Updates on the WHO EML

Cutting-Edge Technologies: Landscape & Perspectives for Health Outcomes
Joint Trilateral Symposium WHO-WIPO-WTO

31st October, 2019

Nicola Magrini
Secretary,
WHO Expert Committee on the Selection and Use of Essential Medicines,
Essential Medicines Department, WHO
Conflict of interests

Global access to essential medicines

I declare I have no conflict of interests

I have been the Secretary of the EML Committee in its three last editions: 2015, 2017 and 2019
Goal 3: Good health and well-being

“Universal health coverage will be integral to achieving SDG 3, ending poverty and reducing inequalities.”
Global Access to Essential Medicines

Contents of the presentation

• At a glance: WHO EML and its role in picking up innovations

• The 2019 recommendations: some important listings
  • Immunotherapies for cancer (melanoma)
  • Antibiotics – when they make a difference
  • Others …

• What’s next for EML 2021
In 1977, the World Health Organization (WHO) published the first Model List of Essential Medicines (Essential Medicines List, EML).

It introduced the idea that some medicines are more important than others.

Many later considered the first EML ‘a revolution in public health’.

‘t Hoen EFM., et al.  
A quiet revolution in global public health: The World Health Organization’s Prequalification of Medicines Programme 
Journal of Public Health Policy, 2014
EML since 1977: an early evidence-based adopter

Since 1977:
- Insulin(s)
- Antibiotics
- Neglected diseases
- Pain
- Mental health
- Chronic diseases
- Cancer

EML is listing:
- All new HepC combinations
- Dolutegravir and PreP for HIV
- All new TB drugs
- Most/all contraceptives, carbetocin, … surfactant, ORS&zinc co-packaged
- … all highly effective treatments/interventions

In EML no medicines for:
- Memory loss and dementia
- “Hepatoprotectants” and “Immunostimulants”
- Medicines with little value (medicalisation of life conditions)
- No medicines subsequently withdrawn for unexpected risks (e.g., cox-2 inhibitors)
Essential medicines ... or why some medicines are more important than others
15 medical milestones during last century

Antibiotics
Imaging
Tissue culture
Anaesthesia
Chlorpromazine
Sanitation
Germ theory
Evidence based medicine
Vaccines
Contraceptive pill
Computer technology
Oral rehydration therapy
Monoclonal antibody technology
Smoking risks
Structure of DNA
15 medical milestones during last century
Yes, in EML

Antibiotics - Yes
Imaging – NA
**Tissue culture** – Yes/NA
Chlorpromazine – Yes
Sanitation - Yes / NA
Germ theory – Yes
Evidence-based medicine
Vaccines - Yes

Contraceptive pill - Yes
Computer technology
Oral rehydration therapy - yes
**Monoclonal antibody technology** - Yes
Smoking risks - Yes/NA
Structure of DNA - NA
New Strategies for Effective Therapeutics in Critically Ill Patients

Over the past 25 years, considerable therapeutic success has been achieved in several areas of clinical medicine, including childhood cancer, some adult cancers, human immunodeficiency virus, and chronic liver disease. However, with the notable exception of surfactant therapy for infant respiratory distress syndrome, there has been limited success in the application of novel therapeutics to improve clinical outcomes in critically ill patients. This leads to the following ques-

However, despite these advances, the list of failed therapeutic strategies for multiple clinical disorders in the intensive care unit (including traumatic brain injury, sepsis, ARDS, and acute kidney injury) is long. This Viewpoint does not discuss novel aspects of clinical trial design that have been proposed for study design or trial end points, and focuses instead on innovations that are needed relative to patient and therapeutic selection.
Over the past 25 years, considerable therapeutic success has been achieved in several areas of clinical medicine, including

childhood cancer,

some adult cancers,

human immunodeficiency virus,

and chronic liver disease.

