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Transferability of a EUnetHTA relative effectiveness assessment to low- and middle-income countries setting

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Abstract

In 2020, European Network for Health Technology Assessment (EUnetHTA) published a relative effectiveness analysis (REA) of Pretomanid in combination with Bedaquiline and Linezolid for the treatment of extensively drug-resistant (XDR) or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB) (REA PTJA14). This REA may have a significant value for low- and middle-income countries (LMICs) outside Europe, particularly those with a high burden of drug-resistant TB. This commentary focuses on whether the REA PTJA14 can be transferred and to what extent a REA can be translated to LMICs context outside Europe. We found that the assessments on the clinical effectiveness and risks of bias reported in REA PTJA14 are useful for LMICs outside Europe. The highly standardized management of TB will support the applicability of the REA to LMICs outside of Europe. Transferring this REA can reduce workload and efficiently use limited resources to conduct health technology assessment (HTA). However, the transfer should consider several critical issues, including variations in health system delivery and clinical practice and setting-specific constraints. In the TB context, the differences in the current standard treatment for XDR or nonresponsive MDR TB, resources availability for drug-resistant TB management, and how healthcare is delivered in the countries can complicate the applicability of the REA PTJA14. Given that LMICs have limitations in doing HTA, it is now critical to develop standard guidelines for transferring REA or other HTA results from high-income countries or other LMICs to maximize the benefits of the REA for LMICs outside Europe.

Health technology assessment (HTA) is a multidisciplinary process to determine the value of a health technology, which aims to inform decision making (1). HTA has been increasingly applied in low- and middle-income countries (LMICs) in the last few years. It plays an important role in determining the approval and coverage of health technologies by considering various dimensions of value for a health technology, including clinical efficacy, safety, and economic implication (1). Through this process, HTA can support governments in implementing an equitable and efficient health system to achieve universal health coverage (UHC) (1–3). The HTA implementation in LMICs varies at different rates. Countries like Thailand and Malaysia have fully implemented and institutionalized HTA, while others may have only applied it informally (2–5). However, LMICs face common challenges in applying HTA, mainly due to the limited local capacity and financial resources to conduct HTA (2–6).

Transferring HTA, that is, applying (wholly or partially) the analyses and results of HTA from one jurisdiction to another, particularly for the value dimension of clinical effectiveness and economic implication, may help overcome the challenges (7;8). The transfer will avoid duplication of effort. It also allows LMICs to concentrate their limited resources on locally relevant activities that add value to the HTA. However, HTA can be context-specific since it is highly influenced by the health system and the culture and social–political characteristics of the country (7–9). Hence, transferring HTA results is not straightforward.

The HTA transfer model that can be applied to LMICs is a core model developed by EUnetHTA, a collaborative network for HTA across Europe (10). The core model includes a relative effectiveness assessment (REA) conducted through a joint assessment by at least four different EUnetHTA member countries (10). A joint assessment is possible since REA is considered transferable across borders and does not affect the value dimensions for a health technology perceived as context-specific, such as the economic or societal dimensions (11). The assessment can help reduce workload and allow several European middle-income countries to transfer the results into their contexts (9). However, the transfer is still challenging for other lower-income European countries, given their poorer health status, limited health resources, and

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different healthcare pathways, leading to different healthcare priorities (9–13). In a broader sense, the REA also contains ethics and legal perspective that may not be transferrable (14). Despite these challenges of transferring REA within European countries, the REAs produced by EUnetHTA are valuable and easily accessible. Therefore, the results can reach wider audiences not only within European countries but also to other LMICs outside Europe.

In 2020, EUnetHTA published a REA of Pretomanid in combination with Bedaquiline and Linezolid (BpaL) for the treatment of extensively drug-resistant (XDR) or treatment-intolerant or nonresponsive multidrug-resistant (MDR) Tuberculosis (TB) (REA PTJA14) (https://eunethta.eu/wpcontent/uploads/2020/08/PTJA14-Final-Assessment-Report-v1.0.pdf) (15). Drug-resistant TB is a significant public health issue in LMICs, and the chance of developing drug-resistant TB, such as XDR-TB and nonresponsive MDR-TB, is higher in LMICs (16). People with TB symptoms in LMICs often receive inadequate TB treatment from either self-medication, inappropriate prescriptions from drug stores or pharmacies, or low-quality care provided by physicians or nonregistered medical staff (17;18). The behaviors and a weak health system increase the risk of MDR- and XDR-TB development. There has been a steady increase in XDR-TB cases in LMICs of Africa and Asia (19;20), and it urges treatment improvement and innovation. Therefore, the REA PTJA14 results can contribute to XDR- and nonresponsive MDR-TB treatment improvements in LMICs outside Europe, which has been struggling to overcome the pitfalls of the prolonged drug-resistant TB regimen (21;22). However, one crucial question is whether the REA can be translated to their contexts.

Upon evaluating the transferability of REA PTJA14 to LMICs, the clinical efficacy of the BPaL regimen stood out. The clinical efficacy was based on a single-arm trial conducted in South Africa (15). The study suggested that BPaL resulted in a high efficacy rate —92 percent at 6-months after the end of treatment evaluation. If the assessment included subjects lost to follow up and died due to a non-TB cause, the efficacy was still high (90 percent). The study also highlighted the earlier sputum culture conversion in all but one patient. It is an essential finding since we are striving for a shorter regimen, which is worthwhile for XDR-TB and nonresponsive MDR-TB treatments. A shorter regimen improves the safety profile of drug-resistant TB treatment and leads to increased patients' adherence and quality of life (23;24).

