

VIEWPOINT

Reforming the World Health Organization's Essential Medicines List

Essential but Unaffordable

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The Model List of Essential Medicines of the World Health Organization (WHO) highlights medicines considered the most effective, safe, and important for priority public health needs. In the years since its first publication in 1977, the Essential Medicines List has shaped the diffusion and reimbursement of new medicines in health systems around the world. The list, which remains a voluntary guideline for national formularies, was established with the goal of making included therapies widely available and affordable. However, the selection of medicines for inclusion in the list has been increasingly complicated by the escalating prices of new drugs entering the market.

With the publication of its 2021 list, which comprised more than 400 medicines, WHO for the first time explicitly acknowledged that several medicines, including checkpoint inhibitors for lung cancers, were not on the list—despite being highly effective—due to prohibitively high prices.¹ In this Viewpoint, we propose restructuring the list to formally remove consideration of cost and cost-effectiveness from the expert committee reviews of clinical effectiveness, safety, and public health

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value and chartering a new framework for pooled global negotiation and procurement of costly medicines eventually included in the list.

The recent update of the Essential Medicines List resurfaced a long-standing tension with some medications between high costs and essential need for health systems and patients. The roots of the current controversy can be traced to the introduction of the first antiretroviral therapies in the late 1990s that were costly; until then, cost (specifically, experts' judgment about the affordability for low-income countries) had a central role in the consideration of whether a therapy should be included in the list. Amid patient and public advocacy around ensuring appropriate access to antiretroviral medications, an overhaul of the procedure for updating the Essential Medicines List was published in 2001, with 2 important caveats: (1) the absolute cost of a medicine should not be a reason to exclude it from the list if it meets the other selection criteria, and (2) cost-

effectiveness comparisons should be considered within, but not between, therapeutic areas.² In the following year, the first antiretroviral agents were added to the list.

Both of these methodological points on cost considerations were challenged in the 2021 update to the Essential Medicines List. Programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) immune checkpoint inhibitors for locally advanced or metastatic non-small cell lung cancer were not recommended for inclusion in the list despite being acknowledged by the expert committee as meeting its threshold level of median overall survival benefit for cancer therapies (minimum 4-6 months). Pembrolizumab is recommended as the preferred first-line therapy for PD-L1-expressing metastatic non-small cell lung cancer in both the US National Comprehensive Cancer Network and European Society for Medical Oncology (ESMO) clinical practice guidelines; furthermore, the drug was scored as providing high benefit with the ESMO-Magnitude of Clinical Benefit Scale, which was cited by the WHO's cancer expert committee as a benchmark for determining cancer drugs that should be prioritized for inclusion in the list.³

In its explanation of the recommendation for noninclusion of this medication, WHO noted that listing the PD-1/PD-L1 inhibitors could result in unsustainable expenditures for patients and health systems (Table). Similarly not recommended for inclusion was pertuzumab in combination with trastuzumab and taxane chemotherapy for first-line treatment of *ERBB2* (formerly *HER2*)-positive unresectable or metastatic breast cancer, even though the

regimen met the survival benefit threshold and received a score of high benefit under the ESMO-Magnitude of Clinical Benefit Scale. In contrast, WHO expert committees moved to include costly but effective therapies in noncancer therapeutic areas. For example, the expert committee for diabetes medicines recommended inclusion of brand-name sodium-glucose cotransporter 2 (SGLT-2) inhibitors for second-line treatment of type 2 diabetes on the basis of renal, cardiovascular, and overall survival benefit (despite the high price of the drugs in this class), as well as costly long-acting insulin analogues.¹ Meanwhile, in 2015, WHO included then-novel direct-acting antiviral drugs for hepatitis C in the list despite noting that their high prices could make these therapies broadly inaccessible.

