Update from the EML secretariat

Benedikt Huttner

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

24.04.2023 (Open session)

World Health Organization

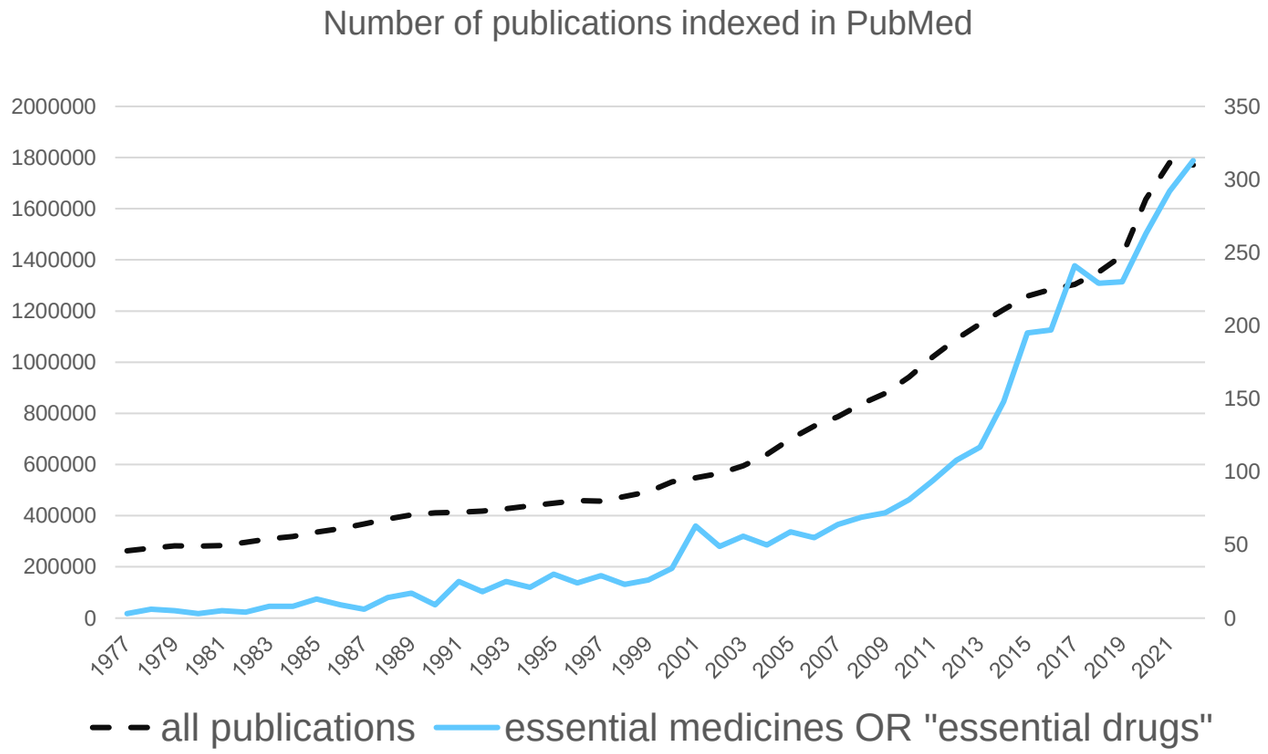
75 HEALTH FOR ALL

Setting global standards

- *"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****."*

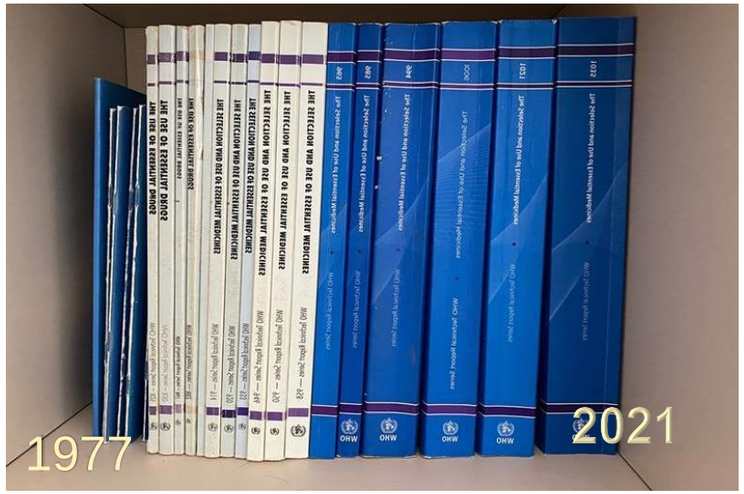
The EML at 46 (or 23 EML “years”…)

Increasing interest in the “essential medicines” concept



- 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)

