Published in final edited form as:

Lancet Respir Med. 2018 July ; 6(7): 486–488. doi:10.1016/S2213-2600(18)30197-8.

Would pan-tuberculosis treatment regimens be cost-effective?

Emily A Kendall^{1,*}, Grania Brigden², Christian Lienhardt^{3,4}, David W Dowdy⁵

¹Center for Tuberculosis Research, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

²The International Union Against TB and Lung Disease, Geneva, Switzerland

³Global TB Programme, World Health Organization, Geneva, Switzerland

⁴Unité Mixte Internationale TransVIHMI (UMI 233 IRD – U1175 INSERM - Université de Montpellier), Institut de Recherche pour le Développement (IRD), Montpellier, France

⁵Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

There is an urgent need for shorter, more-effective treatments for tuberculosis (TB). A simple six-month oral regimen, composed of three new and re-purposed drugs, recently showed encouraging results in the treatment of extensively drug-resistant TB.¹ As better-tolerated analogues are developed, regimens with activity against today's most drug-resistant forms of TB could rival the efficacy and tolerability of the current first-line therapy for rifampin-susceptible (RS-)TB.^{2,3} Besides novel regimens' potential to improve drug-resistant TB outcomes, using the same regimen for RS-TB (i.e. as a "pan-TB regimen") could benefit the many TB patients with undetected drug resistance. A pan-TB regimen might also improve programmatic efficiency, consolidate the market for TB regimens, and potentially improve RS-TB treatment.

Among the uncertainties in developing and implementing pan-TB regimens, one important need is for an economic case that accounts for anticipated budgetary and epidemiologic outcomes. To aid in evaluating this economic perspective, we adapted an existing transmission model⁴ to estimate the impact, affordability, and cost-effectiveness of introducing a novel regimen with pan-TB potential, in a globally-representative, hypothetical high-burden setting.

We modeled a novel regimen's health impact in a setting with TB prevalence of 300 per 100,000, HIV co-prevalence of 10%, multidrug-or rifampin-resistant (MDR/RR) TB in 4% of new TB cases, and gradually-expanding rifampin susceptibility testing. We assumed the regimen⁴ had equivalent efficacy, duration, and tolerability to current RS-TB therapy but offered the same high efficacy against MDR/RR-TB. For simplicity, we assumed the

*CRB2 Room 106, 1550 Orleans St, Baltimore, MD, USA 21230; ekendal2@jhmi.edu.

Authors' contributions: EAK performed the analyses and wrote the original draft of the manuscript. All authors contributed to planning and interpreting the analyses and provided critical review of the manuscript.

Conflict of interest: The authors declare that no conflicts exist.

regimen had a high barrier to resistance and initially required no adjustments for individual patient characteristics.

We estimated total health system cost (measured in 2015 US dollars) by combining estimated health system spending (using median drug and non-drug costs, stratified by MDR/RR notification status, among 30 high-burden countries)⁵ with model estimates of the number of patients receiving each regimen. Calculations incorporated regimen prices, savings on MDR/RR-TB patient management, and reductions in future TB incidence. We evaluated effectiveness (disability adjusted life years [DALYs] averted) by coupling estimates of disability and years of life lost⁶ with 10-year projections of TB prevalence and mortality using 3%/year discounting.

When used only for patients in whom MDR/RR-TB was diagnosed, this novel regimen was estimated to reduce MDR/RR-TB incidence by 33% (95% uncertainty range [UR]: 22–47%) within 10 years. The cost-effectiveness case was also compelling: this new MDR/RR-TB regimen was budget-neutral (i.e., achieving positive epidemiological outcomes at zero net health system cost) at \$5,000 per patient, and could be highly cost-effective in a low-income setting (<\$1,200 per DALY averted) at a price as high as \$10,000 per patient (Table).

Using the novel regimen for both MDR/RR and RS-TB doubled its estimated 10-year impact on MDR/RR-TB incidence, yet this broader indication narrowed the margin for cost-effectiveness. Because current RS-TB treatment is very inexpensive, the additional cost of treating RS-TB with the novel regimen must be recovered in other ways, thereby worsening cost-effectiveness.⁵ For example, the estimated cost-effectiveness of a \$10,000-per-patient novel regimen was \$1,200/DALY averted when used for MDR/RR-TB alone but \$53,000/DALY averted if used universally. A much lower regimen price (around \$1,000 per patient, comparable to the currently recommended 9–12 month MDR-TB regimen⁷) would be needed to bring this cost-effectiveness ratio down (\$3,900/DALY averted), below the per-capita gross national income of many middle-income countries (Table).

