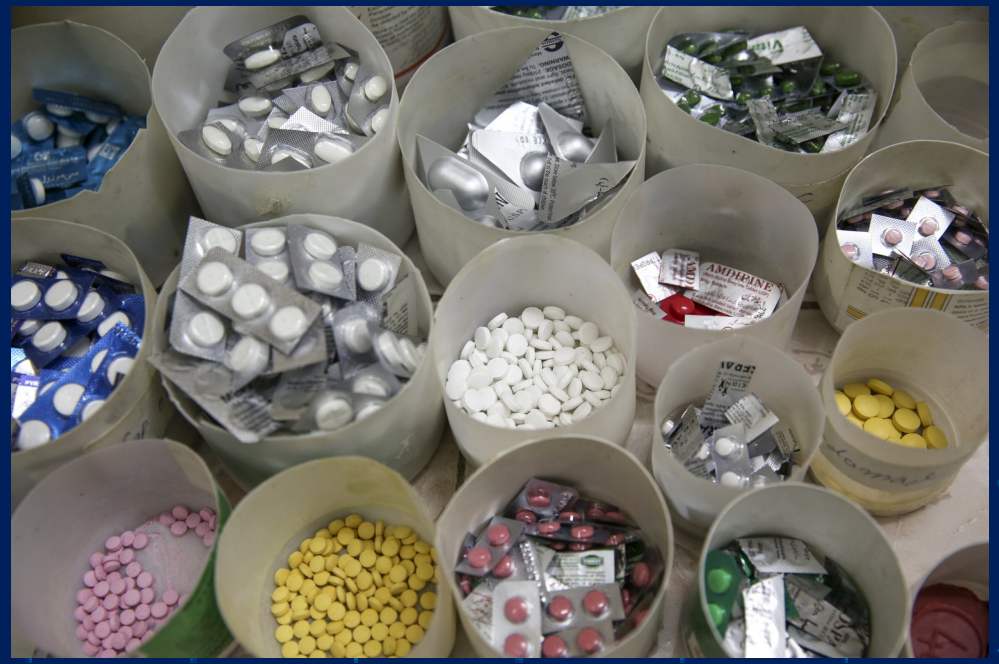
# The WHO Model List of Essential Medicines

## An evidence-based tool to support selection of essential medicines at the national level and improve access



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Technical Officer, Essential Medicines
Department of Health Products Policy & Standards

World Health Organization

INN, EML, ATC and DDD training day, 3 April 2025
Instituto de Salud Pública de Chile, Santiago, Chile

# Personal background:

- Pharmacist, MPH
- WHO Essential Medicines team since 2014, after working as a clinical pharmacist, and with the Australian Government in the evaluation of medicines for the national medicine reimbursement scheme

Canberra, AU

Geneva, CH

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# Essential medicines – WHO definition:

- ✓ Satisfy the priority health care needs of the population
- ✓ Should be available within functioning health systems at all times, in adequate amounts, in appropriate dosage forms, assured quality, and at affordable prices for individuals and the community
- ✓ Selected considering disease prevalence / public health relevance, evidence of efficacy and safety, comparative cost and cost-effectiveness, and other relevant factors

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# Essential medicines concept:

- ✓ A limited range of carefully selected medicines leads to better health care, better medicines management and lower costs
- ✓ Accepted as a powerful means to promote health equity and achieve universal health coverage
- ✓ Incorporates the need to regularly update medicines selection to reflect new therapeutic options and changing therapeutic needs

