EML at 42 (1977 – 2019)

Nicola Magrini, MD
Secretary,
WHO Expert Committee on the Selection and Use of Essential Medicines
1. Essential medicines … linking selection to UHC

2. Next update 2019 and how to improve access

3. Supporting Countries to develop and implement NEMLs
40 years of EML (1977 – 2017)

1977 1st Model list published, approx. 200 active substances

The first list was a major breakthrough in the history of medicine, pharmacy and public health

Médecins sans Frontières, 2000
20th EML & 6th EMLc - 2017

- 20th EML: **433** medicines
  - 6th EMLc (children): **314** medicines

602 pages, >800 references
eEML: database & formats

Search..

ELECTRONIC DATABASE

ONLINE SEARCH ENGINE

LINK TO WHO GUIDELINES

TEMPLATE

EVIDENCE SYNTHESIS
1. Essential medicines … linking selection to UHC
   • EML role and guiding principles: a short overview
   • Priority areas and how to better align EML and GLs

2. Next update 2019 and how to improve access

3. Supporting Countries to develop and implement NEMLS
5 challenges for EM policies
1. Adequate financing
2. Affordability
3. Quality and safety
4. Optimal uses
5. Missing EM
The EML reform in 2001: more explicit criteria

WHO medicines strategy

Revised procedure for updating
WHO’s Model List of Essential Drugs

Report by the Secretariat
Revised procedure for updating and disseminating the Model List

6. At its meeting in 1999, the Expert Committee proposed that the methods for updating and disseminating the Model List be revised because of (1) advances in the science of evidence-based decision-making; (2) the increasing link between essential medicines and guidelines for clinical health care; and (3) the high cost of many new and effective medicines. The Expert Committee concluded that current procedures do not define the range of conditions covered with adequate specificity, nor are the reasons for inclusion recorded with sufficient clarity.
EML criteria (EB 109/8, 2001)

- Disease burden and public health need/relevance
- Sound and adequate data on the efficacy (on relevant outcomes), safety and comparative cost-effectiveness
  - Role of evidence: quality (GRADE), publication bias
  - “Absolute cost of the treatment will not constitute a reason to exclude a medicine from the Model List that otherwise meets the stated selected criteria”
  - “Affordability changed from a precondition into a consequence of the selection” (Hogerzeil, BMJ, 2004)
### EML medicines and WHO technical Dpts GLs

<table>
<thead>
<tr>
<th>WHO guidelines</th>
<th>N. of EML drugs</th>
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</thead>
<tbody>
<tr>
<td>HIV</td>
<td>20</td>
</tr>
<tr>
<td>Hep C / B</td>
<td>11</td>
</tr>
<tr>
<td>TB</td>
<td>24</td>
</tr>
<tr>
<td>Malaria</td>
<td>18</td>
</tr>
<tr>
<td>Contraception</td>
<td>16</td>
</tr>
<tr>
<td>Subtotal</td>
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</tr>
<tr>
<td>NTD</td>
<td>15</td>
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<tr>
<td>MCH</td>
<td>---</td>
</tr>
</tbody>
</table>

**Total in WHO guidelines:** 89

**Total in NO WHO GL:** 240

<table>
<thead>
<tr>
<th>N. of EML drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCD</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>AB/AMR</td>
</tr>
</tbody>
</table>
Essential medicines ... linking selection to UHC
Comprehensive coordination: WHO GLs, priority areas, ...

1. Connection with relevant WHO GLs:
   • HIV, HepB/C, TB and Malaria
   • Reproductive Health
   • Paediatric GLs – specifically on AB
   • Cancer pain

2. Priority areas/chapters in need of a comprehensive update
   • Cancer – EML on a leading role
   • AB/AMR – EML on a leading role
   • CV/Resp
   • Neurology/MH
   • Dialysis
   • Other areas: Rheumatoid arthritis, inflammatory bowel diseases

3. Closer look at high-priced (newly approved) medicines
EML at 42 (1977 – 2019)
EML strategy to improve access - 2018-2023

1. Essential medicines … linking selection to UHC
   • EML role and guiding principles: a short overview
   • Priority areas and how to better align EML and GLs

2. Next update 2019 and how to improve access
   • Priority areas: WGs and how to expand access
   • EML rejections and prioritisation

3. Supporting Countries to develop and implement NEMLs
AB/AWARE

• 1st and 2nd choice AB for 23 syndromes
• Dosages and duration
• New Antibiotics (7)
• AWARE in selection/NEML, GLs and stewardship
• AWARE Index