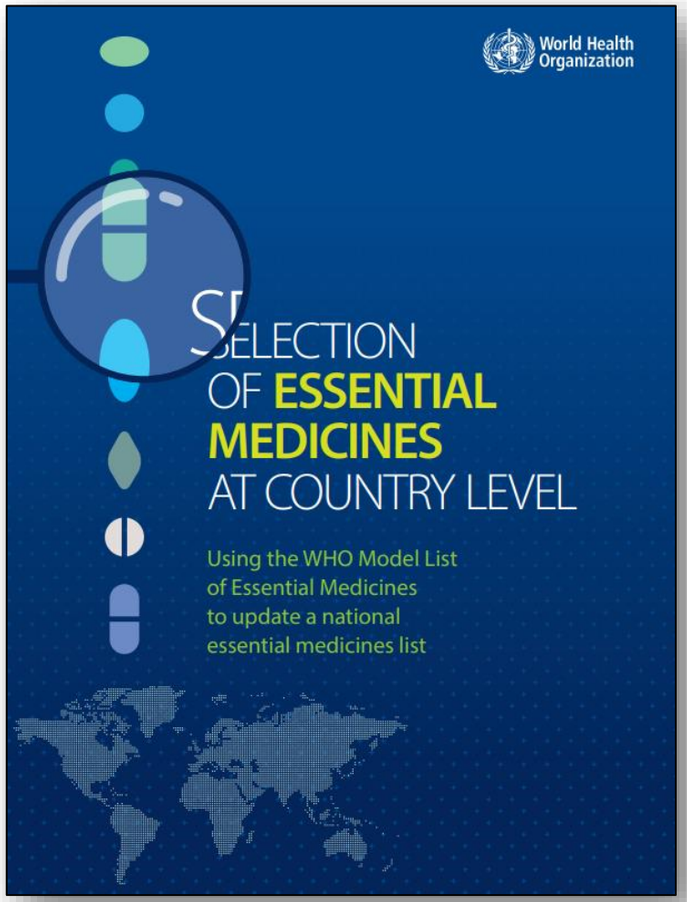


World Health Organization

The EML as a model list for national lists of essential medicines

https://global.essentialmeds.org

Global Essential Medicines



https://apps.who.int/iris/bitstream/handle/10665/330898/9789241515443-eng.pdf

- 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

World Health Organization

Applications to be discussed at the 2023 Expert Committee meeting

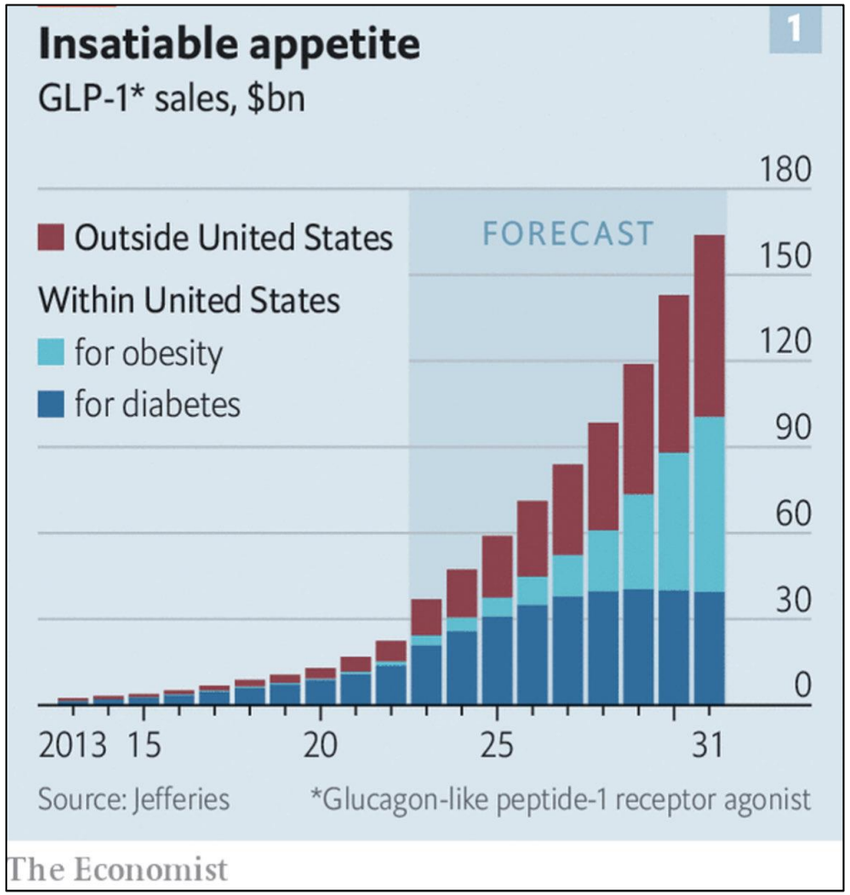
- **52** applications to add new medicines
- **9** applications to include new indications for medicines already listed
- **8** applications proposing inclusion of new formulations / strengths for medicines already listed
- **6** applications proposing removal of formulations / strengths
- **9** applications for other changes to the Model Lists

GLP-1 agonists

Treatment of obesity (indication type 2 diabetes not assessed)

Economist 02.03.2023

- 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

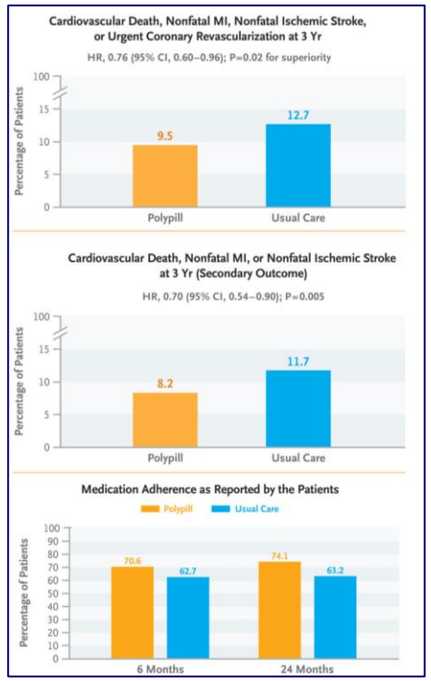


https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

World Health Organization

Cardiovascular “polypill”

Primary and secondary prevention of atherosclerotic cardiovascular diseases



Catellano et al. N Engl J Med 2022; 387:967-977.
Robson et al. Nat Rev Cardiol. 2021 Feb;18(2):72-73.
https://www.who.int/health-topics/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)

World Health Organization

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

DNDi 20 years

APPLICATION FOR INCLUSION OF RAVIDASVIR INTO THE WHO MODEL LIST OF ESSENTIAL MEDICINES (EML) FOR THE TREATMENT OF CHRONIC HEPATITIS C VIRUS (HCV) INFECTION IN ADULTS

MINISTRY OF HEALTH MALAYSIA

CORRESPONDENCE:
DR. NUR SUFIZA AHMAD, DR. ROSLIANA ROSLI, HAARATHI HANDRIAH, NAZATUL SYIMA IDRUS, NG SIN YEE, NABILA ABDUL RAHMAN, COLEEN CHOO SIEW BEE

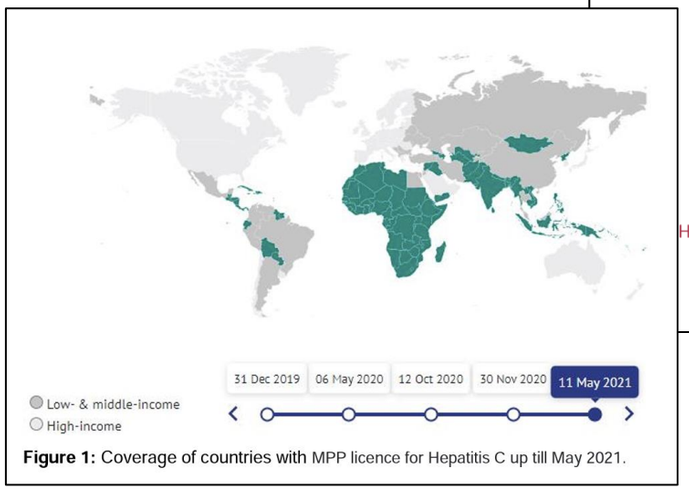
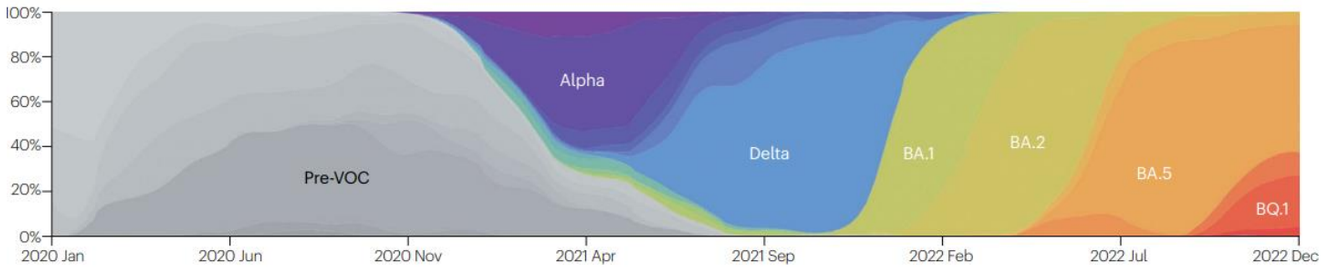


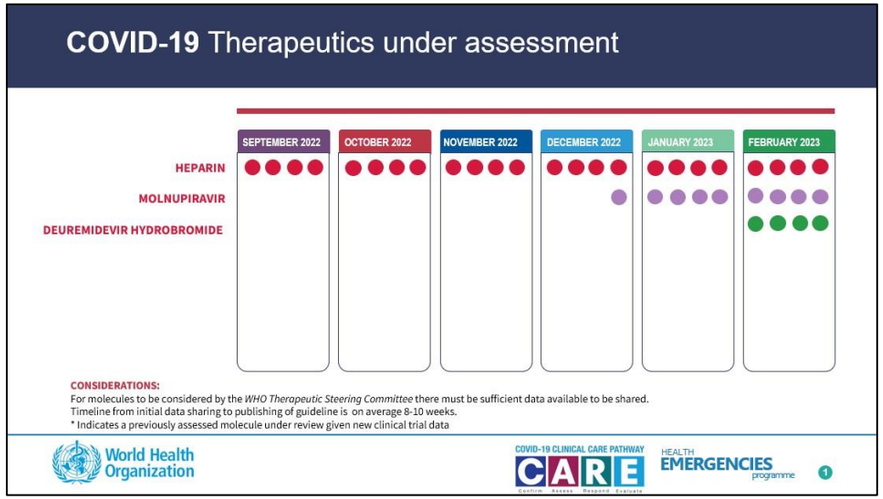
Figure 1: Coverage of countries with MPP licence for Hepatitis C up till May 2021.