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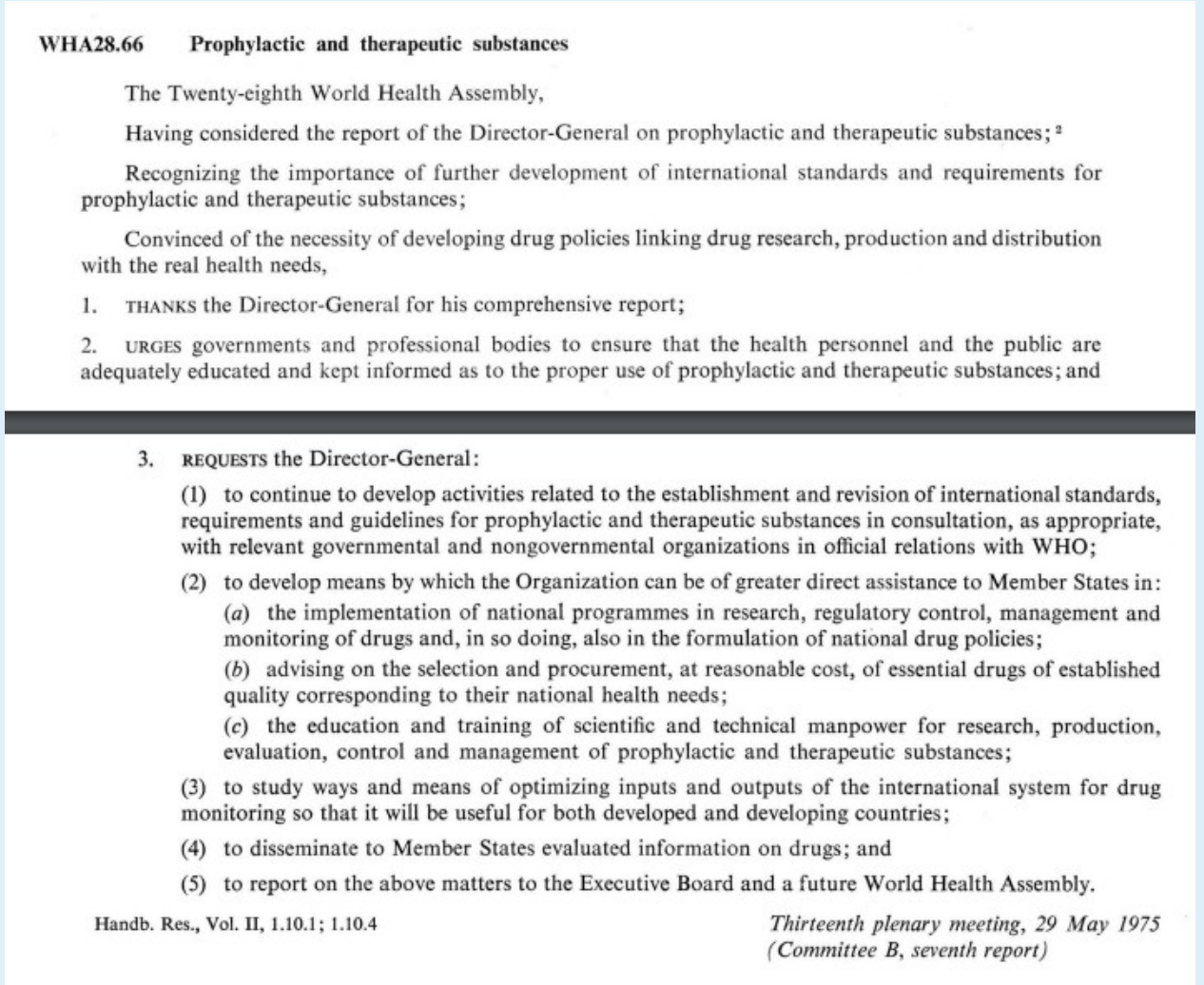
# 50 years of the essential medicines concept:

28th WHA 1975 – essential medicines mandate:

*"..develop means by which the Organization can be of greater direct assistance to Member States in … advising on the selection and procurement, at reasonable cost, of essential drugs of established quality corresponding to their national health needs"*



**WHA28.66 Prophylactic and therapeutic substances**

The Twenty-eighth World Health Assembly,

Having considered the report of the Director-General on prophylactic and therapeutic substances;[2]

Recognizing the importance of further development of international standards and requirements for prophylactic and therapeutic substances;

Convinced of the necessity of developing drug policies linking drug research, production and distribution with the real health needs,