Adoption of a pan-TB regimen is likely to be incremental, the indication expanding as experience with the regimen accrues. The regimen would have to reach an even lower price point for incremental expansion to RS-TB to be cost-effective (Table), and only at a price point approaching \$200 per patient would it fall below a \$1,200-per-DALY-averted threshold. However, the potential for novel regimens' market to grow as their clinical performance becomes well-established, with accompanying price efficiencies, enhances the economic outlook for new regimens.

Other factors (not considered here) could also strengthen the economic case for a pan-TB regimen. If novel pan-TB regimens improve upon the current standard of care for RS-TB, health gains from superior efficacy⁴ or cost reductions from shorter treatment durations⁸ could improve cost-effectiveness. Improvements in programmatic efficiency – for example, reducing the need for specialized centers to manage MDR/RR-TB – could yield additional cost savings. In addition, consolidating the MDR/RR-TB and RS-TB regimens with a unified regimen could ease challenges of volume and forecasting faced by drug manufacturers⁹ and enable economies of scale and market competition to improve

access and affordability. Lastly, a highly-efficacious, easy-to-deliver pan-TB regimen would improve patient experiences and costs, by speeding time to appropriate treatment for patients with MDR/RR-TB who often experience prolonged duration of illness, multiple re-evaluations, and substantial difficulties in initiating care once diagnosed with drug resistance.

Developing an economic case for a pan-TB regimen should not hide, however, the imperative need to strengthen the diagnostic infrastructure. Gaps in detection of TB drug resistance would likely be more efficiently addressed by scaling up suitable point-of-care diagnostics¹⁰ than by expanding the indication for a novel drug regimen. Furthermore, no regimen can remain a pan-TB regimen forever; resistance to novel drugs will eventually develop and require corresponding diagnostic capacity and treatment alternatives.¹¹ Further, as we better understand other patient-level determinants of successful treatment,¹² customizing regimen duration and/or composition to individuals' disease condition may become a preferred strategy.

In summary, new, shorter, simpler regimens with the potential to treat all forms of TB could have transformative impact on MDR/RR-TB epidemics, but using such regimens universally (as “pan-TB” regimens) would be less economically favorable. To make the strongest cost-effectiveness case for universal use, novel regimens will need to hit price points approaching \$200 per patient, be more effective than current RS-TB treatment, offer major benefits to patient care, and/or demonstrate durable gains in programmatic or market efficiency.

Acknowledgments

Funding: EAK was supported by the National Institution of Allergy and Infectious Diseases of the National Institutes of Health under award number K08AI127908. The funding source had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

References

1. Conradie F, Diacon AH, Everitt D, et al. The Nix-TB trial of pretomanid, bedaquiline and linezolid to treat XDR-TB Boston, 2017.
2. Wallis RS, Cohen T, Menzies NA, Churchyard G. Pan-tuberculosis regimens: an argument for. *Lancet Respir Med* 2018; 6: 239–40. [PubMed: 29595501]
3. World Health Organization. Target Regimen Profiles for TB Treatment 2016. <http://apps.who.int/iris/bitstream/10665/250044/1/9789241511339-eng.pdf?ua=1> (accessed Sept 7, 2016).
4. Kendall EA, Shrestha S, Cohen T, et al. Priority-Setting for Novel Drug Regimens to Treat Tuberculosis: An Epidemiologic Model. *PLoS Med* 2017; 14: e1002202. [PubMed: 28045934]
5. Global Tuberculosis Report 2016 Geneva: World Health Organization, 2016 http://www.who.int/tb/publications/global_report/en/ (accessed Oct 27, 2016).
6. Global Burden of Disease Study 2015. Global Burden of Disease Study 2015 (GBD 2015) Results Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2016 <http://ghdx.healthdata.org/gbd-results-tool>.
7. Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Zumla A, Migliori GB. WHO recommendations on shorter treatment of multidrug-resistant tuberculosis. *The Lancet* 2016; 387: 2486–7.