Cancer

• Guiding principles: magnitude of benefits
• Individual drug review expanded to the group (enzalutamide and abiraterone)
• TKI inhibitors from South Asia
• Immunotherapies for cancer
WHO EML AWaRe categories: Access, Watch and Reserve

ACCESS: EML 1\textsuperscript{st} and 2\textsuperscript{nd} choice AB for 23 syndromes

- For each syndrome/disease the recommended AB for empiric treatment:
  - 1\textsuperscript{st} choice AB - recommended option(s)
  - 2\textsuperscript{nd} choice AB - alternative options when 1\textsuperscript{st} choice not available

WATCH: AB classes with higher resistance potential recommended only for specific indications that should prioritized as key targets for stewardship programs. It includes the highest priority agents on the list of Critically Important Antimicrobials (WHO CIA) that should not be used prophylactically in agriculture and food producing animals.

RESERVE: last resort AB or tailored to specific patients or when other options have failed
EML AWaRe 2019: next steps

• Additional syndromes/indications/recommendations:
  • SAP – surgical AB prophylaxis (WHO GL)
  • Dental infections, medical prophylaxis
  • Thyphoid fever
  • New antibiotics reviewed (7) and classified in AWARE
  • Dosages (paed) and optimal duration
  • Modelling on thresholds for gonorrhea (currently 5%)

• Guidance template (electronic) & eEML/AB platform
  • 1st and 2nd choice AB for all syndromes/diseases
  • Algorithms when NOT to prescribe AB

• New AWARE iteration

• AWARE in guidelines for implementation and stewardship
WHO AB Global Report 2018 and AWARE
Consumption of oral antibiotic formulations for young children according to the WHO Access, Watch, Reserve (AWaRe) antibiotic groups: an analysis of sales data from 70 middle-income and high-income countries

Yingfen Hsia, Mike Sharland, Charlotte Jackson, Ian C K Wong, Nicola Magrini, Julia A Bielicki

Summary
Background The 2017 WHO Model List of Essential Medicines for Children (EMLc) groups antibiotics as Access, Watch, or Reserve, based on recommendations of their use as first-choice and second-choice empirical treatment for the most common infections. This grouping provides an opportunity to review country-level antibiotic consumption and a potential for stewardship. Therefore, we aimed to review 2015 levels of oral antibiotic consumption by young children globally.

Methods We analysed wholesale antibiotic sales in 70 middle-income and high-income countries in 2015. We identified oral antibiotic formulations appropriate for use in young children (defined as child-appropriate formulations).
Figure 1: Percentage antibiotic use of child-appropriate oral formulations according to WHO AALKte grouping

Only core Access antibiotics have been included in the Access group. AALKte=Access, Watch, Reserve.
Proposing Essential Medicines to Treat Cancer: Methodologies, Processes, and Outcomes

Lawrence N. Shulman, Claire M. Wagner, Ronald Barr, Gilberto Lopes, Giuseppe Longo, Jane Robertson, Gilles Forte, Julie Torode, and Nicola Magrini

ABSTRACT

Purpose
A great proportion of the world’s cancer burden resides in low- and middle-income countries where cancer care infrastructure is often weak or absent. Although treatment of cancer is multidisciplinary, involving surgery, radiation, systemic therapies, pathology, radiology, and other specialties, selection and management of cancer medicines is challenging in resource-limited settings.

Results
Briefing documents were created for each disease, along with associated standard treatment regimens, resulting in a list of 52 cancer medicines. A comprehensive application was submitted as a revision to the existing cancer medicines on the WHO Model Lists. In May 2015, the WHO announced the addition of 16 medicines to the Adult EML and nine medicines to the Children’s EML.

Methods
Experts identified 29 cancer medicines for inclusion on the list, including common and rare childhood cancers.

Conclusion
The list of medications proposed, and the ability to link each recommended medicine to specific diseases, should allow public officials to apply resources most effectively in developing and supporting nascent or growing cancer treatment programs.