1. THANKS the Director-General for his comprehensive report;

2. URGES governments and professional bodies to ensure that the health personnel and the public are adequately educated and kept informed as to the proper use of prophylactic and therapeutic substances; and

3. REQUESTS the Director-General:

(1) to continue to develop activities related to the establishment and revision of international standards, requirements and guidelines for prophylactic and therapeutic substances in consultation, as appropriate, with relevant governmental and nongovernmental organizations in official relations with WHO;

(2) to develop means by which the Organization can be of greater direct assistance to Member States in:

(*a*) the implementation of national programmes in research, regulatory control, management and monitoring of drugs and, in so doing, also in the formulation of national drug policies;

(*b*) advising on the selection and procurement, at reasonable cost, of essential drugs of established quality corresponding to their national health needs;

(*c*) the education and training of scientific and technical manpower for research, production, evaluation, control and management of prophylactic and therapeutic substances;

(3) to study ways and means of optimizing inputs and outputs of the international system for drug monitoring so that it will be useful for both developed and developing countries;

(4) to disseminate to Member States evaluated information on drugs; and

(5) to report on the above matters to the Executive Board and a future World Health Assembly.

Handb. Res., Vol. II, 1.10.1; 1.10.4

*Thirteenth plenary meeting, 29 May 1975*
*(Committee B, seventh report)*

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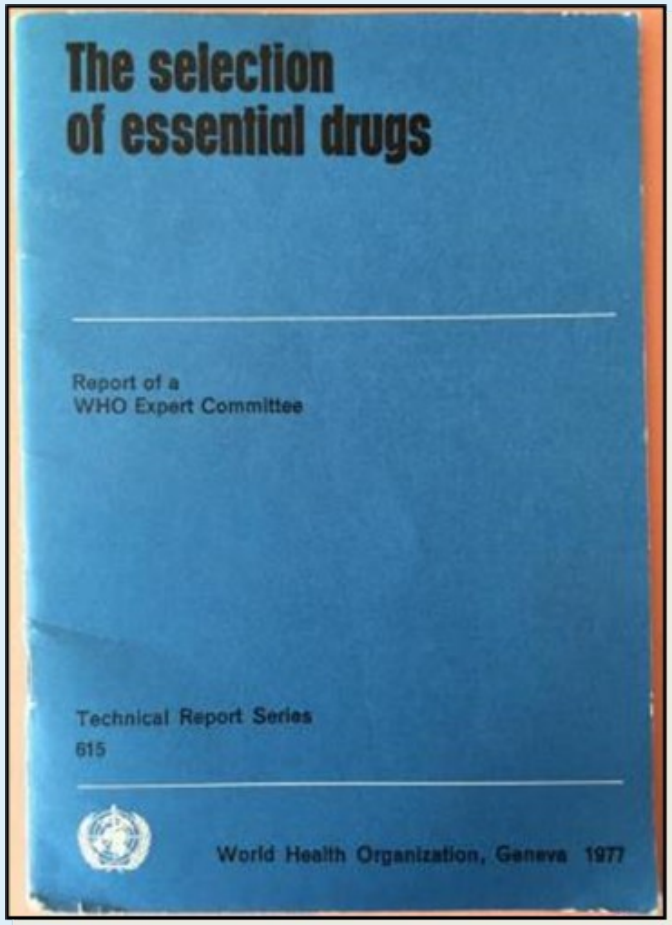
# WHO Model Lists of Essential [Drugs] Medicines

- First published in 1977, containing 208 medicines
- Introduced the idea that “some medicines are more important than others”
- Complemented in 2007 by the Model List of Essential Medicines for Children
- In 2023: 502 and 361 medicines on EML and EMLc, respectively