However, with the notable exception of surfactant therapy (in EML NdT) for infant respiratory distress syndrome, there has been limited success in the application of novel therapeutics to improve clinical outcomes in critically ill patients.
WHO EML 2019: patented medicines

Including primary and secondary patents (out of 460 medicines) listed in the 21st WHO EML (2019)

• 11% of patented medicines
• Expected patent expiry dates: 2020 to 2037
• Source: MedsPaL – Patent and licenses database (www.medspal.org)
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<thead>
<tr>
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<tr>
<td>abacavir (ABC)</td>
<td></td>
<td>Expired except in Belarus (2023), Brazil (2028) Malaysia (2020) and Kazakhstan (2022)</td>
<td>2021 (BY, RU, MY) Oral solution (not in EML) until 2020 in MY and 2023 CL &amp; KZ</td>
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<td>abacavir + lamivudine</td>
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<td>Expired except in Belarus (2023), Brazil (2028) Malaysia (2020) and Kazakhstan (2022)</td>
<td>2021 (BY, RU, MY)</td>
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<tr>
<td>certolizumab pegol</td>
<td>x</td>
<td>2021</td>
<td>2021</td>
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<tr>
<td>Golimumumab</td>
<td>x</td>
<td>2021</td>
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<tr>
<td>bedaquiline</td>
<td></td>
<td>2023</td>
<td>2025, 26, 27</td>
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<tr>
<td>Apixaban</td>
<td>x</td>
<td>2019 (generic disclosure) 2022 (specific, RU until 2027)</td>
<td>2031</td>
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<tr>
<td>Edoxaban</td>
<td>x</td>
<td>2022</td>
<td>2028</td>
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<tr>
<td>Rivaroxaban</td>
<td>x</td>
<td>2020</td>
<td>2024, 2026</td>
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<tr>
<td>daclatasvir</td>
<td></td>
<td>2027</td>
<td>2028, 2030</td>
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<tr>
<td>dasatinib</td>
<td></td>
<td>2020</td>
<td>2024, 2025</td>
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<tr>
<td>delamanid</td>
<td></td>
<td>2023</td>
<td>2026</td>
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<tr>
<td>Medicine Name - 21st List 2019</td>
<td>Added 2019</td>
<td>Patent expiry - compound(s) (primary)</td>
<td>Patent expiry - combinations, formulations/Method Of Treatment, polymorphic forms.. (secondary)</td>
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<tr>
<td>dolutegravir + lamivudine + tenofovir</td>
<td>x</td>
<td>2026 (Extended until 2030/31 in few countries)</td>
<td>2029</td>
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<tr>
<td>dolutegravir</td>
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<td>2026 (Extended until 2030/31 in few countries)</td>
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<td>afatinib</td>
<td>x</td>
<td>2021</td>
<td>2024</td>
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<tr>
<td>glecaprevir + pibrentasvir</td>
<td>x</td>
<td>2031 (Glecaprevir) 2032-2033 (pibrentasvir)</td>
<td>2034, 2036, 2037</td>
</tr>
<tr>
<td>ledipasvir + sofosbuvir</td>
<td>x</td>
<td>2030 (Ledipasvir) 2024 (SOF) 2028 (SOF prodrug)</td>
<td>2032, 2034 (combination)</td>
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<tr>
<td>nilotinib</td>
<td></td>
<td>2023</td>
<td>2026</td>
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<td>raltegravir</td>
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<td>2022 (cmpd), 2025 (salt)</td>
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<tr>
<td>sofosbuvir + velpatasvir</td>
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<td>2024 (SOF) 2028 (SOF prodrug) 2032 (Velpatasvir) - 2032, 2034</td>
<td>2032, 2034</td>
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<tr>
<td>sofosbuvir</td>
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<td>2024 (SOF) 2028 (SOF prodrug)</td>
<td>2032</td>
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Source: MedsPaL - Patents and Licenses Database www.medspal.org
Global access to Essential Medicines

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  • Or … what you call innovative, we call highly effective …

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  • Antibiotics – when they make a difference
  • Others … insulins

• What’s next for EML 2021
Major 2019 decisions – cancer medicines

Additions

• PD-immunotherapies for melanoma (nivolumab, pembrolizumab)
• Abiraterone for prostate cancer
• TKI inhibitors NSCLC (erlotinib, afatinib, gefitinib)
• Bortezomib, lenalidomide, thalidomide, melphalan for multiple myeloma
• Arsenic therapies (oral, IV) and pegasparagase
• 10 medicines, 11 indications for children (EMLc)

