

The long-term impact of bedaquiline-containing regimens on cost burden to the healthcare system and families of patients with drug-resistant tuberculosis in Indonesia

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Overview

This study aims to

- assess the long-term impact of an increase in the use of bedaquiline-based regimens in DR-TB patients in Indonesia on the direct costs to the healthcare system and catastrophic costs to patients associated with DR-TB
- evaluate two scenarios with different expectations of the treatment success rate of bedaquiline-containing regimens

Introduction

- There were 845,000 new cases reported during the year 2018 (incidence rate: 316 per 100,000 population), accounting for 8% of all global cases and placing Indonesia third among all nations.^[1] Moreover, an estimated 24,000 new cases of drug-resistant TB (DR-TB) were reported during the year, translating into an incidence rate of 8.8 per 100,000 and accounting for 2.4% of all DR-TB cases globally.
- Apart from the direct costs associated with DR-TB being significant, another category of costs namely indirect costs (for example, those arising due to loss of employment linked to physical infirmity or time taken to obtain medical care) can also be significant, with some patient families taking drastic steps to meet direct and indirect costs, including reducing food consumption, suspending education of their children, availing of loans, or selling assets.^[2]
- A recent study in Indonesia reported that 36% of families of TB patients and 83% of families of DR-TB patients had to contend with catastrophic costs,^[3] which are defined by the WHO as costs exceeding 20% of the annual household income.^[4]
- While the rates of treatment success of new TB cases worldwide were as high as 85% in 2017, they fell to 56% among patients with DR-TB.^[1] Low rates of treatment success in patients with DR-TB can negatively impact efforts to curb the spread of disease since patients failing treatment can serve as reservoirs of resistant TB and transmit it.^[5,6]
- Bedaquiline, an oral therapeutic agent available for the treatment of DR-TB since 2012,^[7-8] has demonstrated efficacy in multiple clinical trials and effectiveness following approval in diverse patient populations worldwide, revealing success rates as high as 93%.^[9-11]
- This modelling study evaluated the long-term impact of bedaquiline-containing regimens on the overall direct and indirect cost burden of DR-TB in this country setting.

Methods

- A disease-transmission model capturing the TB transmission, resultant latent infection, transition to active infection, diagnosis and treatment, and outcomes of cure, failure and death, was created to mirror the state of pulmonary TB disease in Indonesia.
- A baseline forecast of DR-TB epidemiology was created until 2040 that only considered current therapeutic agents and their associated treatment success rate of 44%.
- This baseline forecast was then used to compare against forecasts created considering the adoption of bedaquiline-containing regimens in Indonesia under two scenarios with treatment success rates of 61% (as reported during clinical trials that evaluated the safety and efficacy of bedaquiline^[12]) and 80% (as reported by Guglielmetti and colleagues^[13]) (Table 1).
- The model was then employed to estimate the economic burden of DR-TB both at the societal as well as individual patient-household level. Costs considered for the analysis included direct medical and non-medical costs for the treated patients (Table 2).
 - The proportion of patients catastrophically affected were separately estimated for 4 pools of patients corresponding to the stage in the disease cascade that they would exit from – a) those cured in LOT1, b) those that die after LOT1 failure but before starting LOT2, c) those cured in LOT2, and d) those that die after LOT2 failure. This exercise was separately carried out for the patient population treated in private and public care hospitals for each year of the forecast for patients starting first line DR-TB therapy. Only patient-incurred costs, adjusted for inflation, were considered. To evaluate indirect costs, the probability of loss of productivity in each disease state was estimated
 - Variance in household income across the entire TB affected population was accounted for by simulating the nominal income distribution at the individual household level using a lognormal distribution of income among the population, with
 - mean of the distribution as the average income of patients – privately treated patients were taken to earn annually the national per capita GDP, and those treated in public hospitals were taken to earn a quarter of the GDP^[13]
 - standard deviation of the distribution as the GINI index of the country

Table 1. Success rates and market shares for bedaquiline used as inputs for scenario analysis

Parameter		Scenario 1	Scenario 2
DR-TB treatment success rate with BDQ in first line treatment (LOT1)		61%	80%
Maximum market share of bedaquiline-containing regimens in DR-TB treatment	LOT1	95%	
	LOT2 ^a	7%	12%
Short-course regimen share in current standard of care and bedaquiline		50%	

^aPatients failing LOT1 treatment with bedaquiline were assumed to be ineligible for re-treatment with bedaquiline in LOT2, while 95% of patients not treated with bedaquiline in LOT1 were assumed to be treated with bedaquiline in LOT2 in both scenarios.