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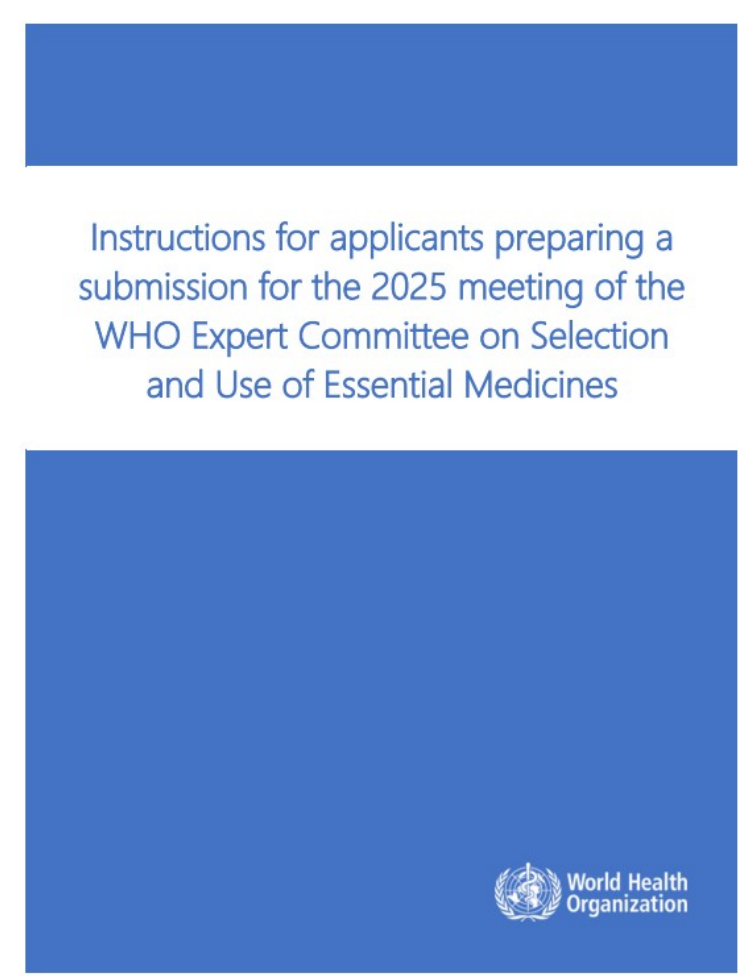
# The WHO Model Lists of Essential Medicines:

The primary purpose of the WHO Model Lists is to provide a blueprint for national or regional authorities to adopt or adapt in accordance with local priorities and treatment guidelines for the development and updating of national EMLs.

# WHO EML update process:

- Updated every 2 years by a multi-disciplinary WHO Expert Committee
- Established, transparent, evidence-based process
- Application driven, with stringent information and evidence requirements

  - ✓ Details of the medicine(s) – INN, ATC code, dosage form(s) and strength(s)
  - ✓ Indication
  - ✓ Public health relevance / burden of disease
  - ✓ Treatment details / requirements
  - ✓ Clinical evidence for benefits & harms
  - ✓ Cost / cost-effectiveness / budget impact
  - ✓ Regulatory status / market availability

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# Applications (>2001)

- May be submitted by anybody – academic/research institutions, WHO technical units, WHO collaborating centres, pharmaceutical companies, procurement agencies, NGOs, patient organizations, individuals…
- Defined information and evidence requirements
- Subject to internal, expert and public review
- Everything published on WHO website → TRANSPARENCY

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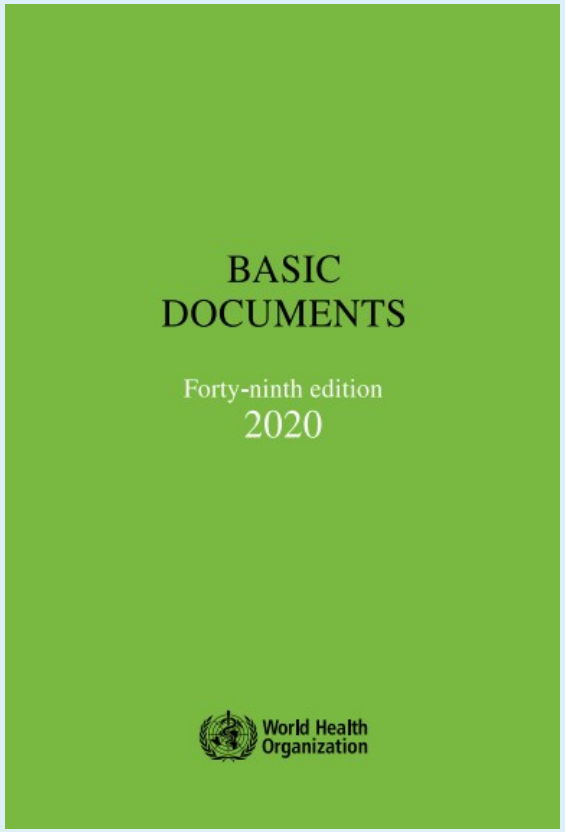
# WHO EML update process:




