Annals of Global Health
VOL. 83, NO. 3-4, 2017

ISSN 2214-9996/$36.00
http://dx.doi.org/10.1016/j.aogh.2017.05.005

ORIGINAL RESEARCH

On Essentiality and the World Health Organization's Model List of Essential Medicines

Victoria A. Marks, BS Candidate, Stephen R. Latham, JD, PhD, Sandeep P. Kishore, MD, PhD
New Haven, CT; and New York, NY

Abstract

BACKGROUND In 1977 the World Health Organization created its first Model List of Essential Medicines—a list designed to aid countries in determining which medicines to prioritize on their National Essential Medicines Lists. In classifying drugs as "essential," the World Health Organization has historically stressed drugs' ability to meet priority health needs of populations and cost.

OBJECTIVES In this paper we trace the fluctuations in the application of cost and priority status of disease as criteria for essential medicines throughout the reports published by the WHO Expert Committee on Selection and Use of Essential Medicines since 1977.

METHODS We analyzed essential medicines lists published on the World Health Organization website since 1977 for trends in criteria concerning cost and priority status of disease. Where, available, analyzed the World Health Organization Expert Committee analysis rationalizing why certain medicines were or were not added and were or were not removed.

RESULTS The application of the criteria of cost and priority status of essential medicines has fluctuated dramatically over the years.

CONCLUSIONS The definition of essential medicines has shifted and now necessitates a new consensus on normative definitions and criteria. A more standardized and transparent set of procedures for choosing essential medicines is required.

KEY WORDS essential medicines, governance, World Health Organization

INTRODUCTION

The World Health Organization (WHO) currently defines essential medicines as "those that satisfy the priority health care needs of the population"[1] and describes the criteria for their selection as "disease prevalence and public health relevance, evidence of clinical efficacy and safety, and comparative costs and cost-effectiveness."[1] These standards for defining and selecting an "essential medicine" are quite general; moreover, their application to particular cases has been unpredictable in recent years. This paper explores some of that recent history, and raises normative questions about how—by whom, and using what procedures—essentiality of medicines should be understood and, ultimately, defined.

The current definition of "essential medicines" is coded into the WHO Model List of Essential Medicines (EML). Developed in 1977, this list was created to serve as a guideline for the National Essential Medicines Lists for countries globally. The WHO's original intent was to assist developing

Conflict of interest: Sandeep P. Kishore, MD, PhD has authored applications to the World Health Organization Expert Committee to add and delete medications.

From the Department of Chemistry, Yale University, New Haven, CT (VAM); Yale Interdisciplinary Center for Bioethics, New Haven, CT (SRL); Arnhold Institute for Global Health at Icahn School of Medicine at Mount Sinai, New York, NY (SPK). Address correspondence to S.P.K. (Sunny.kishore@gmail.com).

Annals of Global Health, VOL. 83, NO. 3-4, 2017
May–August 2017: 637–640

countries in establishing priority lists of medicines by offering to them an expert opinion on the cost and proven efficacy of medicines addressing their priority medical needs.[2] Over the years, however, the notions of both "cost" and "priority" have migrated, sometimes inconsistently.

METHODS

The WHO Model List of Essential Medicines has been updated every two years since 1977 and posted on the website of the WHO. We analyzed each of these lists, as well as the reports released by the WHO Expert Committee on Selection and Use of Essential Medicines rationalizing all additions and deletions from the list. We tracked citation of the criteria cost and priority status of disease for essential medicines throughout these reports. Fluctuation and trends in the application of these criteria were analyzed in order to assess the consistency and transparency of the selection process.

RESULTS

Cost. When the WHO first published its list, it stated that affordability was considered a "major selection criterion."[2] This criterion included not only "cost comparisons between drugs"[2] but also "the cost of the total treatment"[2] for a given drug; for example, a low-cost, efficacious drug that requires constant monitoring to prevent side effects may ultimately be expensive in a country where such maintenance is difficult. The WHO's wording in this era suggested that although cost was not the *only* consideration, a drug *could* be excluded from the list solely on account of high cost, despite having an otherwise favorable profile. At the end of the 1977 report, a recommendation to inquire more about the cost/effectiveness ratio was noted,[2] though not pursued thereafter.

The idea that drugs could be kept off the list based on their "absolute cost" was maintained for 15 years. It was not until the 1992 report[3] that the WHO Expert Committee on the Selection and Use of Essential Medicines first referenced the cost/benefit ratio as a "major consideration in the choice of some drugs for the list."[3] At this point, the WHO began to assert that cost alone should never bar a medicine from the list. In 2000, the term *cost-effectiveness* was introduced.[4] Cost-effectiveness analysis dictates that a high-cost medicine may nonetheless be "essential" if its value outweighs that cost.[4]

In 2001 the WHO outlined a revised procedure for updating the Model List of Essential Medicines.[5] No longer could the absolute cost "constitute a reason to exclude a medicine from the Model List"[5] if that medicine "otherwise met the stated selected criteria."[5] The required cost-effectiveness analysis is to consider not only the total cost of treatment compared with that of other medicines in the same therapeutic group but also the direct and indirect nonmedical costs of each drug,[5] such as costs of, for example, refrigerated storage.