For future iterations of the Essential Medicines List, WHO should formally separate its expert committee reviews of comparative effectiveness, safety, and public health priority from consideration of the price of medicines and their cost-effectiveness. As exemplified

Table. Recommendations for and Against Inclusion of Select Costly New Medicines in the World Health Organization Essential Medicines List 2021

Medicine	Indication	Recommendation	Benefit considerations	Cost considerations
PD-1/PD-L1 immune checkpoint inhibitors	Locally advanced or metastatic NSCLC	Noninclusion	Overall survival benefit exceeding the EML threshold; favorable benefit-to-harm ratio	The committee considered that the financial implications of listing these medications for this indication would result in unsustainable expenditures for many patients and health systems
Pertuzumab (with taxane and trastuzumab)	ERBB2-positive (formerly HER2) unresectable or metastatic breast cancer	Noninclusion	Overall survival benefit exceeding the EML threshold; favorable benefit-to-harm ratio	Concern that adding pertuzumab would result in considerable additional expenditures, diverting resources from improving access to and affordability of trastuzumab, which is highly effective across all breast cancer stages
SGLT-2 inhibitors	Type 2 diabetes	Inclusion	Reduced risk of all-cause mortality, major cardiovascular adverse events, and adverse renal outcomes	Inclusion comes with the recommendation that WHO work with the Medicines Patent Pool to promote access through potential licensing agreements with the patent holders to allow generic manufacturing and supply in low- and middle-income countries

Abbreviations: EML, Essential Medicines List; NSCLC, non-small cell lung cancer; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; SGLT-2, sodium-glucose cotransporter 2.

by the conflicting direction taken for costly medications used for cancer vs for diabetes, any ad hoc process of permitting consideration of drug prices and cost-effectiveness may result in arbitrary decisional disparities across disease areas. Cost and access analyses could be conducted by a separate panel that includes experts in health economics, health equity, bioethics, and global care delivery and should ideally consider cost-effectiveness and affordability analyses conducted from the perspective of health systems in resource-limited settings. The decisions of this committee, and the analyses underlying its decisions, should be transparent and open to public comment and scrutiny. Therapies that meet the clinical and public health benefit criteria for essential medicines but are judged by this independent panel as being potentially unaffordable could be either listed in the primary Essential Medicines List with an asterisk or automatically included in a parallel list of essential medicines with high anticipated costs. The Essential Medicines List already includes a complementary list of medicines that have higher costs or require specialized diagnostics or care, but it is unclear how or why certain costly therapies do or do not qualify for inclusion in this complementary list.

Ultimately, having a 2-stage, independent approach that separates clinical and economic reviews, as is currently done by health technology assessment agencies in France, Germany, and several other countries, could provide a more robust and reproducible basis for establishing the list. This 2-stage process could also help alleviate lingering concerns among public health advocates that reliance on cost-effectiveness analyses could block recommendations for inclusion of important innovations in the list and, consequently, access to them in resource-limited settings.⁴

By introducing a more rigorous and systematic process for considering cost-effectiveness and affordability issues, WHO could

more clearly identify useful medicines, such as PD-1/PD-L1 inhibitors, that countries may have challenges in accessing due to cost. This reform could therefore provide the foundation for the creation of a new financing mechanism for negotiation and procurement of essential medicines at scale for resource-limited countries. Important precedents for such a mechanism are Gavi (for vaccines) and the Global Fund to Fight AIDS, Tuberculosis and Malaria, both of which have substantially increased global access to new technologies for infectious diseases. The first products prioritized for pooled procurement of essential medicines could include costly therapies for cancer. In exchange for receipt of reduced prices, countries and aid organizations could invest in ensuring that all eligible patients receive treatment and minimizing out-of-pocket costs. This mechanism would build on the precedent of the Medicines Patent Pool, which pools intellectual property to speed manufacturing in low- and middle-income countries, and the new Access to Oncology Medicines Coalition to increase access to cancer medicines in low-income countries.

The public health challenge of unaffordable medicines is likely to grow in the coming years, further straining the process of updating WHO's Essential Medicines List. The innovation landscape is markedly different from when the Essential Medicines List was first published in 1977 or even when the rules of procedure were last updated in 2001. The emergence of more effective and highly costly therapies, including gene and cell therapies, will further highlight the need for a new approach to determining which medicines are deemed essential. By separating clinical reviews from cost considerations and by working to strengthen pooled drug price negotiation and procurement, WHO could strengthen trust in the Essential Medicines List and establish a more durable foundation for global access to essential medicines.

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