More treatment options for rifampicin-resistant tuberculosis: the role of economic evaluation in informing uptake

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There have been substantial advances in treatment options for multidrug-resistant and rifampicin-resistant tuberculosis. Just a few years ago, a typical patient faced months of painful injections, life-changing adverse effects, and a very small chance of cure. This year, WHO announced forthcoming updates to global guidelines including 6-month and 9-month all-oral regimens for treatment of multidrug-resistant and rifampicin-resistant tuberculosis.[1] In the context of these rapidly changing options for treating multidrug-resistant and rifampicin-resistant tuberculosis and persisting high costs of newer drugs such as bedaquiline, countries are facing difficult decisions about when and how to incorporate new drug regimens into national guidelines, and the economic effects of new regimens will be a key consideration in their uptake. In their report in *The Lancet Global Health*, Laura Rosu and colleagues[2] present an in-trial cost-effectiveness analysis of rifampicin-resistant tuberculosis treatment regimens from the STREAM stage 2 trial, including a 9-month all-oral regimen with bedaquiline and a 6-month regimen with bedaquiline and an injectable for the first 2 months. Cost-effectiveness of the oral and 6-month regimens versus a 9-month injectable-containing control regimen was estimated in Ethiopia, India, Moldova, and Uganda (oral regimen) and Ethiopia and India (6-month regimen).

This is the first in-trial cost-effectiveness analysis of new treatment regimens for rifampicin-resistant tuberculosis, using cost, income, and patient-reported quality of life data collected from nearly all trial participants every 12 weeks. The rich data included in this study give a detailed picture of resource use and patient experiences, representing a big step forward in the information available to decision makers. However, interpretation of trial results for policy can be challenging where transferability is limited. Unit costs for tuberculosis services vary considerably across countries and overhead costs for outpatient services, which were not included in the current analysis, can be as high as 50% of the total cost.[3] Health state preferences are also affected by sociocultural differences, making transference of quality-adjusted life-years (QALYs) across countries difficult.[4] Careful interpretation of the implications of these study findings to inform prioritised planning might require additional analyses, alongside ethical considerations.

The main composite favourable endpoint of many tuberculosis treatment trials includes several outcomes of varying importance, including death, recurrence or reversion, treatment discontinuation, loss to follow-up, and adverse events. Composites like these are not comparable across interventions and disease areas, making them difficult to interpret for policy decisions.[5] Rosu and colleagues use the participant-reported quality of life (measured in QALYs) as their main outcome measure, which can more easily represent comparative value for money in health system investment. Interestingly, there was no significant improvement in QALYs in the oral or 6-month regimen groups compared with the control regimen, despite the composite outcomes improving. The limited time horizon could mean the longer-term effects of recurrence or adverse events were underestimated. This is a priority area for further research, and we welcome Rosu and colleagues' plan to evaluate longer-term outcomes using follow-up data from week 132. Further modelling work could also help to unravel these complex trade-offs in short-term versus long-term outcomes where granular data are unavailable.

Substantial questions also remain about the impact of improved regimens on the lifelong effects of tuberculosis, including post-tuberculosis lung impairment,[6] and lasting economic impact.[7] There is no evidence as to whether shorter or less toxic regimens can improve economic recovery or reduce the impact of long-lasting health effects. Prevention of long-term effects will most likely require investment across both health and social care, including improved case finding and earlier access to treatment, strengthened social support, and better monitoring for adverse events throughout the treatment period.

In all four countries, a high proportion of patients had catastrophic costs regardless of regimen. The 6-month regimen led to a reduction in participant-incurred costs in both Ethiopia and India. In two of the four countries (Moldova and Uganda), the

participant-incurred cost was lower for the oral regimen than the control regimen, but the provider-incurred costs were higher. Cases like these impose difficult trade-offs in decision making, because in some cases it might be acceptable to incur slightly higher provider-side costs to improve equity, or to reach global targets such as the End TB Strategy target to eliminate catastrophic costs.[8] Tools such as equity-informed economic analysis can help to contextualise these trade-offs and evaluate the value in investments across both health and societal outcomes.[9]

In 2021, 92 countries reported providing an all-oral treatment option for people with multidrug-resistant or rifampicin-resistant tuberculosis.[10] This move was partly inspired by outcries from clinicians and people living with tuberculosis about the high toxicity and adverse events associated with injectable drugs, including irreversible hearing loss.[11] Given persisting uncertainties and competing priorities, the capacity of local decision makers to interpret economic evaluation results will be key in translating this evidence into policy. Integration of local health economists and modellers into the decision-making process can help policy makers interpret seemingly contradictory results, and weigh difficult trade-offs between cost and budget impact, patient experiences, and global priorities.

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*Sedona Sweeney, Maninder Pal Singh
Sedona.sweeney@lshtm.ac.uk

Faculty of Public Health and Policy, London School of Hygiene & Tropical Medicine, London WC1H 9SH, UK (SS, MPS)

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