https://apps.who.int/gb/bd/

## Governance

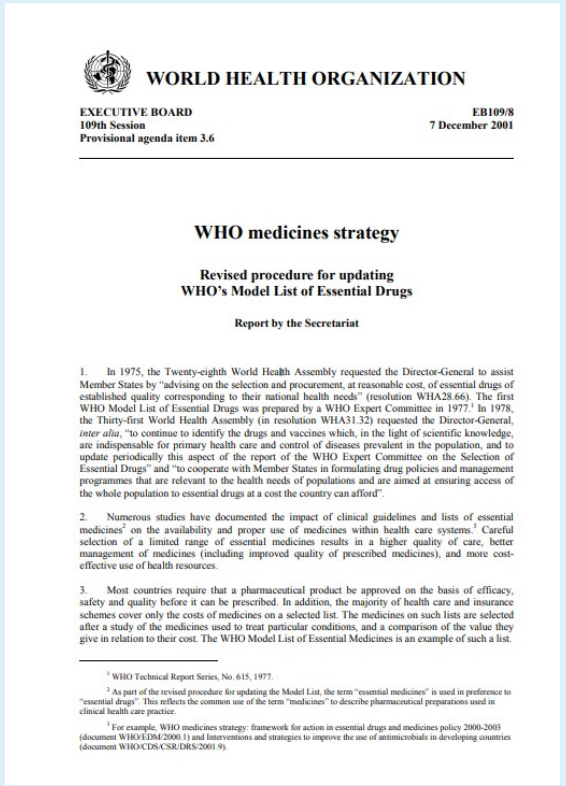
Regulations for expert advisory panels and committees

Rules of procedure for expert committees

Reported as part of WHO's Technical Report Series

## Procedures

- Revised in 2001 and endorsed by the Executive Board (EB109/8)



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**

1. In 1975, the Twenty-eighth World Health Assembly requested the Director-General to assist Member States by "advising on the selection and procurement, at reasonable cost, of essential drugs of established quality corresponding to their national health needs" (resolution WHA28.66). The first WHO Model List of Essential Drugs was prepared by a WHO Expert Committee in 1977.[1] In 1978, the Thirty-first World Health Assembly (in resolution WHA31.32) requested the Director-General, *inter alia*, "to continue to identify the drugs and vaccines which, in the light of scientific knowledge, are indispensable for primary health care and control of diseases prevalent in the population, and to update periodically this aspect of the report of the WHO Expert Committee on the Selection of Essential Drugs" and "to cooperate with Member States in formulating drug policies and management programmes that are relevant to the health needs of populations and are aimed at ensuring access of the whole population to essential drugs at a cost the country can afford".

2. Numerous studies have documented the impact of clinical guidelines and lists of essential medicines[2] on the availability and proper use of medicines within health care systems.[3] Careful selection of a limited range of essential medicines results in a higher quality of care, better management of medicines (including improved quality of prescribed medicines), and more cost-effective use of health resources.

3. Most countries require that a pharmaceutical product be approved on the basis of efficacy, safety and quality before it can be prescribed. In addition, the majority of health care and insurance schemes cover only the costs of medicines on a selected list. The medicines on such lists are selected after a study of the medicines used to treat particular conditions, and a comparison of the value they give in relation to their cost. The WHO Model List of Essential Medicines is an example of such a list.