It is important to note that the relationship between cost and the EML is 2-fold; not only may cost affect the inclusion of a medicine on the list, but the inclusion of a medicine on the list may also affect the cost and availability of the medicine in return.[6] On the supply side, the WHO EML guides mass drug donation by both public and private sector stakeholders.[6] On the demand side, nations adapt the international EML to national EMLs to guide their purchasing and reimbursement of therapies. Inclusion of a medicine on the EML has been reported to increase its availability and affordability.[1,3] This fact makes it vital that cost considerations be treated carefully and consistently.

Nonetheless, throughout the 21st century, cost has been taken into account, though with varying—and sometimes inexplicable—degrees of importance. In 2011 the Expert Committee rejected the inhalation drug sevoflurane, with the only explanation being "due to cost"[7]— not even unfavorable cost-effectiveness. On the other hand, the Expert Committee added artesunate to the Model List without any consideration of cost analysis because of the medication's other advantages.[7] In 2015, cost came to the forefront of the Expert Committee's discussion when several high-cost cancer medicines, including imatinib, trastuzumab, and rituximab, were recommended.[8] Ultimately, the Expert Committee "approved inclusion…on the EML in spite of their high price."[8] Notably, the Expert Committee stated that "where the total cost of a new medicine is high, countries will need to consider the 'opportunity cost' and affordability for the health system as a whole,"[8] acknowledging that regardless of a favorable cost-effectiveness analysis, investment in some essential medicines still might not be beneficial for some countries. Although cost was obviously highly considered in the 2011 and 2015 reports, the 2007 and 2010 reports indicate a marked decrease in cost considerations compared with reports from years both before and after.

Priority Status. In 1997 the Expert Committee concluded, "Essential drugs are those that satisfy the health care needs of the majority of the population."[9] Today essential medicines are defined as "those that satisfy the priority health care needs of the population."[1] The WHO's replacement of the quantifying term *majority* with the qualifying term *priority* has resulted in a vaguer standard, given the ambiguity of what qualifies as a priority health care need. The criteria for the selection of essential medicines, as dictated by the 2001 executive board of the World Health Assembly, state that the choice of essential medicines depends on several factors, including "the disease burden and sound and adequate data on the efficacy, safety and comparative cost-effectiveness of available treatments."[5] Today the WHO maintains the same criteria, though the term *disease burden* has been replaced by *disease prevalence.*[1]

Beginning in 2002, the Model List of Essential Medicines has been divided into core and complementary items. In distinguishing *core* from *complementary* medicines, the WHO stated, "The complementary list presents essential medicines for priority disease which are efficacious, safe, and cost-effective but not necessarily affordable, or for which specialized health care facilities or services may be needed."[10] This makes "complementary" all of the otherwise essential medicines a country cannot afford. This explanation does not differentiate between the burden and prevalence of disease that core and complementary essential medicines treat, suggesting that all essential medicines should treat "priority" disease. It is worth noting that issues related to safety and efficacy are not within the scope of this discussion.

In 2011, when considering the addition of disease-modifying agents used in rheumatoid disorders for children, the Expert Committee's first consideration was whether these conditions represented "a priority health problem for the population,"[7] taking into account not only burden but also prevalence of this low-prevalence but highly symptomatic disease. This raises normative questions on what qualifies as a priority disease. Are high-priority diseases those with the greatest public health relevance? Should medications for diseases with low public health relevance be excluded from the Model List?

Several case studies illustrate these difficulties. In 2003, factors VIII and IX concentrates, treatments for hemophilia, were recommended for fast-track deletion from the list.[11] This action was suggested because hemophilia is a rare disease that affects a very small subset of the population (between 0.0097% and 0.0205% of the male population in the United States).[11] This extremely low disease prevalence, along with a high cost of treatment, suggests low public health relevance. However, because of inferior alternatives and the life-saving characteristic of treatment, the 2005 Expert Committee decided to retain factors VIII and IX concentrates on the Model List, "accepting the inherent inconsistency caused by the fact that hemophilia is a rare disease."[11] The Expert Committee subsequently recommended that a more uniform approach be established regarding the management of medicines for rare diseases.

This case is not unique. Since 2003, various treatments for rare diseases have been added to the Model List. This includes a variety of cancer drugs, such as imatinib, which was added to the complementary list[8] despite treating a type of cancer that affects less than 0.001% of the global population annually.[12] The tension between commitment to public health relevance and to effective treatment of rare disease continues to persist in the Essential Medicines List selection process. Thus far, no procedure for selecting drugs that are effective for rare diseases has been articulated.

DISCUSSION

These issues lead us to ask the following 2 questions:

1. Is affordability to patients a precondition of addition to the EML, or should it instead be a factor considered by individual countries or nongovernmental organizations in making budgetary decisions?
2. Should serious diseases be considered "priority" if they have low public health relevance? Or should effective treatments for serious rare diseases be accepted to the EML?