J Clin Oncol 34:69-75. © 2015 by American Society of Clinical Oncology
Methodology to Develop Proposal for Revisions

**TREATMENT GOAL**
- Cure or “near cure”
- Significant prolongation of survival
- Palliation of symptoms with small benefit in survival

**INCIDENCE OF DISEASE**

- Low
- Medium
- High

**LOW PRIORITY**
- Metastatic Pancreatic Cancer
- Metastatic Bladder Cancer
- Metastatic Lung Cancer

**LOWEST PRIORITY**
- GIST

**HIGH PRIORITY**
- Leukemia and Lymphomas in Children and Adults
- Breast Cancer
- Early-Stage Colon Cancer

- Testicular and ovarian germ cell tumors
- CML
- GTN

**Slides credit: Dr. Gilberto Lopes**
New EML cancer medicines main criterion: magnitude of absolute benefit

**Imatinib**: vast majority of patients in remission at 7 yrs

**Rituximab** (large B cell lymphomas): 15% absolute increase in survival rates (from 50-55% to 70%)

**Trastuzumab**: early stage breast cancer: up to 13% increase in survival in high risk women (from 37% to 50% survival rates at 3-6 yrs)

Same approach (using absolute efficacy estimates) applied to all proposed regimens
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Rejections/standby</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasatinib <em>(CML)</em></td>
<td>Enzalutamide (standby)</td>
</tr>
<tr>
<td>Nilotinib <em>(CML)</em></td>
<td>Trastuzumab emtansine (standby)</td>
</tr>
<tr>
<td>Zoledronic acid <em>(bone metastases)</em></td>
<td>TKIs, crizotinib (standby)</td>
</tr>
<tr>
<td>Fentanyl (transdermal)</td>
<td>Tramadol (cancer pain)</td>
</tr>
<tr>
<td>Methadone <em>(already listed for substitution treatment)</em></td>
<td></td>
</tr>
</tbody>
</table>
WHO EML 2017

Cancer medicines

- The Committee did not recommend listing for:
  - enzalutamide for metastatic prostate cancer;
  - tyrosine kinase inhibitors (erlotinib, gefitinib and afatinib) and ALK inhibitor (crizotinib) for non-small cell lung cancer;
  - trastuzumab emtansine for metastatic breast cancer.

- The Committee considered that listing of these medicines was premature and recommended the establishment of an EML cancer medicines working group to coordinate comprehensive evaluation of cancer medicines for the EML.
The Expert Committee recommended the establishment of an EML cancer medicines working group to coordinate comprehensive evaluation of available treatment options, across treatment lines and including recently approved medicines.

The working group should support WHO in establishing guiding principles, clarifying what constitutes a clinically relevant therapeutic effect, for granting the status of essential medicine to a cancer medicine.
April 2018

Medicine Use and Spending in the U.S.

A Review of 2017 and Outlook to 2022
There have been 52 new cancer medicines launched in the past five years including 33 in the past three years.

Chart 29: Oncology New Active Substances By Year of First Launch in the United States

Source: IQVIA Institute, Mar 2018
Essential Medicines. The CMWG aims to obtain relevant input from experts to guide the selection of optimal cancer medicines under consideration for inclusion in the Essential Medicines List (EML).

- There was agreement on the usefulness and relevance of current magnitude of benefit scales for cancer medicines (ASCO-VF and ESMO-MCBS): these two scales have promoted the involvement of the oncology community (clinicians, researchers) and cancer patients in discussing the value of new cancer medicines and have fostered better understanding of what it is meant by relevant clinical benefit.

- The discussion on what is a clinically relevant magnitude of benefit was examined comparing ASCO-VF and ESMO-MCBS scales. Data from recent cancer trials were used to evaluate medicines recently approved by FDA and EMA using both scales: only a minority of newly approved medicines provide data on survival and quality of life. Indeed clinically relevant data are often lacking at the registration phase.

- It was noted that for the vast majority (i.e. 75%) of cancer medicines approved over the last 15-20 years, there has been a lack of definitive evidence of substantial clinical benefit for patients at registration.
• The CMWG recommended WHO endorse the need to have overall survival as the main eligibility criterion of a medicine proposed for EML listing. Further the CMWG recommended endorsement of an interval for overall survival of at least 4-6 months for first-line treatments as a general guiding principle.

• Among the considerations that supported the 4-6 months overall survival interval were:
  o a strong clinical and ethical conviction that for OS less than 3 months, the benefits seem weak, marginal or not relevant (depending on cancer types);
  o a 3-month survival threshold has been endorsed by both ASCO and ESMO scales, with different implications in their respective scales;
  o clinical trials estimates tend to overestimate the benefits because of patient selection, risk of bias and spurious findings. Patients included in clinical trials often differ from those seen in real life settings: benefits in patients seen in everyday practice might be less convincing as compared to those selected in trials. Trials often have important methodological limitations, leading to biased estimates of intervention effectiveness. Single studies are often exposed to type I error. Finally interventions studied in trials might not be directly transferable in LMICs as capacity of centers to deliver essential medicines and manage related toxicity might be diminished.
EGFR tyrosine kinase inhibitors: erlotinib, gefitinib, afatinib