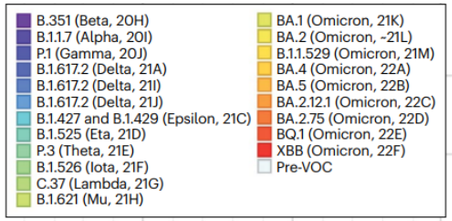
Accelerating access to hepatitis C diagnostics and treatment. WHO 2021. https://www.who.int/publications/i/item/9789240019003

Medicines for the treatment of COVID-19

SARS-CoV-2 lineage prevalence







10. Management of severe COVID-19: severe pneumonia treatment [4]

We recommend immediate administration of supplemental oxygen therapy to any patient with emergency signs during resuscitation to target SpO_2 ≥ 94% and to any patient without emergency signs and hypoxaemia (i.e. stable hypoxaemic patient) to target SpO_2 > 90% or ≥ 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 SpO_2 ≥ 94% [159] [128].
2. Once the patient is stable, target > 90% SpO_2 in non-pregnant adults and ≥ 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 [221].
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 [221].

Remarks for children:

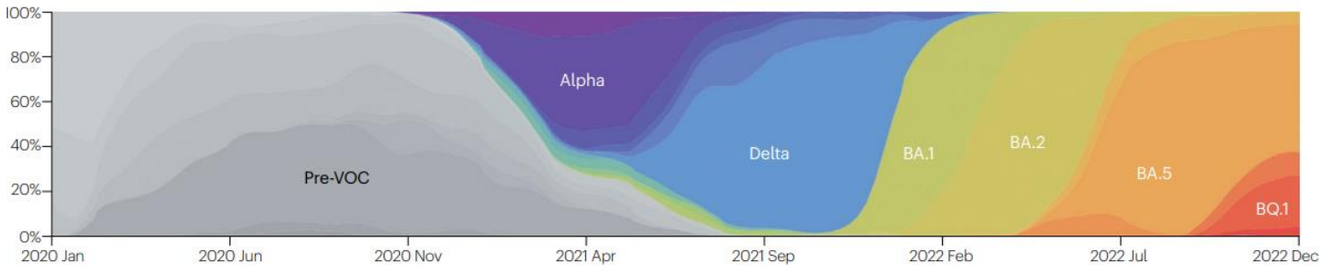
1. Children with emergency signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma or convulsions) should receive emergency airway management and oxygen therapy during resuscitation to target SpO_2 ≥ 94% [159] [128][130].
2. Once patient is stable, the target is > 90% SpO_2 [130].
3. Use of nasal prongs or nasal cannula is preferred in young children, as they may be better tolerated.

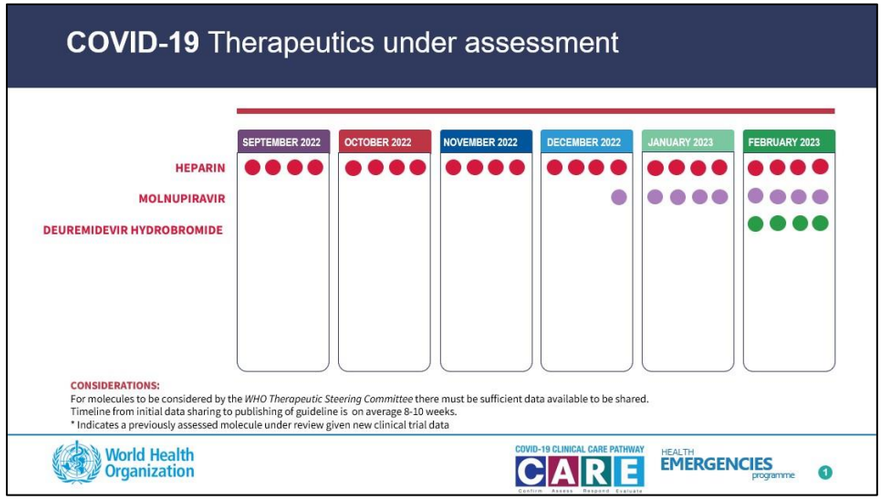
https://app.magicapp.org/#/guideline/6668

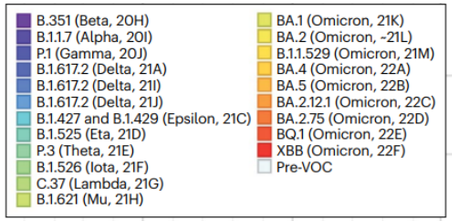
World Health Organization

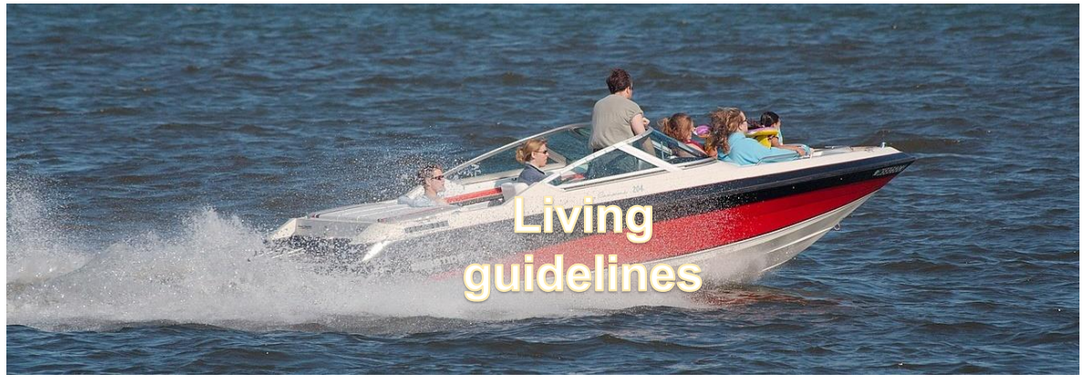
Medicines for the treatment of COVID-19

SARS-CoV-2 lineage prevalence









Cancer medicines on the EML

1977 — First WHO EML published
Six cancer medicines in total

1984 — First review of oncology

1995 — Second review
24 cancer medicines in total

1999 — Third review

2007 — First EMLc for paediatric cancers
22 cancer medicines added for EMLc

2015 — Fourth review (UICC)
First instance of targeted therapies and patented medicines listed on Model Lists
42 cancer medicines in total

2017 — EML Cancer Medicines Working Group established
44 cancer medicines in total

2019 — Major update of medicines recommended for childhood cancers
Trastuzumab prequalified by WHO as first biosimilar medicine
53 cancer medicines in total

2020 — Rituximab biosimilar prequalified

2021 — Three new and one therapeutic alternative, several new indications for children
62 cancer medicines in total

