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Cost-effectiveness of bedaquiline or delamanid plus background regimen for multidrug-resistant tuberculosis in a high-income intermediate burden city of China

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ABSTRACT

Objective: Hong Kong is a high-income city of China with an intermediate tuberculosis (TB) burden, and 1% of TB cases are multidrug-resistant (MDR-TB). The aim of this study was to examine the potential cost-effectiveness of adding bedaquiline or delamanid to the background regimen (BR) for the treatment of MDR-TB in Hong Kong.
Methods: A decision-analytic model was designed to simulate outcomes over a 10-year time horizon for MDR-TB patients treated with bedaquiline plus BR (B-BR), delamanid plus BR (D-BR), or BR alone. Outcome measures included direct medical costs and quality-adjusted life-years (QALYs) gained.
Results: In the base-case analysis, BR was the least costly regimen (USD 47 396) with the lowest QALYs gained (6.347). Compared to BR, B-BR gained an additional 0.731 QALYs with incremental cost of USD 9. The incremental cost-effectiveness ratio (ICER) of B-BR was USD 12/QALY. D-BR was more costly than BR by USD 20 164 and gained an additional 0.012 QALYs. The ICER of D-BR was USD 1 680 333/QALY. In the probabilistic sensitivity analysis with 10 000 Monte Carlo simulations, B-BR and D-BR were cost-effective 99.98% and 5.13% of the time, respectively, using 1× gross domestic product per capita (USD 46 182) as the willingness-to-pay threshold.
Conclusions: Bedaquiline is more likely than delamanid to be cost-effective when added to BR for the treatment of MDR-TB in Hong Kong.

Introduction

Hong Kong is a high-income city of China with an intermediate tuberculosis (TB) burden. This was estimated to be 60.5 per 100 000 population in 2015, and 1% of all culture-confirmed cases were multidrug-resistant (MDR-TB) (Department of Health, 2015). Similar to the global cure rate (52%) (World Health Organization, 2017), approximately 60% of patients with MDR-TB are cured with the background regimen (BR) in Hong Kong (Department of Health, 2012, 2013b, 2014, 2015). Despite the low prevalence of MDR-TB, it still places a burden on the healthcare system of Hong Kong due to the suboptimal cure rate and prolonged duration of treatment.

Bedaquiline, a diarylquinoline compound, was approved by the US Food and Drug Administration (FDA) in 2012 and by the European Medicines Agency (EMA) in 2014 for use in MDR-TB (European Medicines Agency, 2013b; Janssen Therapeutics, 2012). Delamanid, a nitroimidazole compound, was approved by the EMA in 2014 (European Medicines Agency, 2013a). The World Health Organization (WHO) subsequently recommended bedaquiline and delamanid as add-on agents to a WHO-recommended regimen in adult patients with MDR-TB (World Health Organization, 2013, 2014). In clinical studies, the use of bedaquiline or delamanid as add-on therapy to BR for MDR-TB has shown significant bactericidal activity and improved tolerability (Pontali et al., 2016; Sotgiu et al., 2015), yet the cost-effectiveness of adding bedaquiline or delamanid to BR has varied in different countries (subject to drug cost and healthcare resource variations) (Diel et al., 2015; Lu et al., 2017; Park et al., 2016; Wirth et al., 2017; Wolfson et al., 2015).

This study examined the potential costs and gain in quality-adjusted life-years (QALYs) with the use of bedaquiline or delamanid plus BR for the treatment of MDR-TB in Hong Kong.

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Methods

Decision-analytic model

A decision-analytic model was designed to simulate potential outcomes of a hypothetical cohort of adult patients with MDR-TB treated with one of three primary treatment regimens: (1) BR alone for 24 months, (2) bedaquiline plus BR (B-BR) (BR for 24 months plus bedaquiline 400 mg once daily during the first 2 weeks followed by 200 mg three times per week for 22 weeks), and (3) delamanid plus BR (D-BR) (BR for 24 months plus delamanid 100 mg twice daily for 6 months). Two daily regimens were designed as BR in Hong Kong (Centre for Health Protection, 2006; Chan et al., 2008; Department of Health, 2013a; Yew and Leung, 2008): (1) levofloxacin 750 mg, amikacin 750 mg, prothionamide 750 mg, pyrazinamide 2 g, ethambutol 1.2 g; (2) levofloxacin 750 mg, amikacin 750 mg, prothionamide 750 mg, cycloserine 750 mg, para-aminosalicylic acid 10 g (in two divided doses). The injectable agents were used for the first 6 months. The study was conducted by model-based simulation and no samples or subjects were involved; ethics approval was therefore not requested.

