Update from the EML secretariat

Benedikt Huttner

Secretary
24th WHO Expert Committee on the Selection and Use of Essential Medicines

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“The WHO does, however, have a consistent record for establishing itself as the go-to organization for setting global standards for the efficacy, safety and quality of vaccines and medicines.”
The EML at 46 (or 23 EML “years”…)

Increasing interest in the “essential medicines” concept

- Number of publications indexed in PubMed

- Every year FDA and EMA approve between 30 and 60 new medicines
- 54% (20/37) of medicines approved by FDA in 2022 were “first in class”
- 65% (24/37) approved using “Fast Track, Breakthrough Therapy, Priority Review, and Accelerated Approval” pathway

Advancing Health Through Innovation: New Drug Therapy Approvals 2022 (FDA)
The EML as a model list for national lists of essential medicines

https://global.essentialmeds.org

- The database of national essential medicines lists (NEMLs) currently being updated
- About half of all countries with NEMLs updated their national lists in the last 5 years
- NEMLs vary substantially regarding the number of medicines included and the alignment with the WHO Model Lists
Applications to be discussed at the 2023 Expert Committee meeting

- 52 applications to add new medicines
- 9 applications to include new indications for medicines already listed
- 8 applications proposing inclusion of new formulations / strengths for medicines already listed
- 6 applications proposing removal of formulations / strengths
- 9 applications for other changes to the Model Lists
GLP-1 agonists
Treatment of obesity (indication type 2 diabetes not assessed)

- Worldwide obesity has nearly tripled since 1975
- In 2016, more than 1.9 billion (39%) adults were overweight of which 650 million (13%) were obese
- Most of the world's population live in countries where overweight and obesity kills more people than underweight
- 39 million children <5 years overweight or obese in 2020
- For now, no medicines for the treatment of obesity on the EML

https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
Cardiovascular “polypill”
Primary and secondary prevention of atherosclerotic cardiovascular diseases

- Cardiovascular diseases are the leading cause of death globally
  - About 17.9 million deaths each year

- Pharmacologic treatment key for reduction in morbidity and mortality
  - In addition to “cessation of tobacco use, reduction of salt in the diet, eating more fruit and vegetables, regular physical activity and avoiding harmful use of alcohol”

- Adherence to treatment remains suboptimal

- Applications for EML listing rejected in 2013, 2015 and 2017 (lack of mature data)

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https://www.who.int/health-topics/cardiovascular-diseases
Ravidasvir
Hepatitis C virus (HCV) infection

- Globally about 58 million people with chronic HCV infection
  - 1.5 million new infections occurring per year

- With direct acting antivirals (DAAs) chronic HCV infection can be cured in >95% of patients

- Quality-assured DAAs are available in many settings
  - MPP licensing for three DAAs
  - Initially DAA were marketed at a price of > 80’000 USD / treatment
  - Now available at prices often <100 USD / treatment in some countries

Accelerating access to hepatitis C diagnostics and treatment. WHO 2021.
https://www.who.int/publications/i/item/9789240019003
Medicines for the treatment of COVID-19

SARS-CoV-2 lineage prevalence


We recommend immediate administration of supplemental oxygen therapy to any patient with emergency signs during resuscitation to target SpO2 ≥ 94% and to any patient without emergency signs and hypoxaemia (i.e. stable hypoxaemic patient) to target SpO2 > 90% or a 92–95% in pregnant women.

Remarks for adults:
1. Adults with emergency signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma and/or convulsions) should receive emergency airway management and oxygen therapy during resuscitation to target SpO2 ≥ 94% [138] [139].
2. Once the patient is stable, target > 90% SpO2 in non-pregnant adults and a 92–95% in pregnant women.
3. Deliver oxygen flow rates using appropriate delivery devices (e.g. use nasal cannula for rates up to 5 L/min; Venturi mask for flow rates 6–10 L/min; and face mask with reservoir bag for flow rates 10–15 L/min). For more details about oxygen titration, refer to the WHO Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation [161].
4. In adults, techniques such as positioning, e.g. high supported sitting, may help to optimize oxygenation, ease breathlessness and reduce energy expenditure [22].
5. In adult patients with evidence of increased secretion production, secretion retention, and/or weak cough, airway clearance management may assist with secretion clearance. Techniques include gravity-assisted drainage and active cycle of breathing technique. Devices including mechanical insufflation-exsufflation and inspiratory positive pressure breathing should be avoided where possible. Implementation of techniques should be tailored to the individual patient and follow available guidelines [22].

