Are we moving towards a new definition of essential medicines?

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Essential medicines are defined as "those that satisfy the priority health care needs of the population," with the concept being that they are intended to be available within the context of a functioning healthcare system at all times, in adequate amounts, in appropriate dosage forms, with assured quality and at a price that individual and country can afford.[1] The selection depends on the public health importance of the disease or the condition being treated, good-quality clinical evidence of efficacy and safety, along with comparative cost-effectiveness of the different treatments that are available.[2] Individual drugs and dosage forms are selected based on stability, ease of use, and the need for specialized diagnostic, monitoring, or treatment facilities. This concept, though deceptively simple and easy to understand, becomes extremely complex and hard to adhere to when preparing a list for a given country. However, the World Health Organization's (WHO's) Model List stands out like a guiding beacon and is the gold standard to which all countries compare their selections with and turn to in case they face indecision during selection.[3]

WHO came out with its 19th Model List of Essential Medicines (EML) and 5th Model List of Essential Medicines for Children in April 2015. Thirty-six medicines have been added to the adult list and 16 to the children's list. The policy of WHO seems to be shifting ever so slightly to encompass the difficulties facing health care, especially in developed countries. The current list shows quite a few differences from the previous list.

INCREASING FOCUS ON HIGH-COST/PRICED MEDICINES AND INVESTIGATIONAL AGENTS

Some costly medicines can be included on the list, especially if it is for a priority healthcare need and there is good evidence for it to be included. Including very expensive drugs on the list with the hope that prices will be reduced eventually or for the reason of advocacy (to encourage more manufacturers), or to try and encourage drug regulatory authorities/pharmaceutical companies to register the drug is against the principles of selecting essential medicines. Most of these drugs are still on patent, and it would be difficult to get other manufacturers.[4] Moreover, this strategy has been already tried and found unsuccessful. Human immunoglobulin was included in the model list of essential medicines as it was considered vital for some conditions, but this had little effect on the price.

It must also be acknowledged that many of the high-cost medicines need complex, expensive diagnostic tests (immunological/histological) to define their indications and also require sophisticated monitoring methods at times. These are available in very few centers in most low- and middle-income countries (LMIC), if available at all. There seems to be an urgency to start including high-cost medicines, even if the individuals and the community cannot afford them and there is no enough clinical evidence of use in different settings.

Alcohol-based hand rubs are not superior to soap and water, but are more expensive. Daclatasvir and dasabuvir are investigational agents for treatment of hepatitis C infection that find a place in the 19th Model List of Essential Medicines. Including investigational agents defeats the basic purpose of essential medicines list. Moreover, in acute hepatitis C, the rate of clearance of virus without therapy is 15–30%. Antiviral therapy is recommended if viremia (documented by HCV RNA testing) persists 12 weeks after the initial seroconversion. Protease inhibitors like simeprevir are indicated for HCV genotype 1 infection and not recommended for other HCV genotypes. How many centers in the world have facilities to measure HCV RNA levels and HCV genotype testing?

INCLUDING DRUGS FOR INDICATIONS THAT ARE OFF-LABEL

Some drugs are included in the list for indications that are

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off-label. The pharmaceutical companies are not keen to register an old drug for a new indication, and would rather promote off-label use to extend the number of users. In the 18th WHO list, bevacizumab was added for age-related macular degeneration, even though it was not licensed for that use. There was evidence of it being used in developed countries, and in LMIC, and there was a need since the alternative (ranibizumab) which is licensed for this indication was very expensive and it would bring down the price of ranibizumab. Two years down the line, this has not happened. The problem with using a drug for off-label indications is that good information regarding dose (frequency, quantity, route), duration, etc., for the off-label indication is often not easily available. Hence, chances are that they may not be used appropriately. In the case of labeled indications, the healthcare worker has to only look at the drug information sheet which comes with the medicine to know the dose, route, and other information, and chances of the drug being used optimally are high.[5]

The injectable form (ampoule) of midazolam has been included in the list for oromucosal administration. This is off-label use. Since the buccal dosage form is not easily available, the parenteral (injection) formulation is to be used for this.[6] While the reasoning behind its inclusion is that anyone in the community can use this drug in children (and adults) to control seizures when needed, the scientific basis of the justification seems a bit hazy. The oromucosal preparations of midazolam have strict guidelines on the use based on age. As the oromucosal solutions are intended for administration by caregivers of children in the community, the oromucosal syringes are color-coded for easy recognition by laymen. This is important because midazolam is an anesthetic and too large a dose has the potential to cause respiratory depression. If an ampoule is to be used, the correct dose should be loaded in the syringe by the caregiver and as there are two different strengths of midazolam in ampoule (1 mg/ml and 10 mg/ml), there is a high potential for inadvertent overdose administration by people in the community. Hence, including the injectable form of midazolam instead of oromucosal preparation is potentially dangerous.