The time horizon of the decision-analytic model was 10 years. All hypothetical patients first entered the model at a 2-year decision tree (Figure 1a) and received BR, B-BR, or D-BR. At the end of the 2-year decision tree model, a patient might survive or die. Those who survived might experience treatment success or 'not cured' (including treatment failure/loss to follow-up) (Yew et al., 2000). Patients who survived entered the Markov model as 'cured' or as 'not cured' (Figure 1b). The Markov model period was 8 years with a yearly cycle. Patients who were cured might die from all causes in every cycle. Those who entered the Markov model as 'not cured' were treated with secondary treatment for 2 years, and they might die during secondary treatment. The secondary treatment regimen in Hong Kong included levofloxacin 750 mg daily or moxifloxacin 400 mg daily, plus amikacin 1 g daily, prothionamide 750 mg daily, linezolid 600 mg twice daily, and para-aminosalicylic acid 5 g twice daily (Centre for Health Protection, 2006; Chan et al., 2008; Department of Health, 2013a; Yew and Leung, 2008). Patients who completed secondary treatment might be cured. Those who failed secondary treatment would receive palliative care until death.

Clinical inputs

All model inputs are listed in Table 1. A literature search was performed in the MEDLINE database covering the period 2000–2018 using keywords "multi-drug resistant tuberculosis"; "treatment outcome"; "mortality"; "bedaquiline"; "delamanid"; "background regimen"; "Chinese"; and "Hong Kong". The selection criteria for clinical studies were: (1) reports written in English; (2) patients with MDR-TB; and (3) treatment success rate and/or mortality rate reported. All articles retrieved through this process were screened for relevance to the model. For variables reported in multiple studies; the weighted average was used to estimate the base-case value. The highest and lowest values reported in the literature were used as the range examined in the sensitivity analyses.

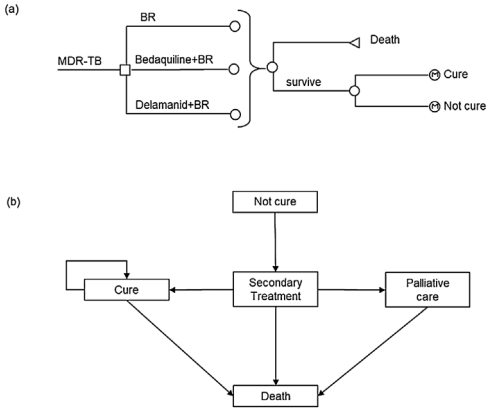

Figure 1. Simplified decision-analytic model: (a) decision tree model (b) Markov model. MDR-TB = multidrug-resistant tuberculosis; BR = background regimen.

The weighted averages of the 24-month treatment success rate (72.9%; 95% confidence interval (CI) 63.3–80.8%) and mortality rate (13.5%; 95% CI 8.4–21.1%) of BR for MDR-TB, and the yearly probability of treatment success with secondary treatment (36.5%; 95% CI 31.7–40.4%) were estimated from findings of four TB annual reports by the Department of Health of Hong Kong (Department of Health, 2012, 2013b, 2014, 2015). The yearly probability of mortality for MDR-TB patients receiving second-line drugs (8%; range 7.2–8.8%) was estimated from the findings of an outcomes study on MDR-TB in Hong Kong followed up to 52 months (Yew et al., 2000). Age-specific all-cause mortality rates were retrieved from the Census and Statistics Department of Hong Kong (Census and Statistics Department, 2017).

The model inputs for treatment success of B-BR and D-BR were retrieved from the WHO reports on the use of bedaquiline and delamanid in the treatment of MDR-TB (World Health Organization, 2016, 2018a). The WHO conducted a meta-analysis on 351 patients who had at least 18–20 months of follow-up data, and the treatment success rate of bedaquiline among survivors was estimated to be 87.3% (95% CI 82.8–90.8%) (World Health Organization, 2016). The relative change of bedaquiline plus BR versus BR alone on mortality (0.39; 95% CI 0.31–0.51) was estimated from data reported in an observational study with 25 095 participants (World Health Organization, 2016).