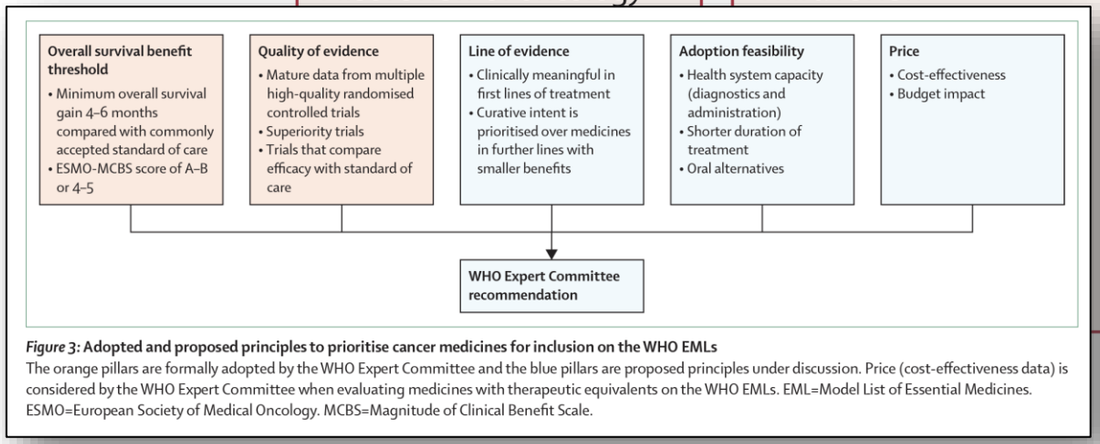


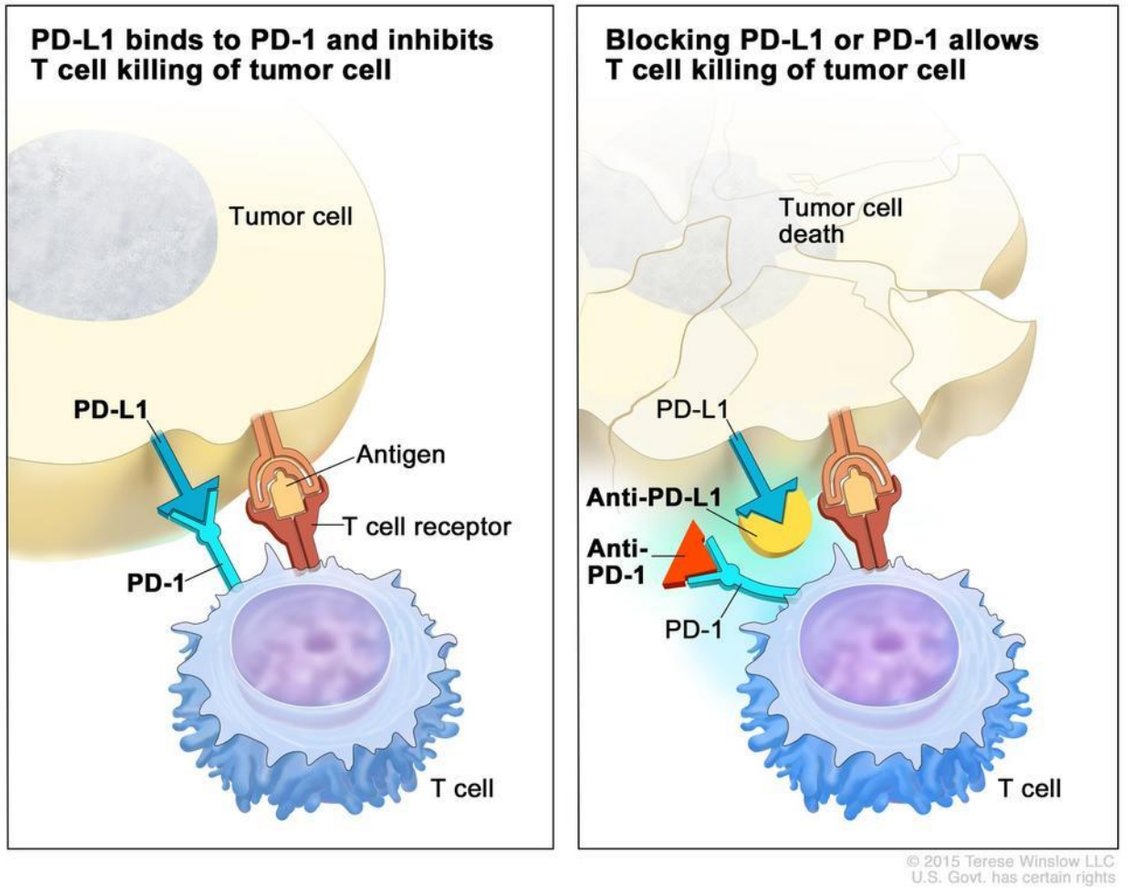
Figure 3: **Adopted and proposed principles to prioritise cancer medicines for inclusion on the WHO EMLs**
The orange pillars are formally adopted by the WHO Expert Committee and the blue pillars are proposed principles under discussion. Price (cost-effectiveness data) is considered by the WHO Expert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

Jenei et al. Lancet Glob Health. 2022 Dec;10(12):e1860-e1866.

World Health Organization

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

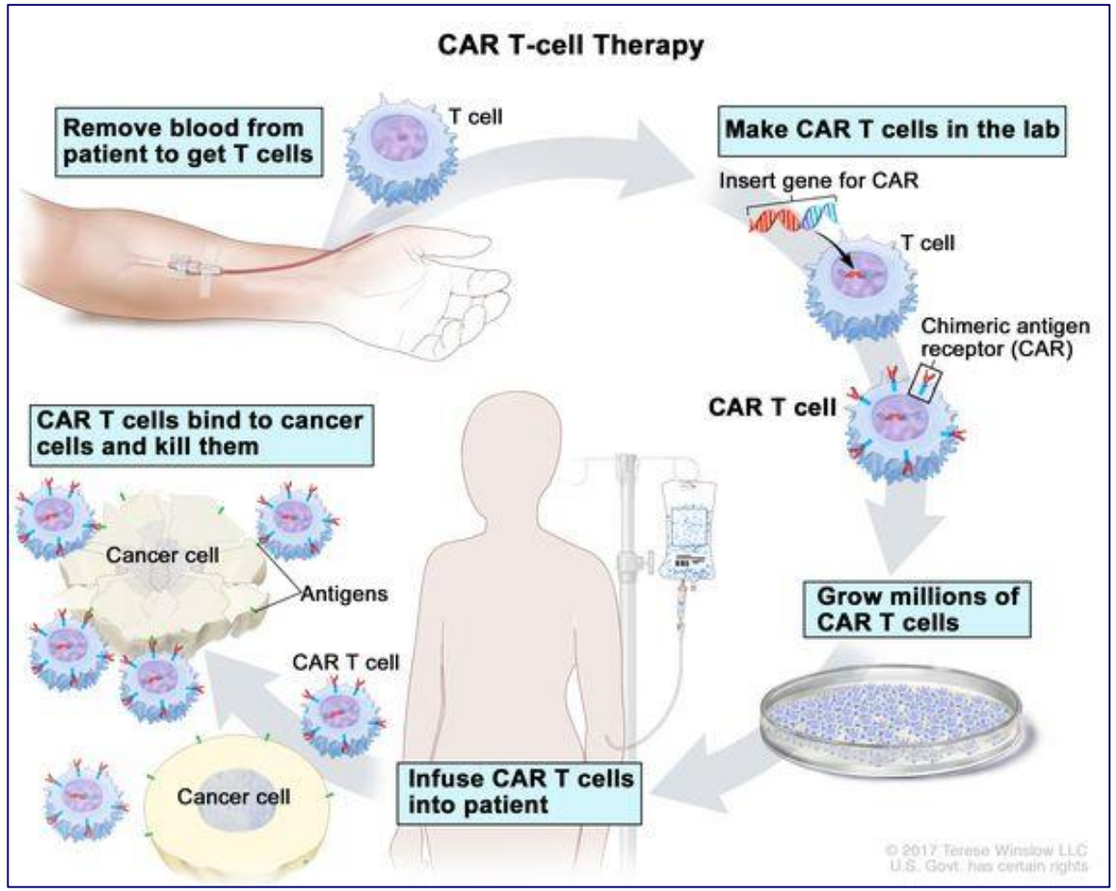
- Nivolumab (with pembrolizumab as alternative) added for melanoma in 2019
- Application for NSCLC rejected in 2019 and 2021
  - Partly because of “prohibitively high price”
- Since the first approval of ipilimumab in 2011 for melanoma
  - > 90 additional indications approved
  - > 11 different checkpoint 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”*



Johnson et al. N Engl J Med 2023; 388:1529-1532.