[1] WHO Technical Report Series, No. 615, 1977.

[2] As part of the revised procedure for updating the Model List, the term "essential medicines" is used in preference to "essential drugs". This reflects the common use of the term "medicines" to describe pharmaceutical preparations used in clinical health care practice.

[3] For example, WHO medicines strategy: framework for action in essential drugs and medicines policy 2000-2003 (document WHO/EDM/2000.1) and Interventions and strategies to improve the use of antimicrobials in developing countries (document WHO/CDS/CSR/DRS/2001.9).

https://apps.who.int/gb/ebwha/pdf_files/EB109/eeb1098.pdf

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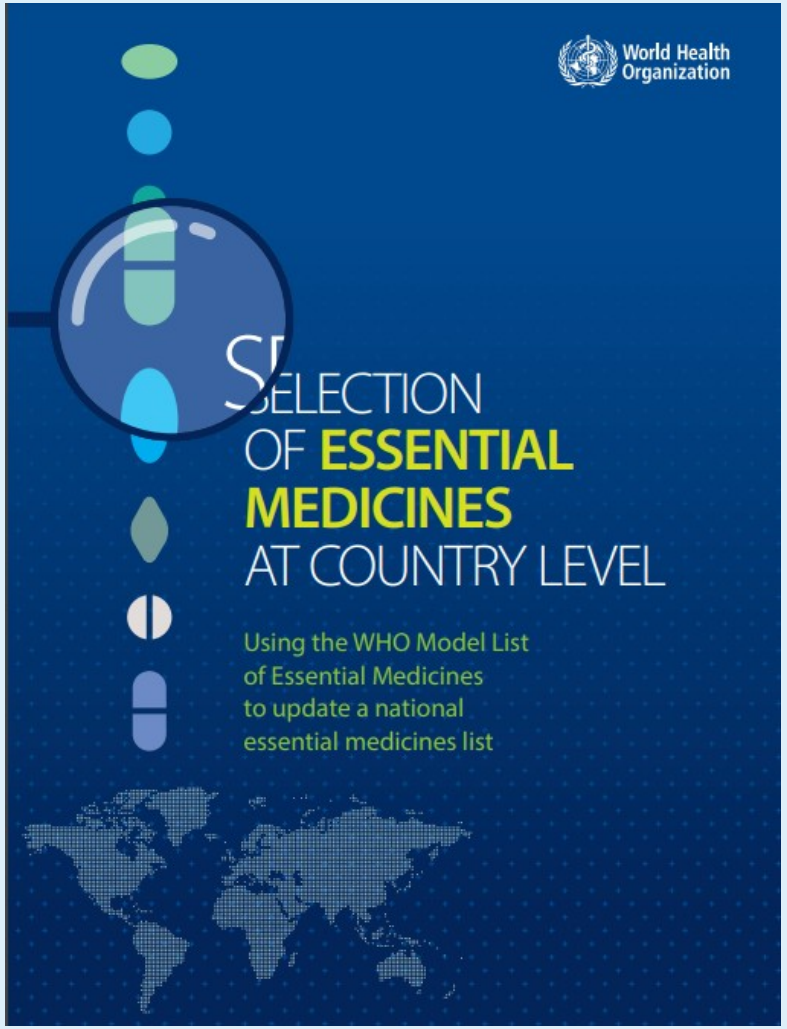
# The WHO Model List and national EMLs:

How can essential medicines evaluation by WHO assist countries in national selection?