The treatment outcomes of delamanid in a phase 3, multicenter, randomized controlled trial ($n = 484$) were included in a WHO position statement on the use of delamanid for MDR-TB, and the treatment success rate of delamanid among survivors at 30 months was estimated to be 81.4% (95% CI 76.8–85.3%). The relative change of mortality with delamanid plus BR versus BR alone (1.12; 95% CI 0.498–2.527) was approximated from the phase 3 trial findings (World Health Organization, 2018a).

Utility inputs

The QALYs gained for each patient were estimated using the utility and duration of time spent in each of the following states: (1) first year of primary treatment for MDR-TB; (2) second year of primary treatment for MDR-TB; (3) secondary treatment for MDR-TB; (4) treatment success with primary or secondary treatment; and (5) palliative care. The age-specific utility value for healthy individuals was adopted as the utility of treatment success. The average age of patients (46 years; range 34–60 years) in a retrospective cohort study on MDR-TB cases ($n = 270$) in Hong Kong was used as the base-case age of the hypothetical cohort (Leung et al., 2013). The age-specific utility values for healthy individuals were reported from a health-related quality of life study (Gold et al., 1998). The utilities for MDR-TB patients in the first year (0.790; range 0.632–0.948) and the second year (0.810; range 0.648–0.972) of the primary treatment were retrieved from a cost-effectiveness study of MDR-TB (Jit et al., 2011). The utility of untreated patients (0.680; range 0.544–0.816) was used for 'not cured' patients treated with secondary treatment (Jit et al., 2011). The utility of palliative care for MDR-TB patients was assumed to be half of the 'not cured' state (0.34; range 0.272–0.408).

Table 1
Model inputs.

	Base-case value	Range for sensitivity analysis	Distribution	Reference
Clinical inputs				
Treatment outcomes at 24 months				
Treatment success rate of BR	0.729	0.633–0.808	Beta	Department of Health (2012, 2013b, 2014, 2015)
Treatment success rate of B-BR	0.873	0.828–0.908	Beta	World Health Organization (2016)
Treatment success rate of D-BR	0.814	0.768–0.853	Beta	World Health Organization (2018a)
Mortality rate of MDR-TB on BR	0.135	0.084–0.211	Beta	Department of Health (2012, 2013b, 2014, 2015)
Relative change of mortality with bedaquiline	0.39	0.31–0.51	Triangular	World Health Organization (2016)
Relative change of mortality with delamanid	1.122	0.498–2.527	Triangular	World Health Organization (2018a)
Probability of mortality with secondary treatment	0.080	0.072–0.088	Triangular	Yew et al. (2000)
Yearly probability of treatment success with secondary treatment	0.365	0.317–0.404	Beta	Department of Health (2012, 2013b, 2014, 2015)
Yearly probability of all-cause death	Age-specific annual mortality rate			Census and Statistics Department (2017)
Utility inputs				
Age (years)	46	34–60	Triangular	Leung et al. (2013)
Age-specific utility				Gold et al. (1998)
<18 years	1	–		
18–65 years	0.92	–		
>65 years	0.84	–		
First year of primary treatment	0.790	0.632–0.948	Triangular	Jit et al. (2011)
Second year of primary treatment	0.810	0.648–0.972	Triangular	Jit et al. (2011)
Not cured on secondary treatment	0.680	0.544–0.816	Triangular	Assumption
Palliative care	0.340	0.272–0.408	Triangular	Assumption
Cost inputs (USD)				
First year of primary treatment drug cost				
BR	5701	4561–6841	Triangular	Local cost
B-BR	20 107	16 086–24 128	Triangular	Local cost
D-BR	35 711	28 569–42 853	Triangular	Local cost
Second year of primary treatment drug cost	4642	3714–5571	Triangular	Local cost
Yearly drug cost of secondary treatment	51 999	41 599–62 399	Triangular	Local cost
Daily cost of hospitalization	654	–		Local cost
Cost of clinic follow-up per time	153	–		Local cost
Length of stay				
First year of primary treatment (days)	8.5	6.8–10.2	Triangular	Chu et al. (2001)
Second year of primary treatment in 'not cured' cases (months)	6	0–12	Triangular	Diacon et al. (2014)
Palliative care (days)	60	30–90	Triangular	Teno et al. (2007)
Number of clinic visits in				
First year of primary treatment	9	7–11	Triangular	Centre for Health Protection (2006)
Second year of primary treatment	4	3–5	Triangular	Centre for Health Protection (2006)
Number of clinic visits per year for secondary treatment	6	4–12	Triangular	Centre for Health Protection (2006)

BR, background regimen; B-BR, bedaquiline plus background regimen; D-BR, delamanid plus background regimen; MDR-TB, multidrug-resistant tuberculosis.