CAR-T cell treatment

Relapsed / refractory large B-cell lymphoma



https://www.cancer.gov/publications/dictionaries/cancer-terms/def/chimeric-antigen-receptor-t-cell-therapy

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

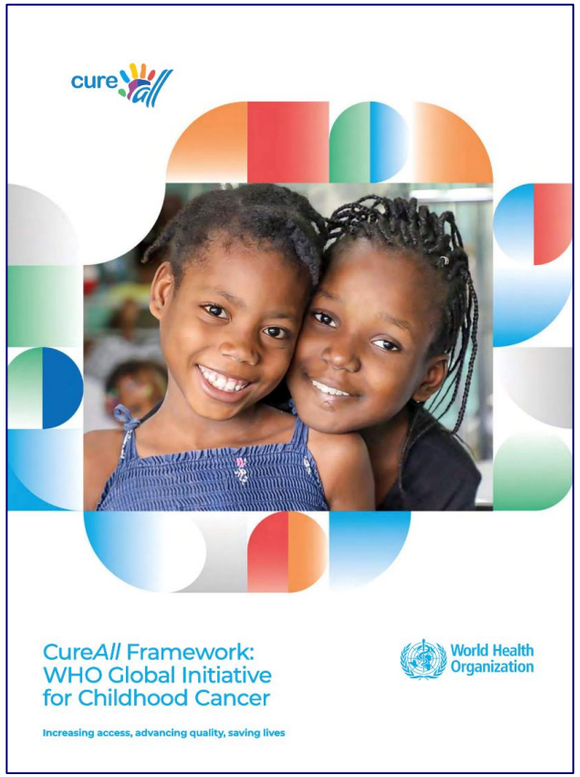
First patients of pioneering CAR T-cell therapy ‘cured of cancer’

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

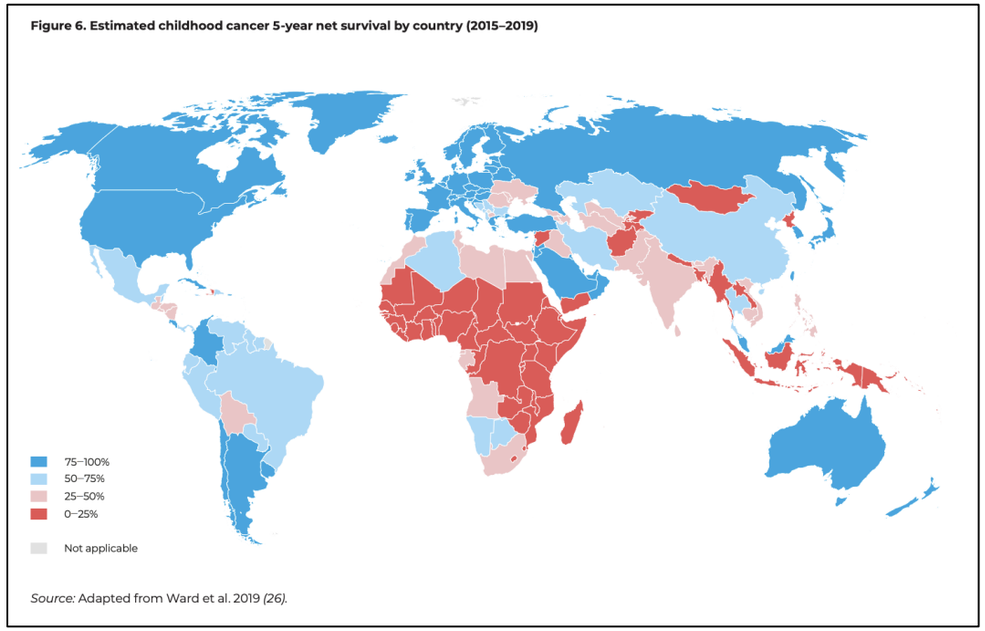
https://www.theguardian.com/society/2022/feb/02/first-patients-pioneering-car-t-cell-therapy-cured-of-cancer

World Health Organization

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://global.stjude.org/en-us/medicines.html
https://www.who.int/initiatives/the-global-initiative-for-childhood-cancer

Age-appropriateness of formulations of essential medicines for children – EMLc

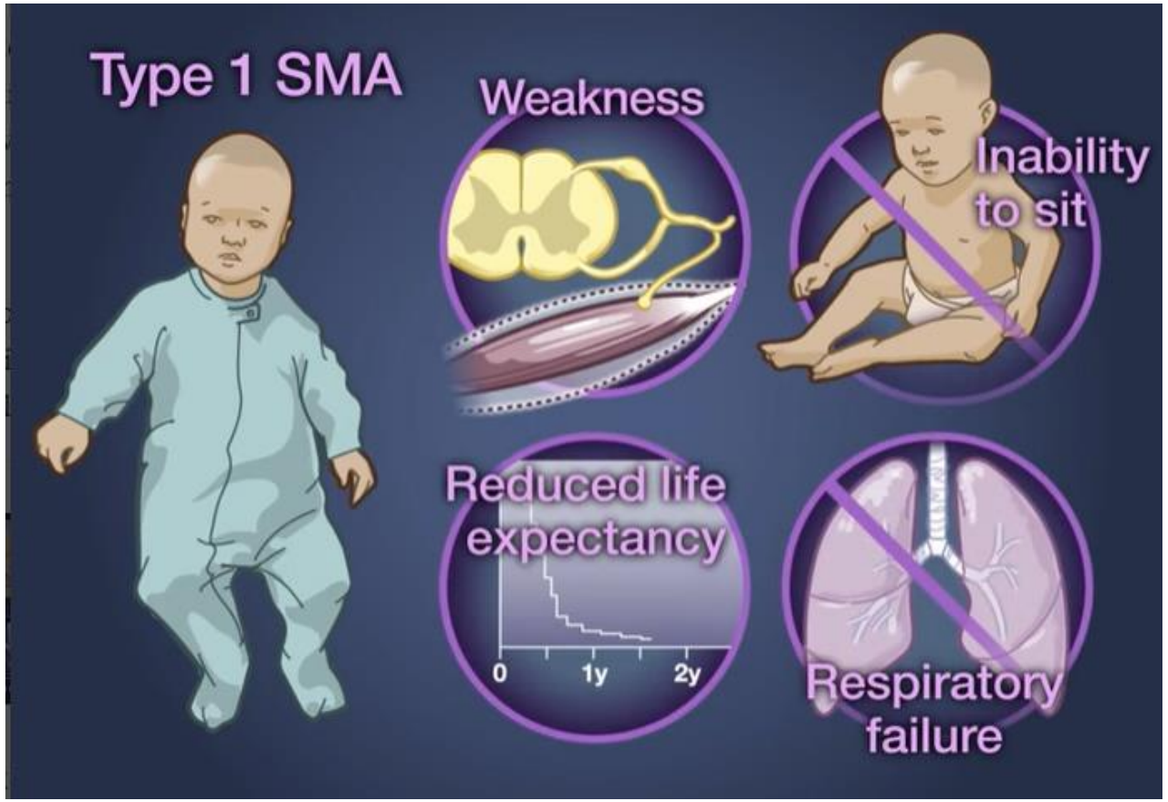
- Review of the age-appropriateness of formulations of medicines listed on the EMLc