INCLUSION OF DRUGS THAT ARE NOT REGISTERED BY A STRINGENT DRUG REGULATORY AUTHORITY

The drug bedaquiline (for multidrug-resistant tuberculosis) has not been registered by any drug regulatory authority as yet. The Phase 3 trials have not been completed and the cost of the drug is not known, as the drug has not yet been marketed.[7] Bedaquiline has been included in WHO guidelines and perhaps the need to align the list with the guidelines is the reason behind.

KEEPING THE NUMBER TO A MINIMUM

The WHO Model List always tried to keep the number of drugs on the list to a bare minimum. This is reasonable as more the number of drugs, the budget will not be enough to cover all the drugs. Similarly, choosing one member in a class or one strength of a particular drug is better than having multiple strengths as drug supply chain systems which are fairly basic in most LMIC cannot cope with too many drugs. Sixteen anticancer drugs are added at a stroke to the new list. Also, the current list has many fixed dose combinations for malaria and HIV. These are included and removed with the updating of the guidelines.

INCLUSION OF STRENGTHS AND DOSAGE FORMS THAT ARE NOT EASILY AVAILABLE

The strengths and dosage forms usually included are those that are widely available in many countries. Folic acid 400 mcg was added to the list for women to take 2 months prior to their getting pregnant and for up to 2 months after they become pregnant, in order to prevent neural tube defects.[8] This was done even though folic acid in 1 mg and 5 mg strengths was already on the list. The inclusion of 400 mcg of folic acid was to align with nutritional guidelines. This particular strength of folic acid is only available in Panama and Switzerland and not in any other country.

ALIGNING WHO GUIDELINES AND THE EML – IS IT NECESSARY?

WHO seems to be under pressure to include all drugs in the latest versions of the numerous WHO treatment guidelines into the WHO EML. The guidelines committee is charged with the responsibility of preparing the guidelines based on the current evidence and usually keeps updating it from time to time. To add and remove drugs in quick succession in keeping with the latest WHO guidelines will be confusing to the LMIC who update their lists some time later on and not as frequently as WHO. In many of the LMIC, drugs belonging to the vertical programs like TB, malaria, and HIV are provided by external agencies and not paid for by the governments. Hence, the inclusion of these drugs into the EML will not impact availability at a local level. Including a large number of expensive drugs, which will be beyond the budgets of many if not all LMIC, will diminish the importance of the WHO Model List for these countries.

When the concept of essential medicines was begun in the mid-1970s, limited lists and reimbursement lists were not known in health care systems of developed countries. The healthcare system could afford any medicine that had been

registered in the country to be prescribed; however, from the late 1980s and 1990s, developed countries faced with an increasing drug budget felt the necessity to limit the medicines that could be prescribed in their healthcare system. This brought them closer to the principle of a restricted list (of which the WHO EML is one); however, unlike the WHO Model List of Essential Medicines, the countries could afford to have multiple medicines in the same therapeutic category, as for example, ACE inhibitors. With the increasing cost of medicines, healthcare systems in the developed world have offered more toward the essential medicines concept. This in itself is laudable, but may make the tool less relevant to those it was primarily intended to help – decision makers in the developing countries. Hijacking the WHO Model List of Essential Medicines for developed country purposes may help 20% of the global population, but leaves 80% of the developing world with a tool that has been enfeebled.

CONCLUSION

I would like to state that including medicines on the list which have not yet been registered by stringent regularity authorities, for off-label indications or healthcare problems that cannot be considered a priority, and for the sake of aligning WHO guidelines with the EML are uncharted territory as far as the EML goes. Previously, there had been very few examples when this was done, making it an exception rather than a rule. Including high-priced medicines, still under patent, with the hope that companies will reduce the price and also permit insurance companies to reimburse is a newer pasture. The selection of drugs for which high-quality clinical data of efficacy and safety are not available (such as bedaquiline, drugs for hepatitis C, and buccal midazolam) may not pay out as expected. The strength of the EML was that the selection was based on solid high-quality evidence; this seems to have been ignored in some of these instances. The current list makes one ponder whether the original definition of what is an essential medicine is blurring. If this is the new direction the list has to take, it should be done after careful discussion with stakeholders from various regions after much open debate. It should not be left to the committee of experts. It would be the ultimate exploitation of the healthcare systems of the developing world by those of the developed world to hijack this proven tool for the benefit of the latter.

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Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.162008

How to cite this article: Manikandan S. Are we moving towards a new definition of essential medicines?. J Pharmacol Pharmacother 2015;6:123-5.