Rejections/stand by

• PD-immunotherapies for lung cancer
• Pertuzumab and trastuzumab emtansine (breast cancer)
• Subcutaneous formulations of MABs rituximab and trastuzumab
Additions

• PD-immunotherapies for melanoma (nivolumab, pembrolizumab)

Rejections/stand by

• PD-immunotherapies for lung cancer

A reflection:

The major reasons for listing or not listing in EML lies in the different magnitude of benefit and confidence in estimates in long term benefits

How this different “value” could become a mechanism for wider access?
Major 2019 decisions: antibiotics

Growing threat by multi drug resistant bacteria – a result of stupid mistakes we should not repeat (Michael Altorfer, first speaker today)

EML antibiotics and AWaRe classification

- All antibiotics classified in 3 different EML classes: Access, Watch and Reserve
- Classification of 180 commonly used AB into AWaRe groups for evaluation/monitoring of use (only 37 of which listed on the Model Lists)
- AWaRe classification database published as a stewardship tool for countries
- GPW13 target of at least 60% of overall antibiotic consumption being from the Access group, as an indicator to monitor access to essential medicines and progress towards UHC.
• Core set of **19 antibiotics** that form 1\(^{st}\) or 2\(^{nd}\) line choice for *empirical* treatment of the priority clinical infection syndromes

• Generally characterized by narrow-spectrum (with limited risk of resistance) and/or low toxicity

• Prioritized for use over Watch and Reserve antibiotics

• Should be available everywhere at an appropriate quantity, dose, and formulation

**EML Access group antibiotics**

- Amikacin
- Amoxicillin
- Amoxicillin + clavulanic acid
- Ampicillin
- Benzathine benzylpenicillin
- Benzylpenicillin
- Cefalexin
- Cefazolin
- Chloramphenicol
- Clindamycin
- Cloxacillin
- Doxycycline
- Gentamicin
- Metronidazole
- Nitrofurantoin
- Phenoxybenzylpenicillin
- Procaine benzylpenicillin
- Spectinomycin
- Sulfamethoxazole + Trimethoprim
EML Watch group antibiotics

- Recommended only for a limited number of specific syndromes – **11 antibiotics**
- These 11 antibiotics are from AB classes that have a higher potential to drive bacterial resistance (e.g., fluoroquinolones and macrolides)
- These Ab are also highest priority agents of CIA List (critically important antimicrobials for human medicine)
- Active stewardship important for optimal (specific) uses
- Active monitoring of Watch antibiotics is encouraged e.g., through point-prevalence surveys as a stewardship tool

### Antimicrobials

- Azithromycin
- Cefixime
- Cefotaxime
- Ceftazidime
- Ceftriaxone
- Cefuroxime
- Ciprofloxacin
- Clarithromycin (or Erythromycin)
- Meropenem (or Imipenem)
- Piperacillin + tazobactam
- Vancomycin (IV & PO)
• Last-resort antibiotics (7) with proven activity against critical and high priority pathogens (according to WHO PPL)
• Restricted to use in specific patients and clinical settings, such as life-threatening infections with MDR- or XDR-resistant bacteria, when all Access or Watch group alternatives have failed or not suitable
• Key targets of high intensity national and international stewardship programs
• New antibiotics are likely (but not automatically) to be placed in this group

Ceftazidime + avibactam
Colistin
Fosfomycin IV
Linezolid
Meropenem + varobactam
Plazomycin
Polymixin B
EML antibiotics and AWaRe classification

- 3 newly registered AB (Ceftazidime + avibactam, Meropenem + varobactam, playomzcin) for multi-drug resistant infections were listed in EML as Reserve (last-resort) antibiotics (out of 7 new Antibiotics evaluated) – the 3 new Ab were listed as RESERVE
- Classification of 180 commonly used AB into AWaRe groups for evaluation/monitoring of use (only 37 of which listed on the Model Lists)
- AWaRe classification database published as a stewardship tool for countries
- GPW13 target of at least 60% of overall antibiotic consumption being from the Access group, as an indicator to monitor access to essential medicines and progress towards UHC.