- 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

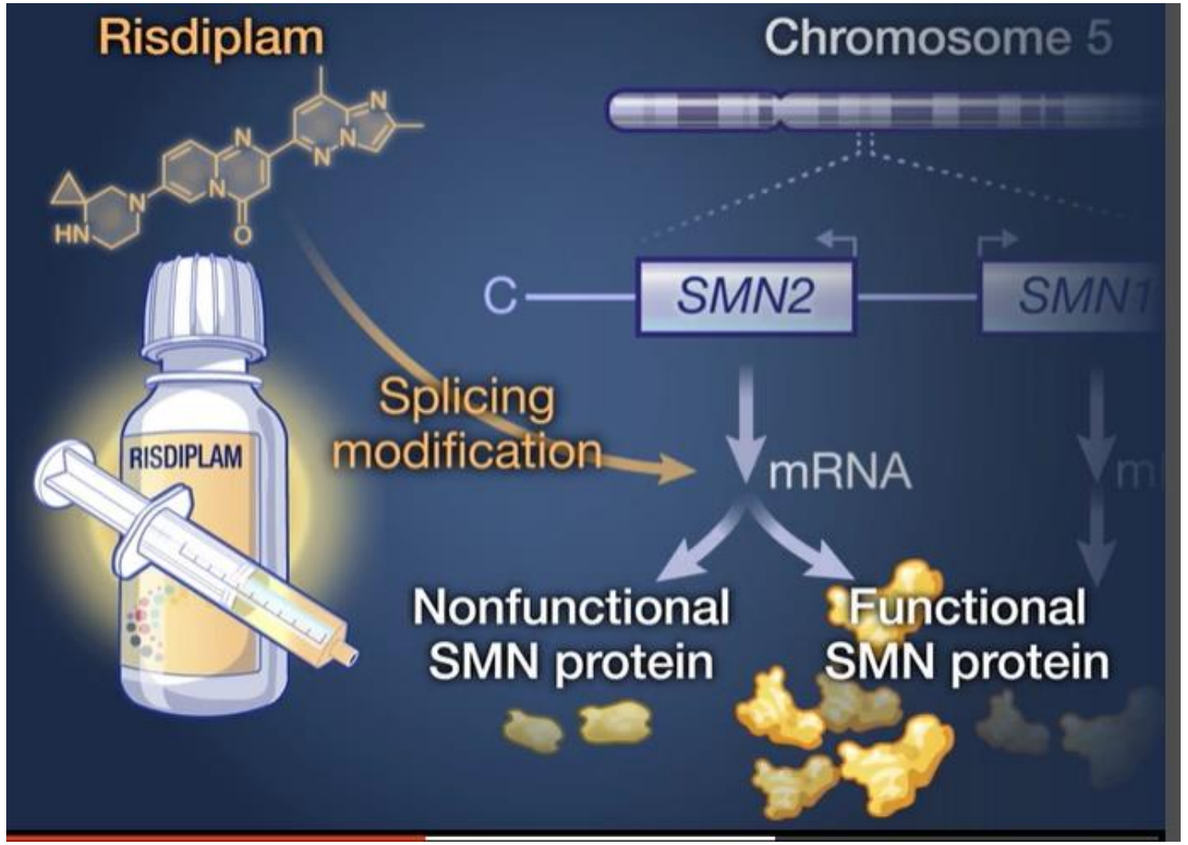


Baranello et al. N Engl J Med.2021 Mar 11;384(10):915-923.

World Health Organization

Risdiplam
Spinal Muscular Atrophy

- “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.”



Baranello et al. N Engl J Med.2021 Mar 11;384(10):915-923.

World Health Organization

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

Essential but unaffordable ?

Viewpoint

October 24, 2022

Reforming the World Health Organization's Essential Medicines List

Essential but Unaffordable

Thomas J. Hwang, MD[1,2]; Aaron S. Kesselheim, MD, JD, MPH[2]; Kerstin N. Vokinger, MD, JD, PhD[2,3]

» Author Affiliations

JAMA. 2022;328(18):1807-1808. doi:10.1001/jama.2022.19459

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.

Call for Experts: WHO Technical Advisory Group on Pricing Policies for Medicines

30 September 2022 | Call for experts

Serial No: 2022/September/76

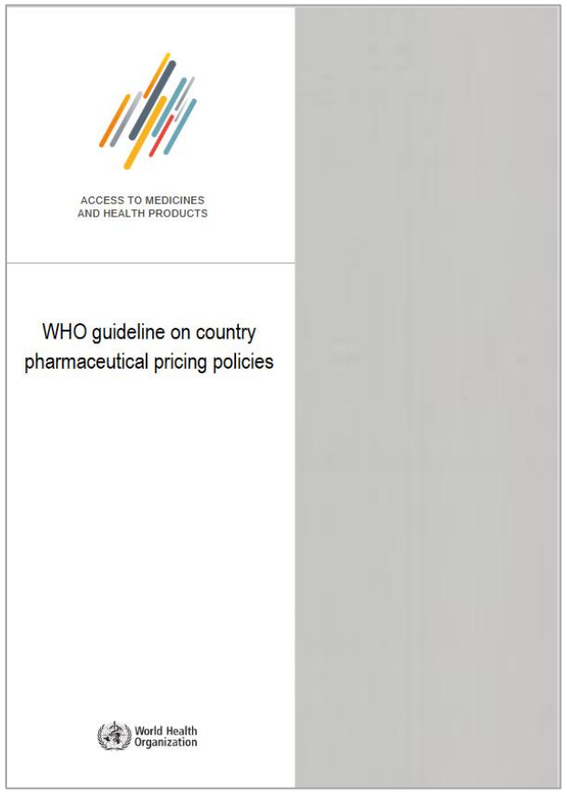
Issued on: 30 September 2022

EXTENDED DEADLINE: 13 March 2023

This open Call for Experts is being reissued to take account of the need for diverse perspectives from different regions, especially from low and middle-income countries, and for gender balance. If you have already submitted an application under this Call for Experts, there is no need to re-apply.

The World Health Organization (WHO) is seeking experts to serve as members of the Technical Advisory Group on Pricing Policies for Medicines. This "Call for experts" provides information about the advisory group in question, the expert profiles being sought, the process to express interest, and the process of selection.

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



https://www.who.int/publications/i/item/9789240011878

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"

Off-label use & EML

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.

The Selection and Use of Essential Medicines Report of the 20th WHO Expert Committee (2015)

IFPMA

STATEMENT

IFPMA's comment on off-label use in the context of the WHO's Model List of Essential Medicines

07 APRIL 2023, GENEVA – IFPMA recognizes the importance of the WHO EML in the global health context. The increasing number of products placed on the EML demonstrates the critical role played by the biopharmaceutical industry in creating therapies that are safe, efficacious and essential in reaching the UN Sustainable Development Goals, chief amongst them achieving universal health coverage.

However, we would like to express our concern with what we consider to be a misuse of the WHO's Square Box Symbol (SqB). While IFPMA supports the revised methodology for a clearer and consistent use of the SqB, extra caution is needed when using this tool to list medicines for off label use. In particular, **the use of products that have been reviewed and approved by regulatory authorities for a certain indication should be prioritized over the use of off-label products for the same indication. Whilst marketing authorization holders do not recommend off-label use when a regulatory approved treatment for that same indication exists, if a treatment is listed on the EML for an off-label indication, this caveat should be clearly indicated in the EML to enable countries, patients and healthcare professionals to make an informed decision about their use.**

IFPMA strongly believes that regulatory approval(s) for a given indication is the best indicator (and a requirement at national level) that a medicine has enough data on quality, efficacy and safety to support its clinical use. For innovative medicines in particular, data submitted to national regulatory authorities for the purpose of granting marketing authorization and life cycle management is often the most detailed source of information regarding these products' safety and efficacy. By listing medicines that have not been approved by a regulatory authority for a given indication, decision-makers may be encouraged to choose medicines that may not be adapted to local healthcare systems' capabilities or that may not be supported by adequate regulatory oversight (e.g. insufficient establishment of safety and effectiveness, adverse events management and traceability…). This practice could lead to negative outcomes for patients and health systems in general.