Abbreviations: LOT: Line of treatment; DR-TB: Drug resistant tuberculosis; Q: Quarter of the year

Table 2. Per patient direct costs to the system (government and patient costs aggregated), as input into the model.

		Value				Remarks
Costs in 2018		Cost per patient per treatment course				See footnotes A, B and C
		SOC LOT1	BDQ LOT1	SOC LOT2 (XDR-TB)	BDQ LOT 2 (XDR-TB)	
Drugs		\$2,959	\$1,940	\$4,620	\$2,713	
Hospitalization		\$233	\$103	\$979	\$423	
Other direct costs		\$6,568	\$3,540	\$17,679	\$9,120	
Total (excluding loss of productivity)		\$9,800	\$5,600	\$23,300	\$12,250	

- Footnote A:
 - Costs related to long course regimen first line of treatment for DR-TB in Indonesia were found using various sources
 - drug regimen costs for standard-of-care for long course regimen, based on a study on low and middle income group countries, adjusted for inflation to 2018, was considered to be \$4,600^[14]
 - hospitalization cost for long course regimen from the same study, adjusted for inflation to 2018, was noted to be around \$300
 - overall treatment cost, for provider and patient combined, based on a 2015 study adjusted for inflation to 2018, was considered to be \$12,500^[15]
- Footnote B:
 - To estimate the direct costs per DR-TB patient treated with standard-of-care regimens on an average in first and second line of treatment, ratio analysis has been carried out on data used for India and South Africa in a study by Ionescu et al.^[16] - ratios of SCR costs to LCR in LOT1 and ratio of XDR costs to LCR costs have been used; a 50% utilization of short-course regimen has been estimated
- Footnote C:
 - To estimate the costs for treatment with regimens containing bedaquiline, ratio analysis based on data from Ionescu et al. has been carried out – ratios of SCR and LCR cost for bedaquiline-containing regimens to standard-of-care regimens for first line of DR-TB treatment was used - similar ratio was used for second line treatment^[16]

DR-TB: Drug-resistant tuberculosis; SOC: Standard of care; LOT: Line of treatment; BDQ: Bedaquiline; XDR-TB: Extensively drug resistant tuberculosis; GDP: Gross domestic product; LCR: Long-course regimen; SCR: Short-course regimen

Results

- The model estimates that the direct economic burden of DR-TB in Indonesia will be approximately \$555M (million) in the five year period 2021-2025 in the baseline scenario without use of bedaquiline, of which drug costs will comprise 26%. The burden will increase cumulatively over time, growing to an estimated \$2.9B (billion) for the 20-year period ending 2040. (Fig. 1)

The cost per successfully treated patient over the 20-year period between 2021 and 2040 is estimated to be \$27.3k. Total cost of lost productivity is expected to be as high as \$2.1B.

- This economic burden reduced by \$1.0B (35% reduction over baseline) and \$1.1B (40% reduction over baseline), (Fig. 1) in scenarios 1 and 2, respectively. Over this duration, the average cost per successfully treated patient was estimated to decline from \$27.3k to \$14.0k (a 49% reduction over baseline) in scenario 1 and to \$10.3k (a 62% reduction over baseline) in scenario 2 (Fig. 2). Productivity gains of \$226M (11% higher than baseline) and \$346M (17% higher than baseline), respectively were observed in the two scenarios
- The study shows a high incidence of catastrophic cost among patients being treated with regimens that do not include bedaquiline in Indonesia - 4.3k in 2020 and increasing to almost 7.7k by 2040 (Fig. 3). Treatment with bedaquiline-containing regimens is predicted to bring down the number of families facing catastrophic costs in 2040 from almost 7.7k in the baseline scenario to 6.4k (a reduction of 17%) in scenario 1 and to 6.0k (a reduction of 23%) in scenario 2 (Fig. 3).