Remarks for children:
1. Children with emergency signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma and/or convulsions) should receive emergency airway management and oxygen therapy during resuscitation to target SpO2 ≥ 94% [138][139].
2. Once patient is stable, the target is > 90% SpO2 [130].
3. Use of nasal prongs or nasal cannula is preferred in young children, as they may be better tolerated.

https://app.magicapp.org/#/guideline/6668
Medicines for the treatment of COVID-19

SARS-CoV-2 lineage prevalence

COVID-19 Therapeutics under assessment

Living guidelines

24th WHO Expert Committee on the Selection and Use of Essential Medicines
Open Session – April 24, 2023
Cancer medicines on the EML

First WHO EML published
Six cancer medicines in total

Second review
24 cancer medicines in total

First EMLc for paediatric cancers
22 cancer medicines added for EMLc

EML Cancer Medicines Working Group established
44 cancer medicines in total

Rituximab biosimilar prequalified


First review of oncology
Third review

Fourth review (UICC)
First instance of targeted therapies and patented medicines listed on Model Lists
42 cancer medicines in total

Major update of medicines recommended for childhood cancers
Trastuzumab prequalified by WHO as first biosimilar medicine
53 cancer medicines in total

Three new and one therapeutic alternative, several new indications for children
62 cancer medicines in total

Figure 3: Adopted and proposed principles to prioritize cancer medicines for inclusion on the WHO EMLs
The orange pillars are formally adopted by the WHO Expert Committee and the blue pillars are proposed principles under discussion. Price (cost-effectiveness data) is considered by the WHO Expert Committee when evaluating medicines with therapeutic equivalents on the WHO EMLs. EML = Model List of Essential Medicines. ESMO = European Society of Medical Oncology. MCBSS = Magnitude of Clinical Benefit Scale.

Immune checkpoint inhibitors (ICI)
Non-small cell lung cancer (NSCLC)

- Nivolumab (with pembrolizumab as alternative) added for melanoma in 2019
- Application for NSCLC rejected in 2019 and 2021
  - Partly because of “prohibitively high price”
- Since the first approval of ipilimumab in 2011 for melanoma
  - > 90 additional indications approved
  - > 11 different checkpoint inhibitors approved
- > 5’600 studies enrolling patients (2021)
- Total revenue >60 billion USD
  - “For reasons that are unclear, the glut of similar products from many different pharmaceutical companies has not led to competitive pricing”

CAR-T cell treatment
Relapsed / refractory large B-cell lymphoma

- Reviewed in 2021
  - without request for addition
- Often 300’000-600’000 USD per treatment
- Highly complex production

First patients of pioneering CAR T-cell therapy ‘cured of cancer’

Cancer-killing cells still present 10 years on, with results suggesting therapy is a cure for certain blood cancers

https://www.theguardian.com/society/2022/feb/02/first-patients-pioneering-car-t-cell-therapy-cured-of-cancer
Several applications for childhood cancer

“...the platform will be focused on procuring and distributing medicines that have been categorized by the World Health Organization (WHO) as ‘Essential Medicines’”

https://www.who.int/initiatives/the-global-initiative-for-childhood-cancer
Age-appropriateness of formulations of essential medicines for children – EMLc

- Review of the age-appropriateness of formulations of medicines listed on the EMLc

- Paediatric formulations assessment
  - Identification of formulations of essential medicines that could be proposed for potential addition / deletion to the EMLc
  - Identification of formulation gaps in essential medicines for children

- EML / EMLc comparison
  - Identify medicines on the EML that have potential therapeutic utility in children but that are not currently included on the EMLc
Rare diseases (RD)

- RDs affect approximately 6% of the worldwide population
- No universal definition
- With more targeted treatments the number of RDs is likely to increase
- What is rare in one population may not be rare in another
- Medicines for rare diseases are sometimes highly priced

“KEI had earlier requested a voluntary license... to manufacture and sell a generic version of risdiplam”

“KEI is currently investigating manufacturing risdiplam from a country where rights in patented inventions, data, or regulatory approval do not present a barrier.”

“The current structure of the EML is not designed to deal rationally and effectively with pricing and affordability issues.”

Accessibility of highly-priced medicines

- “…the absolute cost of a medicine will not be a reason to exclude it from the Model List if it meets the stated selection criteria,…”

- “…cost-effectiveness comparisons be made among alternative medicines within the same therapeutic group (e.g., identifying the most cost-effective drug treatment to prevent mother-to-child transmission of HIV). This approach is in line with WHO’s practice of including cost considerations in the development of public health recommendation.”

“…essential drugs are those that satisfy the health care needs of the majority of the population; they should therefore be available at all times … at a price that individuals and the community can afford.”