The square box system must be used adequately to ensure patients receive the most appropriate and effective medicines wherever they live. We urge the WHO Expert Committee to prevent any precedent-setting whereby the square box system in the WHO EML is misused and inconsistent with the organization's values, principles and guidelines, which ultimately bears the risk of undermining

Chemin des Mines 9
1202 Geneva
Switzerland

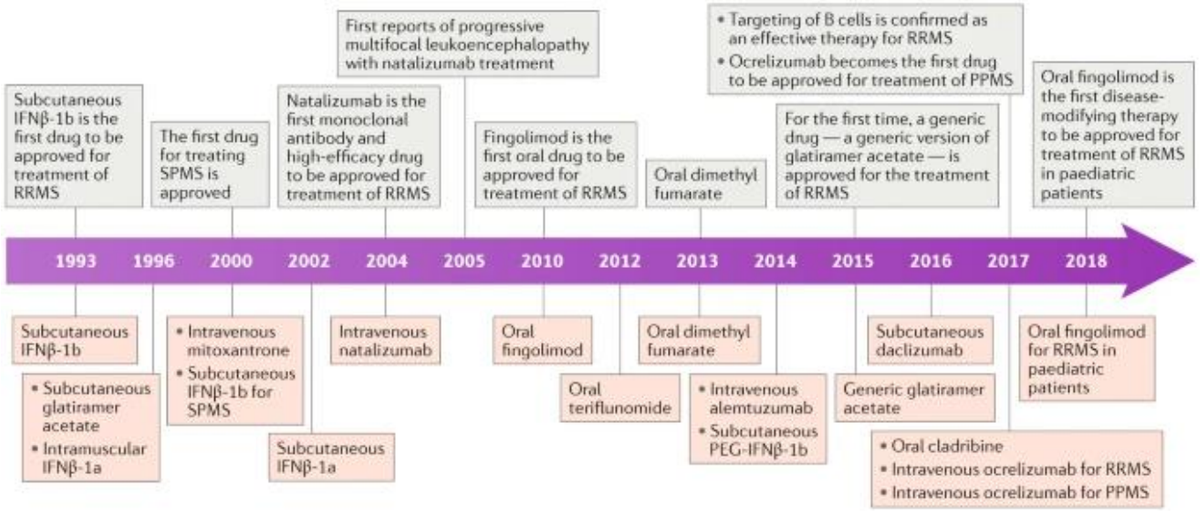
+41 22 338 32 00
info@ifpma.org
ifpma.org

@IFPMA
/IFPMA

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



Lancet Neurol. 2019 May;18(5):459-480.
Tintore et al. Nat Rev Neurol. 2019 Jan;15(1):53-58.

Proposal for inclusion of multiple sclerosis disease-modifying therapies (DMTs) on the complementary WHO Model Lists of Essential Medicines

Applicant:
Multiple Sclerosis International Federation (MSIF)

All DMTs identified in relation to MS

Alemtuzumab	Immunoglobulin	Natalizumab
Azathioprine	Interferon beta-1a	Ocrelizumab
Cladribine	Interferon beta-1b	Ofatumumab
Cyclophosphamide	Laquinimod	Ozanimod
Daclizumab	Leflunomide	PEG interferon beta-1a
Dimethyl fumarate	Methotrexate	Ponesimod
Diroximel fumarate	Minocycline	Rituximab
Fingolimod	Mitoxantrone	Siponimod
Fludarabine	Monomethyl fumarate	Steroid
Glatiramer acetate	Mycophenolate mofetil	Teriflunomide

DMTs shortlisted

Cladribine
Rituximab / Ocrelizumab
Dimethyl fumarate
Fingolimod
Interferon beta 1b / Interferon beta 1a
Glatiramer acetate

Final selection of DMTs

Cladribine
☐ Rituximab / *Ocrelizumab*
Glatiramer acetate

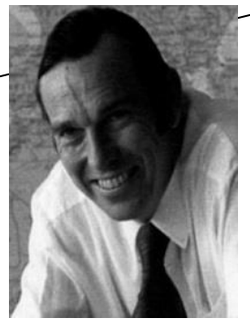
World Health Organization

Appropriate use of essential medicines

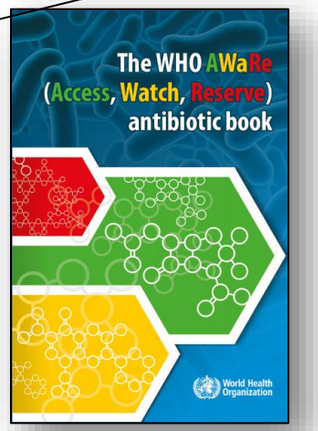
- It is not enough that essential medicines are available and affordable
  - They must be used appropriately

In a report [1] 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"



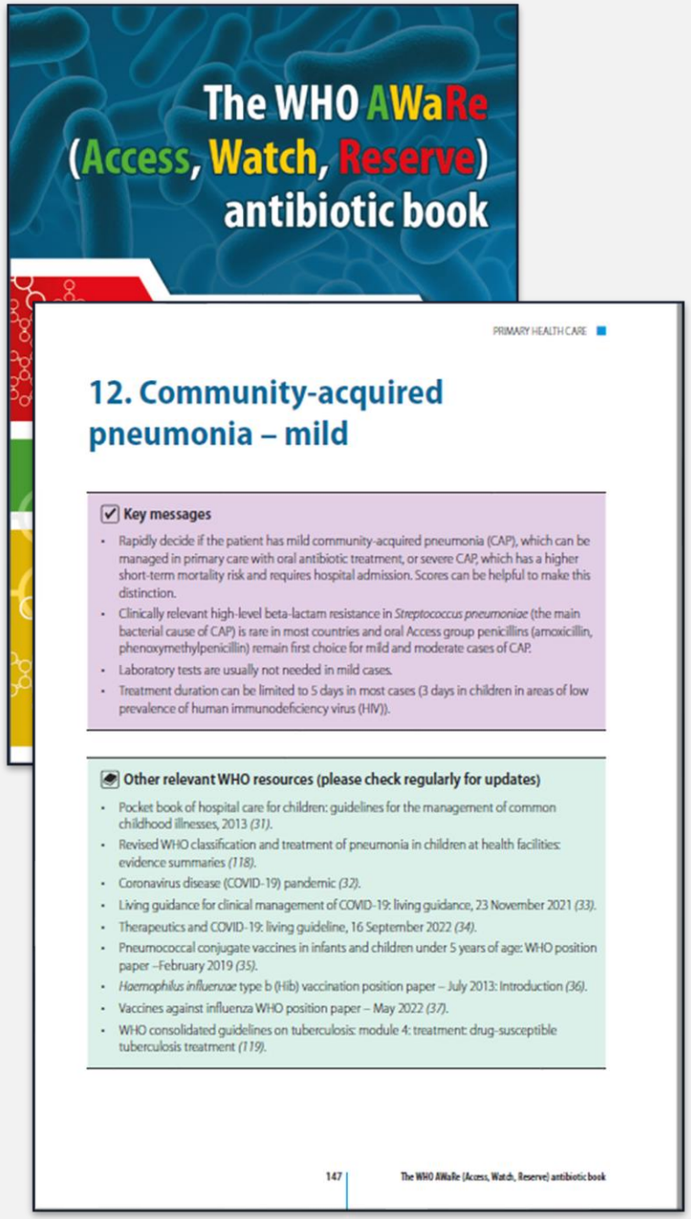
Dr Halfdan Mahler
(WHO DG 1973-1988)