However, the trial has limitations, and the REA is very informative in highlighting the limitations. First, the trial is unreliable for determining the true therapeutic effect because of lacking a control arm. Despite the promising clinical efficacy, the risks of bias due to the design of the single-arm trial should be carefully considered. The potential risks of bias include the noncomparative nature of the trial, the low sample size, the absence of drug-resistance characterization upon baseline for some patients, and the missing long term efficacy data (15). Second, the trial had no robust data to prove the possible benefit of a shortened treatment regimen for XDR-TB and nonresponsive MDR-TB treatment at great length. Third, the REA also cannot assess the impact of the short regimen on the quality of life because of data limitations (15).

The clinical efficacy and limitations in methodology identified by the REA is useful for all settings. However, transferring this REA to the LMICs context should consider other challenges. First, the governments in LMICs should consider the treatment practice applied in their countries when transferring this REA, since it determines the relevance of the health technology and its comparator to the setting. Until now, there has been no current standard practice for XDR- and nonresponsive MDR-TB treatment. Countries may use patient-tailored treatment regimens based on patients' drug sensitivity testing results and past medication use (25). Hence, setting specific treatment practices should be considered when selecting a comparator for the novel regimen. Furthermore, governments in LMICs need to assess the availability of second-line TB drugs and drug sensitivity testing, which are very scarce in LMICs (26). Bedaquiline, for example, was only available to less than 20 percent of the needs (26). This may influence the relevance of the technology addressed in the REA for LMICs. The transfer will become more valuable with the increasing drug availability and systematically lowering drug prices. There has been increasing pressure to lower Bedaquiline price and endorse it as the backbone for future MDR TB regimens (27). Through these movements, the REA is more relevant for transfer and, in parallel, can push a strategy to encourage the wide drug availability in LMICs.

Second, healthcare delivery systems or models of care for drug-resistant TB vary between countries. The treatment for XDR- and nonresponsive MDR-TB is long, complex, and expensive, with a potential for high rates of people lost to follow up. Ambulatory models of care and decentralization of drug-resistant TB services could lower the costs and lost to follow up rate (28). However, this model of care needs massive trainings for healthcare workers and investment. Otherwise, the delivery system will be nonoptimal, fail to widen patients' access to adequate treatment (29), and eventually worsen patients' treatment adherence and outcome (30).

The third challenge is the clinical practice variations of TB comorbidity management, such as TB coinfection on HIV or TB with diabetes mellitus. The comorbidities are significant risk factors to the high TB burden. The risk of contracting TB is three times higher among those with diabetes than nondiabetic individuals, while one-fourth of TB deaths are HIV-positive cases. The REA dismissed potential drug interactions between the BpaL regimen with an antiretroviral, Efavirenz because the drug is no longer used in the European setting. However, LMICs, such as Indonesia, still include Efavirenz in their guideline of HIV management (31). The treatment of TB treatment along with the comorbidities, therefore, should be carefully addressed.

Another challenge is the different countries' methodological preferences in HTA. In general, HTA has two main parts: clinical and cost-effectiveness evaluations. Another part is exploring ethical, patient engagement, legal perspectives, and other relevant value dimensions. Countries have their specific preference in conducting HTA. For example, some LMICs like Indonesia often do not perform a separate clinical effectiveness evaluation but prefer to use an integrative method, that is, economic evaluation. Therefore, transferring REA, which mostly only provides clinical effectiveness evaluation, still needs to perform the economic evaluation before reaching the decision. However, the REA can still be used to inform the economic evaluation design.

Despite the challenges, the REA PTJA14 highlights the importance of developing XDR- and nonresponsive MDR-TB treatment regimens. Treatment for drug-sensitive and resistant TB is highly standardized worldwide, but the standard for XDR- and nonresponsive MDR-TB is still lacking. Nevertheless, REA in TB has advantages. The global standard of TB treatment can facilitate the REA transfer to LMICs outside Europe. Other health technologies do not have this advantage, and the REA transfer to LMICs context is more challenging because of the absence of supra-national guidelines on disease management.

Transferring this REA, and other HTA results from other jurisdictions, can help LMICs save their resources. Governments in

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LMICs can concentrate on setting-specific assessments, such as the economic evaluation of the BpaL Regimen. They can also focus more on developing a comprehensive assessment involving other elements influencing the success of TB treatment, such as drug surveillance to prevent inappropriate use and nonadherence, diagnosis, and equity of access to the medicine. This comprehensive assessment is helpful to strengthen the TB-related health system in LMICs, which is currently still weak (32).

Another essential point is that a REA and HTA transfer guidance from high-income countries or other LMICs, which is now lacking, is urged. Many guidelines have been developed, such as the Agency for Care Effectiveness (ACE, Singapore) guide to assess generalizability (33) and the Swedish Agency for HTA (Sweden) handbook to assess transferability (34); however, nothing has been developed for LMICs. The guidance for LMICs can be adapted from those well-developed guidances with critical adjustment. Therefore, the guidance will help LMICs perform the transfer without abandoning their capacity building and compromising the integrity of their decision-making process (35). This movement should also promote collaborative assessment for HTA or REA through regional HTA agencies network, such as HTAsiaLink for Asian countries. It will also allow the adaptation of clinical practice guidelines between countries, for example, adapting MDR-TB guidelines between Vietnam, Thailand, Malaysia, and Indonesia.

In conclusion, the REA PTJA14 by EUnetHTA is partly useful for LMICs outside Europe, particularly those with a high burden of drug-resistant TB. However, careful assessment is still required in transferring the REA. Assessments on the clinical effectiveness and risks of bias provided by the REA were beneficial. However, transferring the REA should consider variations in applied treatment practice, healthcare delivery system or model of care, clinical variation in comorbidities or coinfection management, and countries' HTA methodological approach.

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