Cost inputs

The cost analysis was conducted on direct medical costs from the perspective of the public healthcare provider. Cost items included TB-associated hospitalization, anti-TB drugs, and follow-up visits. The MDR-TB-associated hospitalization cost was calculated from the daily cost of local hospitalization and the estimated length of hospital stay in different TB treatment states (Chu et al., 2001; Diacon et al., 2014; Teno et al., 2007). The cost of the clinic visit for follow-up was calculated using the cost per clinic visit and number of follow-up visits needed in different states as recommended by local guidelines (Centre for Health Protection, 2006). Both costs and QALYs were discounted by an annual rate of 3%.

Cost-effectiveness analysis and sensitivity analysis

If B-BR or D-BR gained more QALYs at higher cost than BR, the incremental cost-effectiveness ratio (ICER) was calculated, as follows: Δ cost/Δ QALYs gained. The threshold of willingness-to-pay (WTP) for the highly cost-effective option previously recommended by the WHO was 1× gross domestic product (GDP) per capita (World Health Organization, 2002). The GDP per capita of Hong Kong in 2017 was USD 46 182; (USD 1 = HKD 7.8) (Census and Statistics Department, 2018) and this was adopted as the WTP threshold.

The sensitivity analysis was performed using TreeAge Pro 2009 (TreeAge Software Inc, Williamstown, MA, USA) and Excel 2013 (Microsoft Corporation, Redmond, WA, USA). All model inputs were examined by one-way sensitivity analysis. The probabilistic sensitivity analysis was performed using Monte Carlo simulation to examine the impact of uncertainty in all variables simultaneously. The cost and QALYs gained in each study arm was recalculated 10 000 times by randomly selecting each model input from the probability distribution specified in Table 1. The probabilities of B-BR and D-BR being cost-effective were examined over a wide range of WTP thresholds (USD 0–100 000/QALY).

Results

Base-case analysis

In the base-case analysis (Table 2), BR was the least costly regimen (USD 47 396) with the lowest QALYs gained (6.347).

Table 2
Base-case analysis of MDR-TB-related direct medical cost and QALYs gained.

Strategy	Cost per patient (USD)	QALYs gained	ICER (USD/QALY gained) compared to BR[a]
BR	47 396	6.347	–
B-BR	47 405	7.078	12
D-BR	67 560	6.359	1 680 333

BR, background regimen; B-BR, bedaquiline plus background regimen; D-BR, delamanid plus background regimen; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; MDR-TB, multidrug-resistant tuberculosis.
[a] ICER = Δ cost/Δ QALYs. The strategy was accepted to be cost-effective when ICER was lower than 1× gross domestic product per capita in Hong Kong (USD 46 182).

Compared to BR, B-BR gained an additional 0.731 QALYs with an incremental cost of USD 9. The ICER of B-BR was USD 12/QALY and it was lower than the WTP threshold of USD 46 182. D-BR was more costly than BR by USD 20 164 and gained an additional 0.012 QALYs. The ICER of D-BR was USD 1 680 333/QALY and this was higher than the WTP threshold.

Sensitivity analysis

The one-way sensitivity analysis found the base-case results to be robust to variation of all model inputs. The probabilistic sensitivity analysis was performed by 10 000 Monte Carlo simulations. Scatter plots were drawn to show the incremental cost against incremental QALYs gained by B-BR versus BR (Figure 2) and D-BR versus BR (Figure 3). When compared with BR (Figure 2), B-BR gained higher QALYs in 100% of simulations and it was cost-saving 48.15% of the time. B-BR gained more QALYs at higher cost than BR 51.85% of the time (51.83% below WTP and 0.02% above WTP). The mean incremental cost was USD −150 (95% CI USD −278 to −22; $p = 0.022$) and the mean incremental QALYs gained was 0.722 (95% CI 0.719–0.725; $p < 0.001$).

