors declare no conflict of interest.

Data availability

All data generated or analyzed during this study are included in this published article.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2020.05.082.

References

Abu-Raddad LJ, Sabatelli L, Achterberg JT, Sugimoto JD, Longini Jr. IM, Dye C, et al. Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. Proc Natl Acad Sci U S A 2009;106:13980–5, doi:http://dx.doi.org/10.1073/pnas.0901720106.

Blower SM, Gerberding JL. Understanding, predicting and controlling the emergence of drug-resistant tuberculosis: a theoretical framework. J Mol Med 1998;76:624–36, doi:http://dx.doi.org/10.1007/s001090050260.

Chan DC, McCloskey EV, Chang CB, Lin KP, Lim LC, Tsai KS, et al. Establishing and evaluating FRAX® probability thresholds in Taiwan. J Formos Med Assoc 2017;116:161–8, doi:http://dx.doi.org/10.1016/j.jfma.2016.03.006.`

ClinicalTrials.gov, U.S. National Library of Medicine. https://clinicaltrials.gov/ct2/home, 2020 (accessed 26 April 2020) .

Diel R, Lampenius N. Cost-effectiveness analysis of interventions for tuberculosis control: DALYs versus QALYs. Pharmacoeconomics 2014;32:617–26, doi:http://dx.doi.org/10.1007/s40273-014-0159-5.

Dye C, Garnett GP, Sleeman K, Williams BG. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Lancet 1998;352:1886–91, doi:http://dx.doi.org/10.1016/s0140-6736(98)03199-7.

Fofana MO, Knight GM, Gomez GB, White RG, Dowdy DW. Population-level impact of shorter-course regimens for tuberculosis: a model-based analysis. PLoS ONE 2014;9:e96389, doi:http://dx.doi.org/10.1371/journal.pone.0096389.

Fox-Rushby JA, Hanson K. Calculating and presenting disability adjusted life years (DALYs) in cost-effectiveness analysis. Health Policy Plan 2001;16:326–31, doi:http://dx.doi.org/10.1093/heapol/16.3.326.

Gomez GB, Dowdy DW, Bastos ML, Zwerling A, Sweeney S, Foster N, et al. Cost and cost-effectiveness of tuberculosis treatment shortening: a model-based analysis. BMC Infect Dis 2016;16:726, doi:http://dx.doi.org/10.1186/s12879-016-2064-3.

Gospodarevskaya E, Tulloch O, Bunga C, Ferdous S, Jonas A, Islam, et al. Patient costs during tuberculosis treatment in Bangladesh and Tanzania: the potential of shorter regimens. Int J Tuberc Lung Dis 2014;18:810–7, doi:http://dx.doi.org/10.5588/ijtld.13.0391.

Jamison DT, Mosley WH. Disease control priorities in developing countries: health policy responses to epidemiological change. Am J Public Health 1991;81:15–22, doi:http://dx.doi.org/10.2105/ajph.81.1.15.

Knight GM, Griffiths UK, Sumner T, Laurence YV, Gheorghe A, Vassall A, et al. Impact and cost-effectiveness of new tuberculosis vaccines in low-and middle-income countries. Proc Natl Acad Sci U S A 2014;111:15520–5, doi:http://dx.doi.org/10.1073/pnas.1404386111.

Koh L, Glaetzer C, Li SC, Zhang M. Health technology assessment, international reference pricing, and budget control tools from China's perspective: what are the current developments and future considerations?. Value Health Reg Issues 2016;9:15–21, doi:http://dx.doi.org/10.1016/j.vhri.2015.06.004.

Li YH, Tsai WC, Khan M, Yang WT, Lee TF, Wu YC, et al. The effects of pay-for-performance on tuberculosis treatment in Taiwan. Health Policy Plann 2010;25:334–41, doi:http://dx.doi.org/10.1093/heapol/czq006.

Liao CM, Cheng YH, Lin YJ, Hsieh NH, Huang TL, Chio CP, et al. A probabilistic transmission and population dynamic model to assess tuberculosis infection risk. Risk Anal 2012;32:1420–32, doi:http://dx.doi.org/10.1111/j.1539-6924.2011.01750.x.

Ma TC. The cost benefit analysis of inpatient care for patients with tuberculosis. Taipei, Taiwan, ROC: Centers for Disease Control, Department of Health and Welfare; 2003.

National Development Council, Taiwan, ROC. Taiwan statistical data book, 2018. 2018 https://www.ndc.gov.tw/en/News_Content.aspx?n=607ED34345641980&sms=-B8A915763E3684AC&s=B3B7911F9063C75F [accessed 28.01.19].

Neumann PJ, Thorat T, Zhong Y, Anderson J, Farquhar M, Salem M, et al. A systematic review of cost-effectiveness studies reporting cost-per-DALY averted. PLoS ONE 2016;11:e0168512, doi:http://dx.doi.org/10.1371/journal.pone.0168512.

Owens JP, Fofana MO, Dowdy DW. Cost-effectiveness of novel first-line treatment regimens for tuberculosis. Int J Tuberc Lung Dis 2013;7:590–6, doi:http://dx.doi.org/10.5588/ijtld.12.0776.

Salomon JA, Lloyd-Smith JO, Getz WM, Resch S, Sánchez MS, Porco TC, et al. Prospects for advancing tuberculosis control efforts through novel therapies. PLoS Med 2006;3:e273, doi:http://dx.doi.org/10.1371/journal.pmed.0030273.

Silva DR, Mello FCQ, Migliori GB. Shortened tuberculosis treatment regimens: what is new?. J Bras Pneumol 2020;46:e20200009, doi:http://dx.doi.org/10.36416/1806-3756/e20200009.

Taiwan CDC (Centers for Disease Control, Department of Health and Welfare, Taiwan, ROC). Taiwan tuberculosis control report 2015. 2017 https://www.cdc.gov.tw/uploads/files/201702/785d5fb9-d98d-47d7-860f-9d5178668530.pdf [accessed 29.02.18].

TB Alliance. TB Alliance 2014 annual report. 2014 https://www.tballiance.org/annualreport2014/ [accessed 25.01.18].

TB Alliance. Regimens. 2020 https://www.tballiance.org/portfolio/regimens [accessed 26.04.20].

WHO. Global tuberculosis report 2017. 2017 https://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf [accessed 29.04.18].

WHO. Implementing the End TB strategy: the essentials. 2015 https://www.who.int/tb/publications/2015/end_tb_essential.pdf?ua=1 [accessed 20.03.18].

WHO. The world health report 2002: reduction risks, promoting healthy life. 2002 https://apps.who.int/iris/bitstream/handle/10665/42510/WHR_2002.pdf;jsessionid=C0F239B5BAFBB3FA27E7C7AB029999DF?sequence=1 [accessed 15.01.18].

WHO. WHO guide to cost-effectiveness analysis. 2003 https://www.who.int/choice/publications/p_2003_generalised_cea.pdf [accessed 04.05.20].

Yang KC, Hung HF, Chen MK, Chen SL, Fann JC, Chiu SY, et al. Cost-effectiveness analysis of universal influenza vaccination: application of the susceptible–infectious–complication–recovery model. Int J Infect Dis 2018;73:102–8, doi:http://dx.doi.org/10.1016/j.ijid.2018.05.024.