Figure 1 Estimated costs associated with DR-TB in Indonesia cumulatively in 2021-2040 under baseline (no bedaquiline use) and two bedaquiline use scenarios

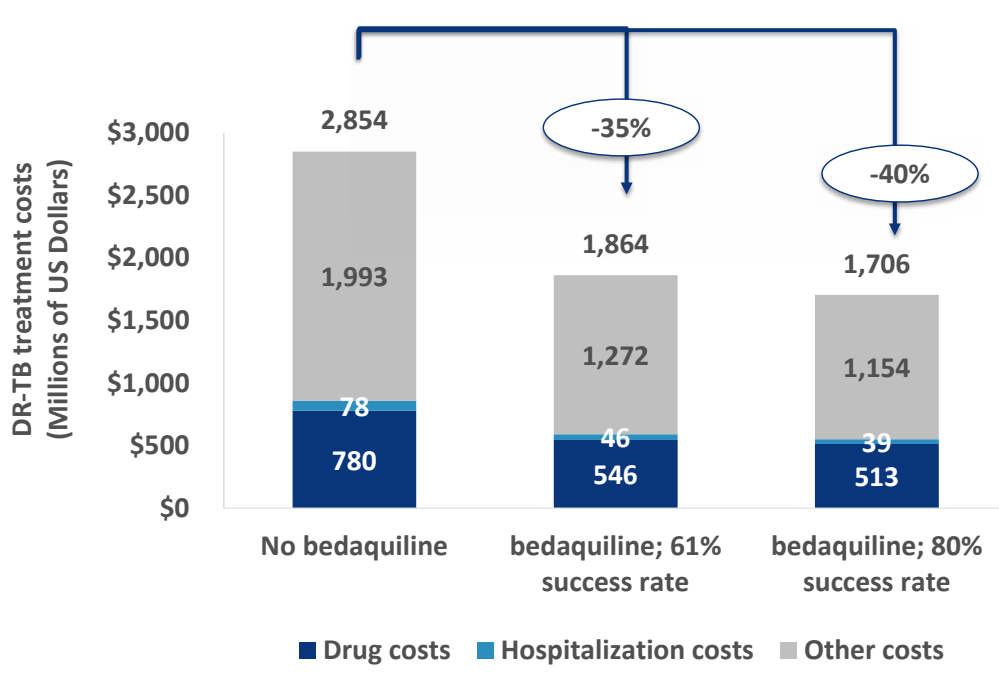


Figure 2 Estimated cost per successfully treated patient of DR-TB in Indonesia cumulatively in 2021-2040 under no baseline (no bedaquiline use) and two bedaquiline use scenarios