Medicines for metastatic prostate cancer

Anti PD-1 immune-checkpoint inhibitors: Pembrolizumab, Nivolumab, Atezolizumab

Pertuzumab

Trastuzumab emtansine

Medicines for Children with Cancer

Aprepitant

Arsenic trioxide

Pegasparagase

Rituximab and Trastuzumab sc
«Late papers» contributing to EML discussion

Dr. Mariângela Simão
Assistant Director-General
Prequalification and Technology Assessment
World Health Organization
Avenue Appia 20
1202 Geneva, Switzerland

Dear Dr. Simão,

We would like to thank the WHO Secretariat for sharing the Cancer Medicines Working Group (CMWG) meeting report and the technical report on temporal trends in clinical trials and the benefit of new cancer therapies. We recognize the efforts of the CMWG to bring greater transparency around the criteria for inclusion of oncology medicines in the Essential Medicines List (EML), however we are concerned with several of the core pillars outlined in these reports. Therefore, we would like to take this opportunity to address some of these concerns in the points outlined below.

1. Having overall survival (OS) benefit of 4-6 months as the main criterion for inclusion on the EML will potentially leave out many therapies with great clinical value.

   The strategy of listing medicines based on the magnitude of their OS benefit in clinical trials should be put into context. Many treatments offer clinical benefits beyond OS, detectable and measurable on the level of novel clinical endpoints (reflecting the specificities of innovative treatments), including, very importantly, patient reported quality of life\textsuperscript{1}. Nonetheless, as explained below in point 2, many of these results will in fact be translated into real clinical benefit when used in a clinical setting and given the necessary time to generate data.

How to prioritize essential medicines for cancer
Tito Fojo, MD, PhD on behalf of
WHO Essential Medicines List Cancer WG 2018-9
Professor of Medicine
Department of Medicine
Division of Hematology / Oncology
Columbia University
New York, New York

Background

With citizens of the entire world as its constituents regarding matters of health, the challenges faced by the World Health Organization as it tries to help provide the best possible cancer care are understandably complex. Viewed by some as a personal tragedy but not a societal health challenge, the importance of cancer medicines was first addressed as a problem of low- and middle-income [LMl] countries in need of World Health Organization support in 1977 when the first essential medicines list was published including some essential medicines for cancer. Recognizing the diverse income structure of the world’s countries and the challenge a diagnosis of cancer presents to any human, the World Health Organization has tried, through its list of Essential Medicines, to highlight cancer therapies it considers valuable because they can meaningfully change outcomes for cancer patients throughout the world.

While in developed countries one often encounters a clamoring for the latest novel therapy that “cures” cancer, in fact as the data will show, with only rare exceptions, novel therapies are increasingly not novel and rarely curative; indeed, the majority provide only marginal benefits. Furthermore, it is often incorrectly assumed that developed countries, with well-funded health care systems can afford to pay for such novel therapies with marginal improvements at what many consider exorbitant prices. A long overdue reconciliation will soon force even the richest countries to confront the unavoidable truth that budgets are not infinite, much more public good can be reaped from many less expensive options and that investing in prevention and vaccinations can deliver much more, albeit in the future. These tenets, long recognized by the World Health Organization, provide the foundation for much of what follows.

With this monograph we hope to provide background that will help the reader understand some of the variables that must be considered in deciding what constitutes an Essential Medicine. It is designed to complement the report of a working group of international experts convened by the World Health Organization in its Geneva Headquarters on March 22/23 of 2018. The charge for that working group was to begin the process of identifying the cancer therapies that would be added to the 2019 Essential Medicines List and define guiding principles for EML candidates.

21 March 2019
1. Essential medicines … linking selection to UHC
   - EML role and guiding principles: a short overview
   - Priority areas and how to better align EML and GLs
   - Impact of standing Working Groups: AB/AWARE and Cancer

2. Next update 2019 and how to improve access
   - Priority areas (WGs and GLs)
   - EML rejections and prioritisation

3. Supporting Countries to develop and implement NEMLs
   - DB of NEMLs and eEML (and e-AWARE)
   - Reimbursement and procurement
   - Inputs from countries & drug utilisation
   - Other priorities: insulins and …
eEML: database & formats

ELECTRONIC DATABASE

ONLINE SEARCH ENGINE

TEMPLATE

LINK TO WHO GUIDELINES

EVIDENCE SYNTHESIS
1. EML as a guide to procurement:
   • Square box examples (qualified therapeutic equivalence)
**Erythropoiesis-stimulating agents**