In the comparison between D-BR and BR (Figure 3), D-BR gained higher QALYs in 33.56% of simulations (at higher cost in 33.29% and at lower cost in 0.27%). Of the 33.29% simulations with higher QALYs at additional cost, 4.67% of simulations had ICER below WTP. D-BR gained lower QALYs 66.44% of the time (at higher cost in 66.01% and at lower cost in 0.43%). The mean incremental cost was USD 19 022 (95% CI USD 18 887–19 158; $p < 0.001$) and the mean incremental QALYs gained in the D-BR group was −0.207 (95% CI −0.215 to −0.200; $p < 0.001$).

The probabilities of B-BR and D-BR being cost-effective when compared with BR were presented in acceptability curves over a wide range of WTP (USD 0–100 000/QALY) (Figure 4). Using 1× GDP per capita (USD 46 182) as the WTP threshold, B-BR and D-BR were cost-effective 99.98% and 5.13% of the time, respectively.

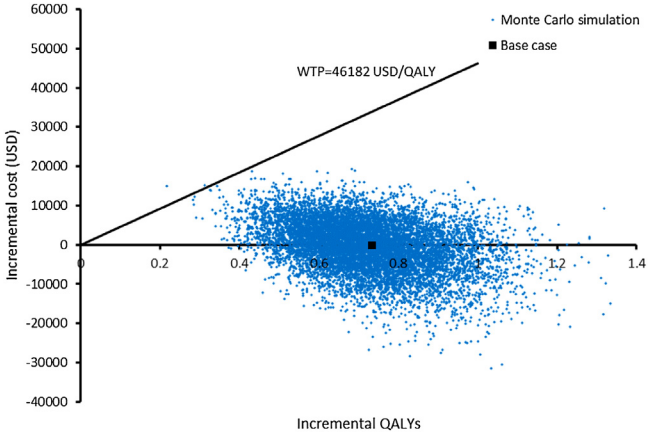

Figure 2. Scatter plot of the incremental costs against incremental QALYs gained by B-BR versus BR. BR = background regimen; B-BR = bedaquiline plus BR; QALYs = quality-adjusted life-years; WTP = willingness-to-pay.

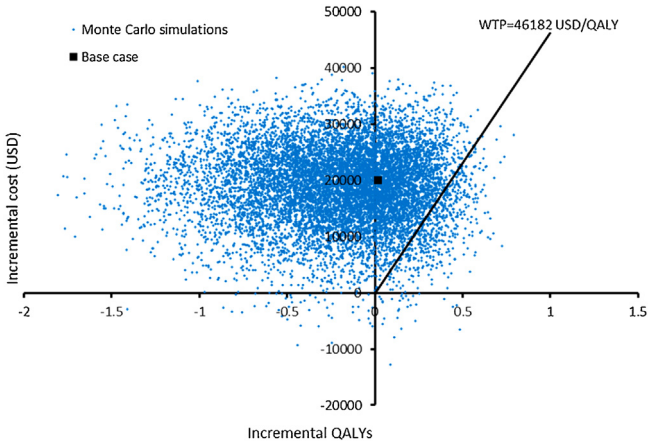

Figure 3. Scatter plot of the incremental costs against incremental QALYs gained by D-BR versus BR. BR = background regimen; D-BR = delamanid plus BR; QALYs = quality-adjusted life-years; WTP = willingness-to-pay.

Discussion

This study compared the cost-effectiveness of bedaquiline or delamanid plus BR versus BR alone for the treatment of MDR-TB in Hong Kong. The base-case analysis results showed that B-BR was the strategy accepted to be cost-effective when compared to BR. The one-way sensitivity analysis found the cost-effective option of B-BR to be highly robust and no threshold value was identified throughout variation of all model inputs. The results of the probabilistic sensitivity analysis also supported B-BR to be cost-effective in over 99.9% of 10 000 Monte Carlo simulations at WTP of 1× GDP per capita in Hong Kong.