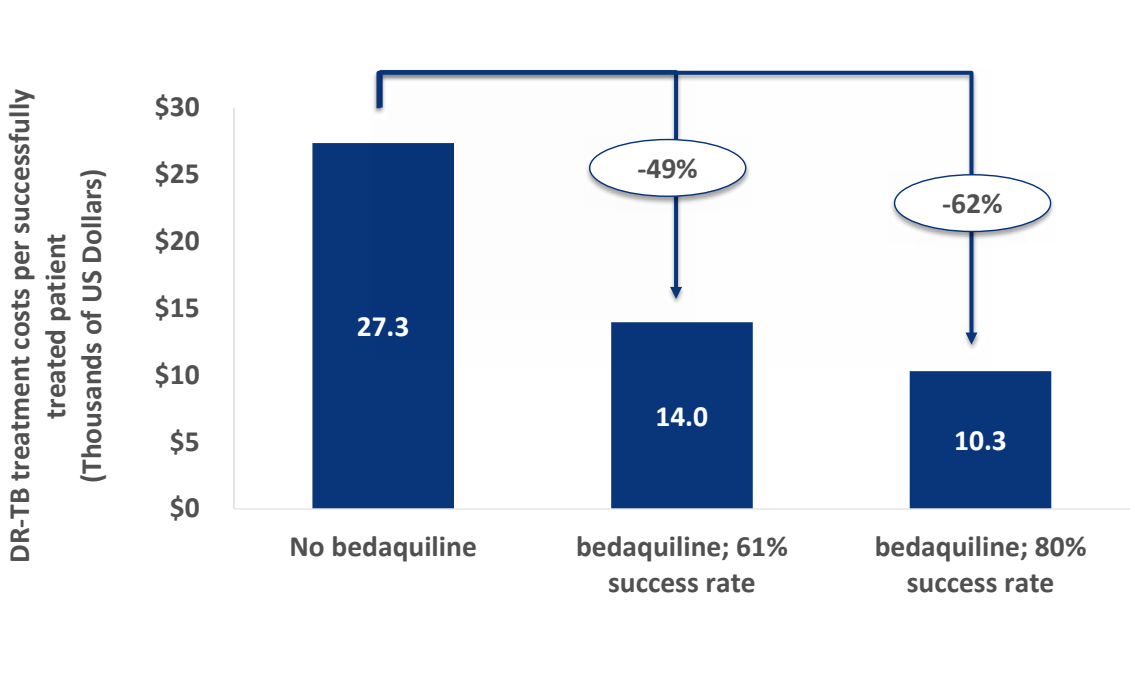
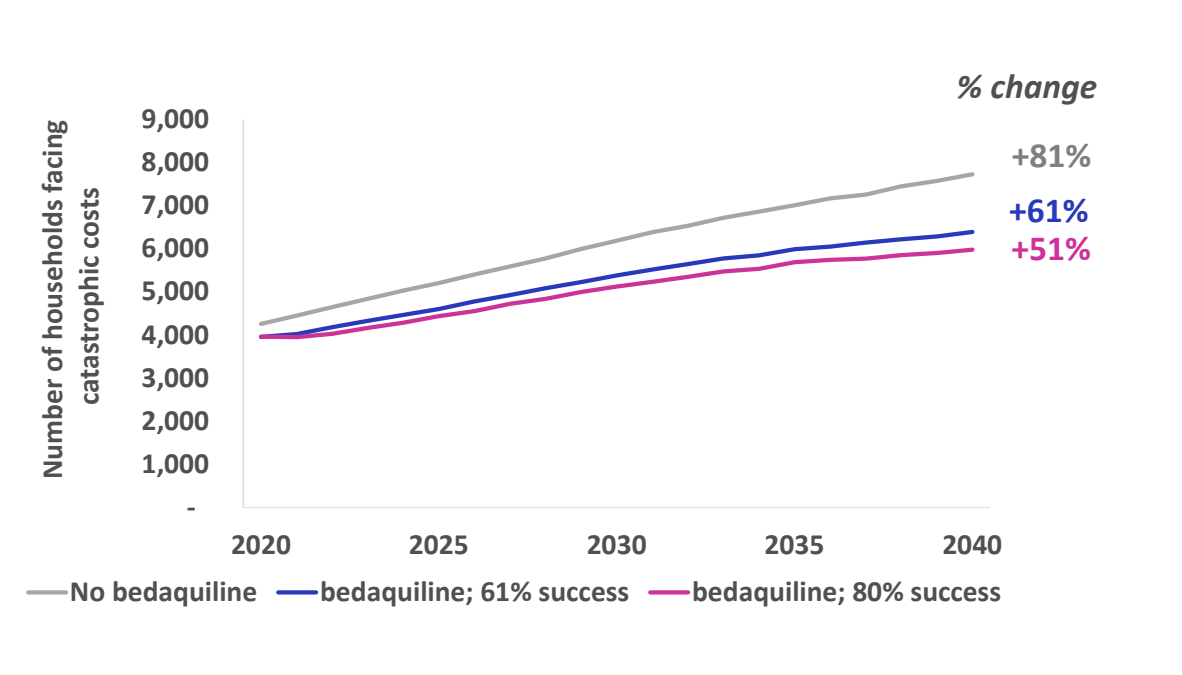


Figure 3 Estimated number of catastrophically affected households in Indonesia in 2020-2a040 under baseline (no bedaquiline use) and 2 bedaquiline use scenarios, YoY



Conclusions

- This study revealed that the use of bedaquiline-containing regimens in Indonesia brings about significant reductions in the economic burden of DR-TB by way of declines in overall healthcare costs, cost per successfully treated patient and catastrophic costs faced by families.
- DR-TB patients today constitute a small proportion of all TB patients in Indonesia. However, the DR-TB treatment cost is seen to be 44-fold that of DS-TB in Indonesia as observed in a study.^[15] This translates into a negative impact at the societal level due to the need to spend a significant portion of the total available budget to treat the small proportion of the total population that is afflicted by DR-TB. At the individual patient level also, the direct and indirect financial impact of DR-TB is significant, saving many families from a catastrophic event.
- The findings of this analysis have wide-ranging public health and social benefits. Bringing the cost per successfully treated DR-TB patient to at least half its baseline value, in the scenarios of enhanced utilization of bedaquiline-containing regimens, offers the opportunity to double up the treatment access with the same set of resources.
- Positive economic impact of enhanced use of bedaquiline-containing regimens, at societal level by freeing up resources, thereby helping fight the DR-TB menace faster in Indonesia, and at individual level by reducing the number of families facing catastrophic events, supports the rationale for its incorporation into DR-TB treatment regimens in Indonesia.