**Complementary List**

- erythropoiesis-stimulating agents*

**Injection: pre-filled syringe**

- 1000IU/0.5 mL; 2000IU/0.5 mL; 3000IU/0.3 mL; 4000IU/0.4 mL; 5000IU/0.5 mL; 6000IU/0.6 mL; 8000IU/0.8mL; 10 000IU/1 mL; 20 000IU/0.5 mL; 40 000IU/1 mL

* the square box applies to epoetin alfa, beta and theta, darbepoetin alfa, and their respective biosimilars
EML consultation with countries: objectives
(end of January 2019)

• There is a need to facilitate feed-backs and inputs from countries

• Countries should propose priorities and hot topics (for which they request WHO EML to respond or take a position on)

• WHO EML to propose a simple/facilitated process for countries (in parallel with the standard application process)
Support to countries: access to EM

Use / DU

Selection
Coverage/UHC
Procurement & therapeutic equivalence

EML

Shortages
EML: other priorities

Insulins
Migrants
Why insulin access is a global priority

- Insulin was discovered in 1921 and first used in 1922 - yet remains unavailable and unaffordable to many patients globally.
- Insulin is essential medicine needed daily for the survival of people with Type 1 diabetes and increasingly also in Type 2 diabetes.
- Discuss an EML independent working group on the issue of access to insulin to:
  - Strengthen supply & improve delivery of care
  - Evaluate current health system challenges
  - Discuss insulin inclusion in WHO prequalification program and pooled procurement mechanisms
  - ... think how to celebrate insulin 100 years in EML/WHA 2021
Evidence-based clinical guidelines for immigrants and refugees

Kevin Pottie MD MCISc, Christina Greenaway MD MSc, John Feightner MD MSc, Vivian Welch MSc PhD, Helena Swinkels MD MHSc, Mob Rashid MD, Lavanya Narasiah MD MSc, Laurence J. Kirmayer MD, Erin Ueffing BHSc MHSc, Noni E. MacDonald MD MSc, Ghayda Hassan PhD, Mary McNally DDS MA, Kamran Khan MD MPH, Ralf Buhrmann MDCM PhD, Sheila Dunn MD MSc, Arunmozh Dominic MD, Anne E. McCarthy MD MSc, Anita J. Gagnon MPH PhD, Cécile Rousseau MD, Peter Tugwell MD MSc; and coauthors of the Canadian Collaboration for Immigrant and Refugee Health

Competing interests: See end of document for competing interests.


This document has been peer reviewed.

Correspondence to: Dr. Kevin Pottie, kpottie@uottawa.ca


Consider also the WHO EML in our approach to immigrants and refugees health
The costs of an intervention are, in theory, easy to define.

...The evidence of the effectiveness of an intervention might seem easy to define.

The resources available to finance health care in increasingly resource-poor settings are an intervention’s greatest uncertain cost. Pharmaceutical manufacturers often sell their new drugs in developing countries at list prices, which are usually lower than the prices they charge in developed countries. Even when the list price is lower, governments and other health authorities, for understandable reasons, do not always immediately pay the full list price. In addition, confidential discounts that payers in many developed countries negotiate and are often substantially less than the list price. In developing countries, payers should similarly negotiate for lower prices for products from developed countries. But, again, there are difficulties.
We need less research, better research, and research done for the right reason

Doug Altman, BMJ 1994
22nd Expert Committee on the Selection and Use of Essential Medicines—applications for:

Additional medicines

- Fixed-dose combination antihypertensives - EML
- Bedaquiline - MDR-TB in children - EMLc
- Glipizide + glimepiride - EML
- Fonazide - EML and EMLc
- Sunitinib - EML
- EGFR tyrosine kinase inhibitors - EML
- Pertuzumab - EML
- Trastuzumab emtansine - EML
- Multiple micronutrient powders - EMLc
- Atorvastatin - EML
- Diazoxide - EMLc
- Carbetocin - EML
- Dolutegravir + lamivudine + tenofovir DF - EML
- Dabigatran - EML
- Direct oral anticoagulants (DOACs) - EML
- Multiple sclerosis disease modifying therapies - EML and EMLc
- Medicines for multiple myeloma EML
- Escitalopram - EML
- Methylphenidate - EML and EMLc
- Medicines for metastatic prostate cancer - EML
- Pegaspargase - EML and EMLc
- TNF-alpha inhibitors - EML and EMLc
- Tiotropium - EML
- Dolutegravir - EMLc
- Anti PD-1 immune-checkpoint inhibitors - EML
- Aprepitant - EML and EMLc