The additional QALYs gained by D-BR versus BR in the base-case analysis was not robust in the probabilistic sensitivity analysis. In the 10 000 Monte Carlo simulations, only one-third of the simulations showed incremental QALYs gained by D-BR, and the

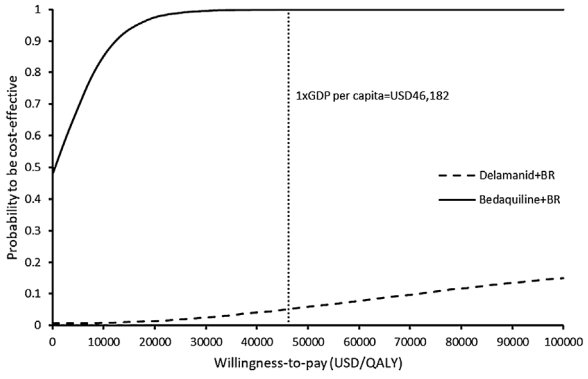

Figure 4. Acceptability curves of the probabilities of B-BR and D-BR being cost-effective against willingness-to-pay. BR = background regimen; B-BR = bedaquiline plus BR; D-BR = delamanid plus BR.

QALYs gained by D-BR were significantly lower than those gained by BR. D-BR was therefore less effective than BR in QALYs gained.

Bedaquiline and delamanid are two novel anti-TB agents for the treatment of MDR-TB. The phase 2b trial showed a significantly higher culture conversion rate and cure rate at 120 weeks for MDR-TB patients randomized to bedaquiline plus BR versus BR alone. The 120-week mortality rate was, however, significantly higher in the bedaquiline group, despite no evident causal pattern being identified (Diacon et al., 2014). The WHO further presented the findings of a systematic review and meta-analysis on bedaquiline plus BR, including data from both randomized clinical trials and observational data ($n = 25\ 095$), in the guideline development group recommendations report in 2016 (World Health Organization, 2016). Treatment success was reported to be more likely (risk ratio 1.81; 95% CI 1.26–2.31) and the risk of mortality lower (odds ratio 0.39; 95% CI 0.31–0.51) with bedaquiline plus BR versus BR alone.

In the present model, the treatment success rate and mortality risk reported by the WHO were adopted in the B-BR arm. The study findings were consistent with recent cost-effectiveness analyses in the Republic of Korea and Germany, in which B-BR was accepted as cost-effective with more QALYs gained at additional cost. The comparable cost-effectiveness findings are possibly related to similar WTP thresholds applied for the acceptance of cost-effectiveness (USD 46 182/QALY in Hong Kong; USD 23 636/QALY in Korea; USD 35 431–59 053/QALY in Germany), as well as the well-established healthcare systems in these developed regions (Park et al., 2016; Wirth et al., 2017).

The WHO recently published a position statement (early 2018) on the use of delamanid for MDR-TB, including the key findings of the phase 3 clinical trial data of delamanid added to an optimized background MDR-TB regimen (World Health Organization, 2018a). Different to the findings of the phase 2 trial (Skripconoka et al., 2013), it showed a high 30-month treatment success rate (77.1% of the intention-to-treat (ITT) population) and low 30-month mortality rate (5.3% of the ITT population), yet no clinically relevant or statistically significant difference between the delamanid and placebo arms with regard to treatment success or mortality. The WHO position statement recommended only adding delamanid when other effective and well-tolerated MDR-TB regimens cannot be composed. Two cost-effectiveness analyses in Germany showed that adding delamanid to BR was effective and possibly cost-saving (Diel et al., 2015) or cost-effective with an ICER below the WTP threshold of Germany (Wirth et al., 2017). These prior studies adopted findings from the phase 2 clinical trial that add-on therapy using delamanid improved treatment success and reduced mortality (Skripconoka et al., 2013). The results of the D-BR arm in the present study were therefore different to the findings of the cost-effectiveness analysis on delamanid published previously, as the key findings of the phase 3 trial were adopted in the D-BR arm of the present model.

This is the first cost-effectiveness analysis to compare adding bedaquiline and delamanid to BR for the treatment of MDR-TB in Hong Kong. The study revealed that despite the additional drug cost of bedaquiline, it was offset by the reduced use of secondary treatment or palliative care. The QALYs gained by B-BR were also higher than for BR due to the higher cure rate and lower odds of mortality. This study is also the first cost-effectiveness analysis to adopt the findings of a phase 3 clinical trial of delamanid plus BR. The cost-effectiveness of the novel drug plus BR is highly subject to the relative effect of the new regimen compared to the standard treatment. The current study therefore found delamanid plus BR to be unlikely to gain more QALYs than BR, and therefore not cost-effective.