Implications for antibiotics prices?

It is clear it cannot be market sales the reward: we should/can have different mechanisms in place.
A reflection on some of today’s common quotations: penicillin, vaccines, ...

From Tedros speech:

“Think of penicillin, vaccines, anesthesia or the MRI. None of us can imagine health care without them, and yet at one point they were all considered cutting edge.”

All these cutting edge leap forwards are on the WHO EML …

- **Vaccines** have important mechanisms in place for wider access – can we learn from vaccines on how to improve access?

- **Penicillin** lessons: resistance and market but also the beginning/first RCT also for its scarcity … - can we learn on mechanism we should have adopted?

How can we find different/new/ad hoc mechanisms for universal access?
The Committee recommended that a WHO-led approach should be multi-factorial and multi-disciplinary and should include:

- establishment of an independent **WHO technical working group** on access to insulin;
- consultation with Member States and other stakeholders to **identify/clarify barriers** to access at country level;
- strategies to address current regulatory barriers for biosimilar insulins, such as the expansion of the **WHO Prequalification Programme**;
- development of a comprehensive approach to address insulin prices, including mechanisms for **pooled procurement** (at global/UN and national level);
- identification of **evidence and research gaps** regarding insulin use and supply, including setting-specific differences in clinical practice and health systems (e.g., food insecurity, displaced populations, emergencies).
OECD countries - 2018

Pharmaceutical spending Total % of health spending, 2018 or latest available

Countries listed in order of pharmaceutical spending: Denmark, Norway, Netherlands, Sweden, Iceland, Luxembourg, United Kingdom, United States, Austria, Finland, Ireland, France, Israel, Switzerland, Costa Rica, Germany, Belgium, Portugal, Australia, Canada, Czech Republic, Italy, Estonia, Slovenia, Spain, Japan, Poland, Korea, Mexico, Lithuania, Slovak Republic, Greece, Latvia, Hungary, Russia.
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• What’s next for EML 2021
all highly effective treatments are essential

Effectiveness must be supported by high quality evidence or high confidence in magnitude of benefits.

Not only evidence on benefits and harms, but also value of main outcome, feasibility, resource requirements and long term sustainability.
WHO current activities on gene/cell therapies

1. **INN (International Nonproprietary Names Expert Group):** Nomenclature schemes for advanced therapies

2. **ECBS (Expert Committee on Biologic Standardization):** Standards
   - Developing a white paper on: terminology, regulatory framework, and key elements for quality, safety and efficacy
   - WHO 1st International reference panel for lentiviral vector copy numbers for gene therapy products adopted

3. WHO established in 2019 a multi-disciplinary Expert Advisory Committee to examine the scientific, ethical, social and legal challenges associated with human genome editing (both somatic and germ cell) – co-chaired by Peggy Hamburg & Edwin Cameron
   - State of the research and its applications, and societal attitudes towards the different uses
   - Appropriate oversight and governance mechanisms, both at the national and global level

4. WHO EML will evaluate the new gene and cell therapies for:
   - Magnitude of benefit (survival benefit threshold for cancer therapies)
   - Relevance of benefits / harms and feasibility
EML and cutting-edge technologies

- Essential medicines is a global concept to prioritise the most important innovations (highly effective treatments)

- EML is a Model List for both selection and implementation - it is not a regulatory tool

- It is not a basic List for poor countries

- Selection and reimbursement are countries’ responsibility

- Inclusion in EML should have consequences … in terms of wider access to the most effective and impactful innovative treatments
Innovation and access in UHC era

Innovation

Innovation / essential – for all, universal

Most important dimension of WHO cube

Innovation with Access should go together from the beginning

Innovation with Equity / feasibility issues

Innovation / essential with (long-term) sustainability should go together
The long run is a misleading guide to current affairs. In the long run we are all dead.

Economists set themselves too easy, too useless a task if in tempestuous seasons they can only tell us that when the storm is past the ocean is flat again.

J. M. Keynes

Let’s try to do more together to improve access and improve public trust we are not just describing our imperfect times