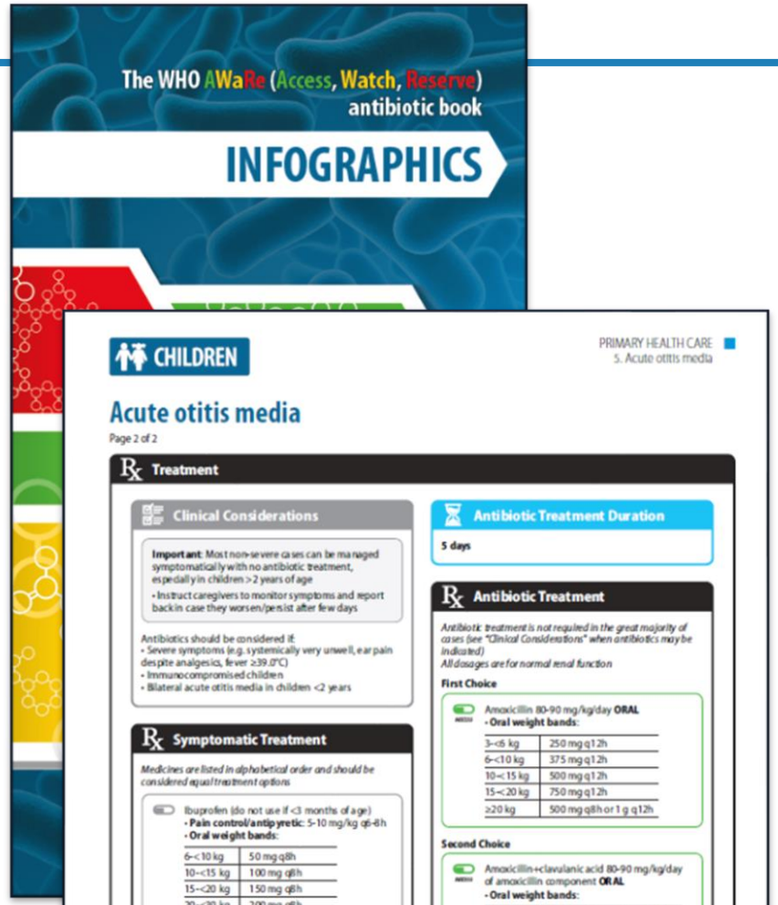
Several applications for addition of new Reserve antibiotics and one old antibiotic with activity against resistant pathogens

World Health Organization

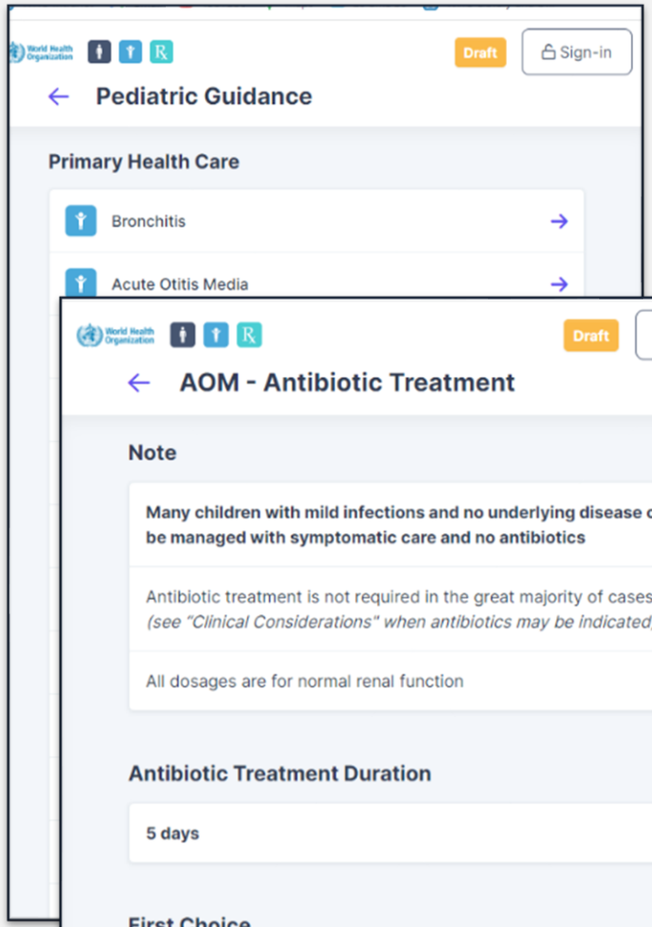
(1) Book



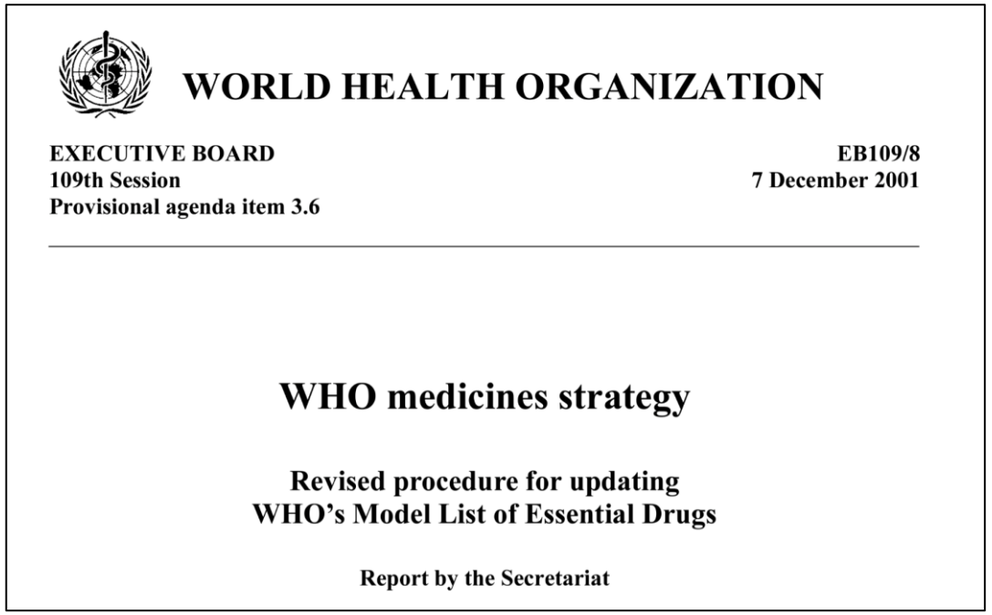
(2) Infographics



(3) App



WHO medicines strategy: revised procedure for updating WHO's Model List of Essential Drugs



WORLD HEALTH ORGANIZATION

EXECUTIVE BOARD
109th Session
Provisional agenda item 3.6

EB109/8
7 December 2001

WHO medicines strategy

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

Report by the Secretariat

- 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

Executive Board 109th session

Thank you !

Bernadette CAPPELLO

Elleanie TEWOLDE

Lorenzo MOJA

Jimmy ODONGO

A big thank you to:

- Members of the working groups
- Expert committee members
- Consultants working with the EML team
- WHO colleagues from within the department and outside
- Teams preparing applications
- …

Veronica ZANICHELLI

Kristina JENEI

Jenny WALSH

Tiziana MASINI

World Health Organization