The study model was limited by the sources of model inputs. The outcome events with bedaquiline and delamanid were both simulated by adopting overseas clinical data. Extended ranges were therefore used in the sensitivity analysis. The model also simplified the outcomes of MDR-TB. TB relapse or re-infection with TB in cured cases, and the tolerability and compliance of patients to the anti-TB regimens were not included. Therefore the total costs in all treatment arms might be underestimated.

The WHO conducted a meta-analysis on new data from over 25 countries (acquired through a public call for data), and recently issued a rapid communication on key changes to the treatment of MDR-TB in August 2018 (World Health Organization, 2018b). The key changes included a revised grouping of anti-TB medication. Bedaquiline is listed as one of the prioritized agents recommended in longer MDR-TB regimens for 18–20 months. Extending the use of bedaquiline beyond the label indicated duration (6 months) has significant implications for both health economic and clinical outcomes. Further cost-effectiveness evaluations on the use of bedaquiline in longer MDR-TB regimens are highly warranted.

In conclusion, add-on bedaquiline with BR appears to be cost-effective, with an ICER below the WTP, while add-on delamanid with BR is unlikely to be cost-effective for the treatment of MDR-TB from the perspective of healthcare providers in Hong Kong.

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None.

Ethical approval

Not required.

Conflict of interest

None.

References

Census and Statistics Department, Hong Kong SAR. Women and men in Hong Kong key statistics 2017 Edition. 2017 Available at: https://www.censtatd.gov.hk/hkstat/sub/sp180.jsp?productCode=B1130303. [Accessed 10 October 2017].

Census and Statistics Department, Hong Kong SAR. National income. 2018 Available at: https://www.censtatd.gov.hk/hkstat/sub/sp250.jsp?tableID=030&ID=0&productType=8. [Accessed 19 March 2018].

Centre for Health Protection, Department of Health. Tuberculosis manual. 2006 Available at: http://www.info.gov.hk/tb_chest/doc/Tuberculosis_Manual2006.pdf. [Accessed 10 October 2017].

Chan CK, Leung CC, Yew WW, Mok YW, Law WS, Leung CC, et al. Guideline on the management of multi-drug resistant and extensively drug resistance tuberculosis in Hong Kong. 2008 Available at: www.info.gov.hk/tb_chest/doc/MDRTB%20guideline_0812.pdf. [Accessed 10 October 2017].

Chu CM, Yung CY, Leung WS, Chan VL, Leung EM. Early unplanned readmission of patients with newly diagnosed tuberculosis discharged from acute hospital to ambulatory treatment. Respirology 2001;6:145–9.

Department of Health. Annual report 2012: tuberculosis & chest service of the department of health. 2012 Available at: www.info.gov.hk/tb_chest/doc/AnnualReport2012.pdf. [Accessed 10 October 2017].

Department of Health. Ambulatory treatment and public health measures for a patient with uncomplicated pulmonary tuberculosis an information paper. 2013 Available at: http://www.info.gov.hk/tb_chest/doc/Information_paper_-ambulatory_tb_2013.pdf. [Accessed 10 October 2017].

Department of Health. Annual report 2013: tuberculosis & chest service of the department of health. 2013 Available at: www.info.gov.hk/tb_chest/doc/AnnualReport2013.pdf. [Accessed 10 October 2017].

Department of Health. Annual report 2014: tuberculosis & chest service of the department of health. 2014 Available at: www.info.gov.hk/tb_chest/doc/AnnualReport2014.pdf. [Accessed 10 October 2017].

Department of Health. Annual report 2015: tuberculosis & chest service of the department of health. 2015 Available at: www.info.gov.hk/tb_chest/doc/Annual_Report_2015.pdf. [Accessed 10 October 2017].

Diacon AH, Pym A, Grobusch MP, de Los Rios JM, Gotuzzo E, Vasilyeva I, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med 2014;371:723–32.

Diel R, Hittel N, Schaberg T. Cost effectiveness of treating multi-drug resistant tuberculosis by adding Deltyba™ to background regimens in Germany. Respir Med 2015;109:632–41.

European Medicines Agency. Summary of opinion (initial authorisation)-Deltyba (delamanid). EMA/CHMP/713909/2013. 2013 Available at: www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002552/WC500155458.pdf. [Accessed 10 October 2017].

European Medicines Agency. Summary of opinion (initial authorisation)-Sirturo (bedaquiline). EMA/CHMP/771324/2013. 2013 Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002614/WC500158728.pdf. [Accessed 10 October 2017].