8. Knight GM, Gomez GB, Dodd PJ, et al. The Impact and Cost-Effectiveness of a Four-Month Regimen for First-Line Treatment of Active Tuberculosis in South Africa. PLoS ONE 2015; 10: e0145796. [PubMed: 26717007]
9. UNITAID. Tuberculosis Medicines Technology and Market Landscape Geneva, 2014 https://unitaid.eu/assets/UNITAID-TB_Medicines_Landscape-2nd_edition.pdf (accessed Jan 29, 2018).
10. Dheda K, Gumbo T, Maartens G, et al. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. Lancet Respir Med 2017; published online March 15. DOI:10.1016/S2213-2600(17)30079-6.
11. Dheda K, Gumbo T, Lange C, Horsburgh CR, Furin J. Pan-tuberculosis regimens: an argument against. Lancet Respir Med 2018; 6: 240–2. [PubMed: 29595502]
12. Savic R An integrative analysis of the fluoroquinolone phase III TB clinical trials (TB-ReFLECT) 2017; published online March 29. http://www.cptrinitiative.org/wp-content/uploads/2017/05/20_04_SavicFINAL.pdf (accessed March 27, 2018).

Table:

Cost effectiveness of a potential-pan-TB regimen in a high-TB-burden setting¹

	Impact on overall TB incidence ²	Impact on MDR/RR-TB incidence	Budget-Neutral price per patient ³	Incremental cost-effectiveness, per DALY averted, at specified price point ⁴			
Indication for use of novel regimen with pan-TB potential	Cases averted (over 10 years, per 100,000 population)	Percent Reduction (at 10 years)	MDR/RR cases averted (over 10 years, per 100,000) ⁵	Percent Reduction (at 10 years)	\$200 per patient	\$1000 per patient	\$10,000 per patient
Relative to no use of regimen							
Diagnosed MDR/RR-TB only	15 (8–30)	1.2% (0.7–2.6%)	16 (8–32)	33% (22–47%)	\$5600 (4300–7000)	Cost-saving	\$1200 (600–2100)
All TB	25 (13–49)	1.8% (0.7–3.9%)	36 (23–65)	67% (54–79%)	\$290 (210–430)	Cost-saving	\$3,900 (1,800–8,300)
Relative to use for diagnosed MDR/RR-TB only (incremental adoption)							
All TB, incremental epidemiologic impact	11 (3–24)	0.6% (0–1.5%)	20 (13–35)	33% (24–42%)			
All TB, incremental cost effectiveness					\$128 (100–170)	\$900 (200–3200)	\$130,000 (55,000–360,000)

¹The setting modeled has a TB prevalence 300 per 100,000, HIV co-prevalence 10%, MDR/RR-TB in 4% of new TB cases, and rifampicin susceptibility testing currently provided to 24% of new and 53% of retreatment patients (increasing linearly over time), reflecting averages among high TB burden countries.

²All results are expressed as median (95% uncertainty range) of 476 model simulations.

³Price-per-patient of the novel regimen which results in net-neutral health system TB expenditure over 10 years. Estimates of each budget category use the median budget, per drug-susceptible or MDR/RR TB patient notified, among 30 high TB burden countries. We assumed that the novel regimen could reduce non-drug spending per MDR/RR-TB patient (e.g., costs of diagnosis and treatment monitoring, as well as drug-resistance surveillance, second-line DST, contact investigation, etc.) to the midpoint between the current non-drug costs of MDR-TB and drug-susceptible TB.

⁴DALY: disability-adjusted life year. Prices are per patient treated with the novel regimen. Cost-effectiveness is calculated over 10 years following the introduction of the novel regimen, with costs and DALYs discounted 3%/year, and reported in 2015 US dollars.

⁵Exceeds overall TB cases averted because some averted cases of MDR/RR-TB are replaced by cases of TB that are resistant to the novel regimen but susceptible to rifampicin.

⁶Reductions in TB and MDR/RR incidence are calculated relative to the incidence projected at 10 years with no use of the novel regimen. Relative to the incidence projected when the novel regimen is used for MDR/RR-TB only, the projected incidence with a pan-TB regimen represents 0.6% (0–1.6%) and 50% (38–64%) relative reductions in TB and MDR/RR-TB incidence, respectively.