Given that the WHO's Model List of Essential Medicines is a suggestion rather than a mandate, it may be best that considerations of affordability follow, rather than act as a precondition of, the addition of any given drug to the list. No country will be forced to purchase a medicine that its health care system cannot financially support; however, it is important for countries to know what the best options available are. The WHO has a strong normative role to play in providing transparency on drug pricing, including hidden costs. Taking this approach would leave the Model List acting as an ideal, comprehensive list of the best medicines to

Annals of Global Health, VOL. 83, NO. 3-4, 2017
May–August 2017: 637–640

treat priority disease—a list from which countries can make admittedly difficult purchasing choices.

As for the definition of "priority disease," burden and prevalence of disease are important factors, but effectiveness against rare disease is also a reasonable consideration. The WHO should provide some guidance as to the point at which high-severity/low-frequency diseases have low public health relevance and the point at which medications for such diseases become irrelevant enough to bar drugs from the list.

The changing membership of the WHO Expert Committee responsible for inclusion and deletion of medicines in the EML may be one key factor explaining the variability in application of the cost and priority standards over the years. The WHO should ensure that the selection of Expert Committee members is made more transparent.

CONCLUSIONS

Here we argue that "essentiality" is linked primarily to the clinical benefit of the medicine in question. Cost considerations may be important practically for countries consulting the list but should not result in exclusion from the list. This is particularly true given that inclusion on the list can itself affect a drug's cost. We argue, finally, that the WHO should make its standards for public health relevance and "priority" clear.

REFERENCES

1. World Health Organization (WHO). Essential Medicines and Health Products. Geneva, Switzerland: WHO. Available at: http://www.who.int/medicines/services/essmedicines_def/en/; 2016. Accessed October 21, 2016.
2. World Health Organization (WHO). The Selection of Essential Drugs. 12, 34/WHO Technical Report Series/615. Geneva, Switzerland: WHO. Available at: http://apps.who.int/iris/bitstream/10665/41272/1/WHO_TRS_615.pdf?ua=1; 1977. Accessed October 21, 2016.
3. World Health Organization (WHO). The Use of Essential Drugs: Model List of Essential Drugs (Seventh List). 4/WHO Technical Report Series/825. Geneva, Switzerland: WHO. Available at: http://apps.who.int/iris/bitstream/10665/39646/1/WHO_TRS_825.pdf?ua=1; 1992. Accessed October 21, 2016.
4. World Health Organization (WHO). The Use of Essential Drugs. 1–4/WHO Technical Report Series/895. Geneva, Switzerland: WHO. Available at: http://apps.who.int/iris/bitstream/10665/42373/1/WHO_TRS_895.pdf?ua=1; 2000. Accessed October 21, 2016.
5. World Health Organization (WHO). WHO Medicine Strategy: Revised Procedure for Updating WHO's Model List of Essential Drugs, 8–9. Geneva, Switzerland: WHO. Available at: http://www.who.int/selection_medicines/ExpertCommittees/subExpertCommittee/2/eeb1098%5b1%5d.pdf?ua=1; 2001. Accessed October 21, 2016.
6. World Health Organization (WHO). Guidelines for Medicine Donations. Geneva, Switzerland: WHO. Available at: http://apps.who.int/iris/bitstream/10665/44647/1/9789241501989_eng.pdf; 2010. Accessed April 27, 2017.
7. World Health Organization (WHO). The Selection and Use of Essential Medicines. 51, 65/ WHO Technical Report Series/965. Geneva, Switzerland: WHO. Available at: http://apps.who.int/iris/bitstream/10665/44771/1/WHO_TRS_965_eng.pdf; 2011. Accessed October 21, 2016.
8. World Health Organization (WHO). The Selection and Use of Essential Medicines. 5-6, 77/WHO Technical Report Series/994. Geneva, Switzerland: WHO. Available at: http://apps.who.int/iris/bitstream/10665/189763/1/9789241209946_eng.pdf?ua=1; 2015. Accessed October 21, 2016.
9. World Health Organization (WHO). The Use of Essential Drugs. 5/WHO Technical Report Series/867. Geneva, Switzerland: WHO. Available at: http://apps.who.int/iris/bitstream/10665/41938/1/WHO_TRS_867.pdf?ua=1; 1997. Accessed October 21, 2016.
10. World Health Organization (WHO). The Selection and Use of Essential Medicines. 20/WHO Technical Report Series/914. Geneva, Switzerland: WHO. Available at: http://apps.who.int/iris/bitstream/10665/41938/1/WHO_TRS_867.pdf?ua=1; 2002. Accessed October 21, 2016.
11. World Health Organization (WHO). The Selection and Use of Essential Medicines. 15–16/WHO Technical Report Series/933. Geneva, Switzerland: WHO. Available at: http://apps.who.int/iris/bitstream/10665/41938/1/WHO_TRS_867.pdf?ua=1; 2005. Accessed October 21, 2016.
12. Food and Drug Administration (FDA). Gleevec (Imatinib Mesylate) Questions and Answers. Silver Spring, MD: FDA. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm110505.htm; 2013. Accessed October 21, 2016.