Gold MR, Franks P, McCoy KI, Fryback DG. Toward consistency in cost-utility analyses: using national measures to create condition-specific values. Med Care 1998;36:778–92.

Janssen Therapeutics, Division of Janssen Products, LP Titusville, NJ 08560. SirturoTM (bedaquiline) product package insert. 2012 Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf. [Accessed 10 October 2017].

Jit M, Stagg HR, Aldridge RW, White PJ, Abubakar I, Find and Treat Evaluation Team. Dedicated outreach service for hard to reach patients with tuberculosis in London: observational study and economic evaluation. BMJ 2011;343:d5376.

Leung EC, Leung CC, Kam KM, Yew WW, Chang KC, Leung WM, et al. Transmission of multidrug-resistant and extensively drug-resistant tuberculosis in a metropolitan city. Eur Respir J 2013;41:901–8.

Lu X, Smare C, Kambili C, El Khoury AC, Wolfson LJ. Health outcomes of bedaquiline in the treatment of multidrug-resistant tuberculosis in selected high burden countries. BMC Health Serv Res 2017;17:87.

Park HY, Ku HM, Sohn HS, Seo HS, Yung Lee H, Hwa Lim K, et al. Cost-effectiveness of bedaquiline for the treatment of multidrug-resistant tuberculosis in the Republic of Korea. Clin Ther 2016;38:655–67.

Pontali E, Sotgiu G, D'Ambrosio L, Centis R, Migliori GB. Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence. Eur Respir J 2016;47:394–402.

Skripconoka V, Danilovits M, Pehme L, Tomson T, Skenders G, Kummik T, et al. Delamanid improves outcomes and reduces mortality for multidrug-resistant tuberculosis. Eur Respir J 2013;41:1393–400.

Sotgiu G, Pontali E, Centis R, D'Ambrosio L, Migliori GB. Delamanid (OPC-67683) for treatment of multi-drug-resistant tuberculosis. Expert Rev Anti Infect Ther 2015;13:305–15.

Teno JM, Shu JE, Casarett D, Spence C, Rhodes R, Connor S. Timing of referral to hospice and quality of care: length of stay and bereaved family members' perceptions of the timing of hospice referral. J Pain Symptom Manag 2007;34:120–5.

Wirth D, Dass R, Hettle R. Cost-effectiveness of adding novel or group 5 interventions to a background regimen for the treatment of multidrug-resistant tuberculosis in Germany. BMC Health Serv Res 2017;17:182.

Wolfson LJ, Walker A, Hettle R, Lu X, Kambili C, Murungi A, et al. Cost-effectiveness of adding bedaquiline to drug regimens for the treatment of multidrug-resistant tuberculosis in the UK. PLoS One 2015;10(3)e0120763.

World Health Organization. The world health report 2002: reducing risks, promoting healthy life. 2002 Geneva.

World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance, 2013. 2013 Available at: http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf. [Accessed 15 January 2018].

World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis. Interim policy guidance [WHO/HTM/TB/2014.23]. 2014 Available at: http://apps.who.int/iris/bitstream/10665/137334/1/WHO_HTM_TB_2014.23_eng.pdf. [Accessed 15 January 2018].

World Health Organization. Report of the Guideline Development Group Meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis, 2016. 2016 Available at: http://apps.who.int/iris/bitstream/handle/10665/254712/WHO-HTM-TB-2017.01-eng.pdf?sequence=1. [Accessed 15 January 2018].

World Health Organization. Global tuberculosis report 2017. 2017 Available at: www.who.int/tb/publications/global_report/en/. [Accessed 15 January 2018].

World Health Organization. WHO position statement on the use of delamanid for multidrug-resistant tuberculosis. 2018 Available at: http://www.who.int/tb/publications/2018/WHOPositionStatementDelamanidUse.pdf?ua=1. [Accessed 20 February 2018].

World Health Organization. Rapid Communication Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). 2018 Available at: http://www.who.int/tb/publications/2018/rapid_communications_MDR/en/. [Accessed on 9 October 2018].

Yew WW, Chan CK, Chau CH, Tam CM, Leung CC, Wong PC, et al. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. Chest 2000;117:744–51.

Yew WW, Leung CC. Management of multidrug-resistant tuberculosis: update 2007. Respirology 2008;13:21–46.