Revised procedure for updating WHO’s Model List of Essential Drugs. Executive Board document EB109/8, 7 December 2001
Reforming the World Health Organization's Essential Medicines List
Essential but Unaffordable

Thomas J. Hwang, MD; Aaron S. Kesselheim, MD, JD, MPH; Kerstin N. Vokinger, MD, JD, PhD

Author Affiliations

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.
In September 2020, WHO Guideline on country pharmaceutical pricing policies was published

Ten pricing policies

1. External reference pricing
2. Internal reference pricing
3. Value-based pricing
4. Mark-up regulation across the pharmaceutical supply and distribution chain
5. Promoting price transparency
6. Tendering and negotiation
7. Promoting the use of quality-assured generic and biosimilar medicines
8. Pooled procurement
9. Cost-plus pricing for setting the price of pharmaceutical products
10. Tax exemptions or tax reductions for pharmaceutical products

The only policy with strong recommendation and for the first time includes “biosimilar medicines”

https://www.who.int/publications/i/item/9789240011878
3.2 Note on evaluation of “off-label” medicines

The Expert Committee noted that several medicines that it considered were evaluated for indications described as “off-label”. With respect to this issue, the Committee noted that:

- “Label” is a national regulatory authority responsibility and there may consequently be many different labels for the same product in different countries. There is thus no global standard for what is “off-label”.
- Updating the approved labels for old products is a commercial decision in each national jurisdiction and there are many examples of old products whose labels are inconsistent with current clinical evidence and thus with clinical practice.

In making its decisions, the Expert Committee therefore evaluated the current clinical evidence for products that were submitted; national labelling decisions were not considered.
From a single medicine approach to a more comprehensive evaluation: example medicines for multiple sclerosis

- Over 2.2 million prevalent cases worldwide
- 2019 application to add glatiramer acetate, fingolimod, ocrelizumab rejected with request for a revised application “that considers the relative roles of all available medicines for MS”

Timeline of developments in the treatment of multiple sclerosis

Appropriate use of essential medicines

- It is not enough that essential medicines are available and affordable
  - They must be used appropriately

In a report to the Twenty-eighth World Health Assembly in 1975, the Director-General reviewed the main drug problems facing the developing countries and outlined possible new drug policies. The Director-General also referred to the experience gained in some countries where schemes of basic or essential drugs had been implemented. Such schemes were intended to extend the accessibility of the most necessary drugs to those populations whose basic health needs could not be met by the existing supply system. The Director-General pointed out that the selection of these essential drugs would depend on the health needs and on the structure and development of health services of each country, and that lists of essential drugs should be drawn up locally, and periodically updated, with the advice of experts in public health, medicine, pharmacology, pharmacy and drug management. He also considered that adequate information on the properties, indications and use of the drugs listed should be provided. By resolution WHA28.66, the Health Assembly requested the Director-General to implement the proposals contained in his report and, in particular, to advise Member States on the selection and procurement, at reasonable cost, of essential drugs of established quality corresponding to their national health needs.

“He also considered that adequate information on the properties, Indications and use of the drugs listed should be provided”

Dr Halfdan Mahler (WHO DG 1973-1988)
12. Community-acquired pneumonia – mild

- Key messages:
  - Rapidly decide if the patient has mild community-acquired pneumonia (CAP), which can be managed in primary care with oral antibiotic treatment, or severe CAP, which has a higher short-term mortality risk and requires hospital admission. Success can be helpful to make this distinction.
  - Clinically relevant low-level beta-lactam resistance in Streptococcus pneumoniae (the main bacterial cause of CAP) is seen in some countries and can affect treatment if β-lactams are used in mild cases. Treatment duration can be limited to 5 days in most cases (5–7 days in children in areas of low prevalence of human immunodeficiency virus (HIV)).
  - Other relevant WHO resources (please check regularly for updates):
    - Coronavirus disease (COVID-19) pandemic (13).
    - Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper - February 2019 (12).

- Symptomatic Treatment: Multi-drug therapy is an effective treatment for CAP and requires close monitoring.

- Clinical Considerations:
  - Antibiotic treatment duration: 5 days.

- Antibiotic Treatment:
  - First Choice: Amoxicillin 80-90 mg/kg/day ORAL

- Oral weight bands:
  - 3–6 kg: 250 mg twice daily
  - 6–10 kg: 375 mg twice daily
  - 10–15 kg: 500 mg twice daily
  - 15–20 kg: 750 mg twice daily
  - ≥20 kg: 1 g three times daily or 1 g twice daily
WHO medicines strategy: revised procedure for updating WHO's Model List of Essential Drugs

- The medicines landscape is becoming increasingly complex
- The application process focused on single medicines makes it difficult to get a holistic picture especially in areas without dedicated WHO technical teams / guidelines
- The quality of the applications is varying, some applications are incomplete and / or contain misleading information
- Many medicines included on the Model Lists do not have corresponding WHO guidelines covering their use
- The role of the EML regarding products that are not “classic” medicines
- The role of the Model Lists in public health emergencies needs to better defined

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Thank you!

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