References

- World Health Organization. Global Tuberculosis Report 2019 (WHO/CDS/TB/2019.15; Licence: CC BY-NC-SA 3.0 IGO). Geneva, Switzerland: World Health Organization 2019.
- Barter DM, Agboola SO, Murray MB, Barnighausen T. Tuberculosis and poverty: The contribution of patient costs in sub-Saharan Africa – A systematic review. BMC Public Health. 2012; 12:980.
- Fuady A, Houweling TAJ, Mansyur M, Richardus JH. Catastrophic total costs in tuberculosis-affected households and their determinants since Indonesia’s implementation of universal health coverage. Infect Dis Poverty. 2018; 7(1):3.
- World Health Organization: Global TB Programme. Protocol for survey to determine direct and indirect costs due to TB and to estimate proportion of TB-affected households experiencing catastrophic total costs due to TB (field testing version). 2015 [July 22, 2019] Available from: https://www.who.int/tb/advisory_bodies/impact_measurement_taskforce/meetings/tf6_background_5a_patient_cost_surveys_protocol.pdf
- Dhedra K, Limberis JD, Pietersen E, Phelan J, Esmail A, Lesosky M, et al. Outcomes, infectiousness, and transmission dynamics of patients with extensively drug-resistant tuberculosis and home-discharged patients with programmatically incurable tuberculosis: A prospective cohort study. Lancet Respir Med. 2017; 5(4):269-81.
- Nsofor CA, Jiang Q, Wu J, Gan M, Liu Q, Zuo T, et al. Transmission is a noticeable cause of resistance among treated tuberculosis patients in Shanghai, China. Sci Rep. 2017; 7(1): 7691
- Mahajan R. Bedaquiline: First FDA-approved tuberculosis drug in 40 years. International Journal of Applied & Basic Medical Research. 2013; 3(1):1-2.
- Riccardi N, Del Puente F, Magne F, Taramasso L, Di Biagio A. Bedaquiline: A new hope for shorter and better anti-tuberculosis regimens. Recent patents on anti-infective drug discovery. 2018; 13(1):3-11.
- 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(8):723-32.
- Skrachina A, Hurevich H, Falzon D, Zhilevich L, Rusovich V, Dara M, et al. Bedaquiline in the multidrug-resistant tuberculosis treatment: Belarus experience. International Journal of Mycobacteriology. 2016; 5 Suppl 1:S62-s3.
- Guglielmetti L, Jaspard M, Le Du D, Lachatre M, Marigot-Outtandy D, Bernard C, et al. Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis. Eur Respir J. 2017; 49(3).
- Culture conversion status in patients with MDR-TB at week 120 in study 1, Sirturo clinical trials. <https://www.sirturo.com/sirturo-clinical-trials.html>
- Tiemersma E, Hafidz F, Mahendradhata Y, Dwiwardiani B, Burhan E, Abdullahi O. Costs faced by (multidrug resistant) tuberculosis patients during diagnosis and treatment: Report from a pilot study in Indonesia. https://www.challengetb.org/publications/tools/costing/Costs_Faced_by_MDR-TB_Patients_Indonesia.pdf
- Laurence Y, Griffiths U, Vassall, A. Costs to health services and the patient of treating tuberculosis: A systematic literature review. Pharmacoeconomics. 2015; 33(9):939-955. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4559093/>
- Collins D, Hafidz F, Mustikawati D, The economic burden of tuberculosis in Indonesia. The International Journal of Tuberculosis and Lung Disease. 2017; 21(9):1041-1048.
- Ionescu AM, Mpobela Agnarson A, Kambili C, Metz L, Kfoury J, Wang S, et al. Bedaquiline- versus injectable-containing drug-resistant tuberculosis regimens: A cost-effectiveness analysis. Expert Review of Pharmacoeconomics & Outcomes Research. 2018; 18(6):677-89.

Acknowledgments

This study was funded by Johnson & Johnson Global Public Health. This poster was created with the assistance of Amandeep of SmartAnalyst India Pvt. Ltd.