- *When a medicine is listed on the Model List, it becomes a priority for access and reimbursement*
- *A recommendation NOT to include a medicine on the Model List should also have implications at country level*




https://www.who.int/publications/i/item/9789241515443

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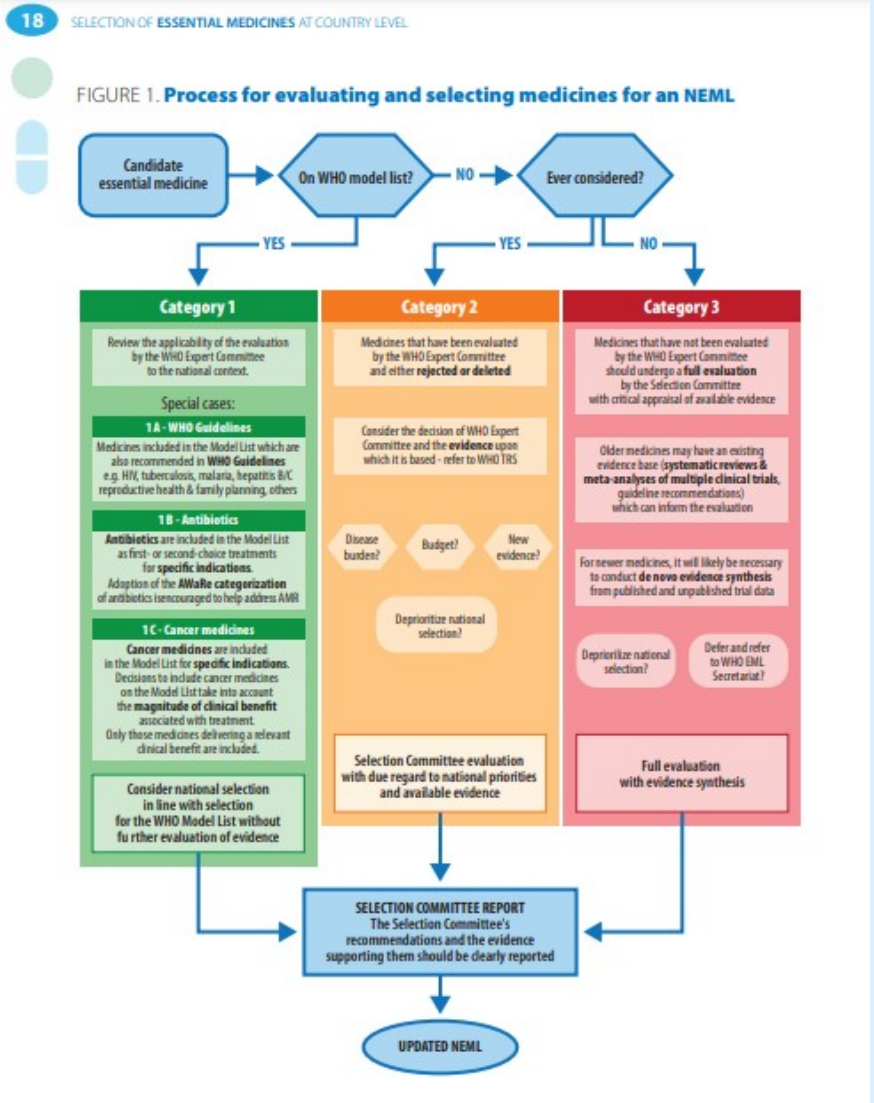
# The WHO Model List and national EMLs:

Consider 3 categories:

1. Medicines already included on the WHO Model List
2. Medicines evaluated by WHO and either not recommended or removed from the Model List
3. Medicines not evaluated by WHO

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## Medicines already included on the WHO Model List

- Have already undergone full evaluation of the available evidence and have been determined by WHO to meet the criteria of 'essential'
- Could be considered for national selection without further evaluation of the clinical evidence
- National consideration of disease burden, national guidelines, budget impact, feasibility etc

## Medicines that have been evaluated by WHO and were not recommended or removed

- Have already undergone full evaluation of the available evidence and have been determined by WHO to **NOT** to meet the criteria of 'essential'
- Could be deprioritized for national selection ?
- May be considered for national selection if considered a priority, with evaluation of new evidence

## Medicines that have not been evaluated by WHO

- Require full evaluation and appraisal of available evidence
- May or may not necessitate de novo evidence synthesis
- Defer consideration and refer to WHO EML Secretariat ?

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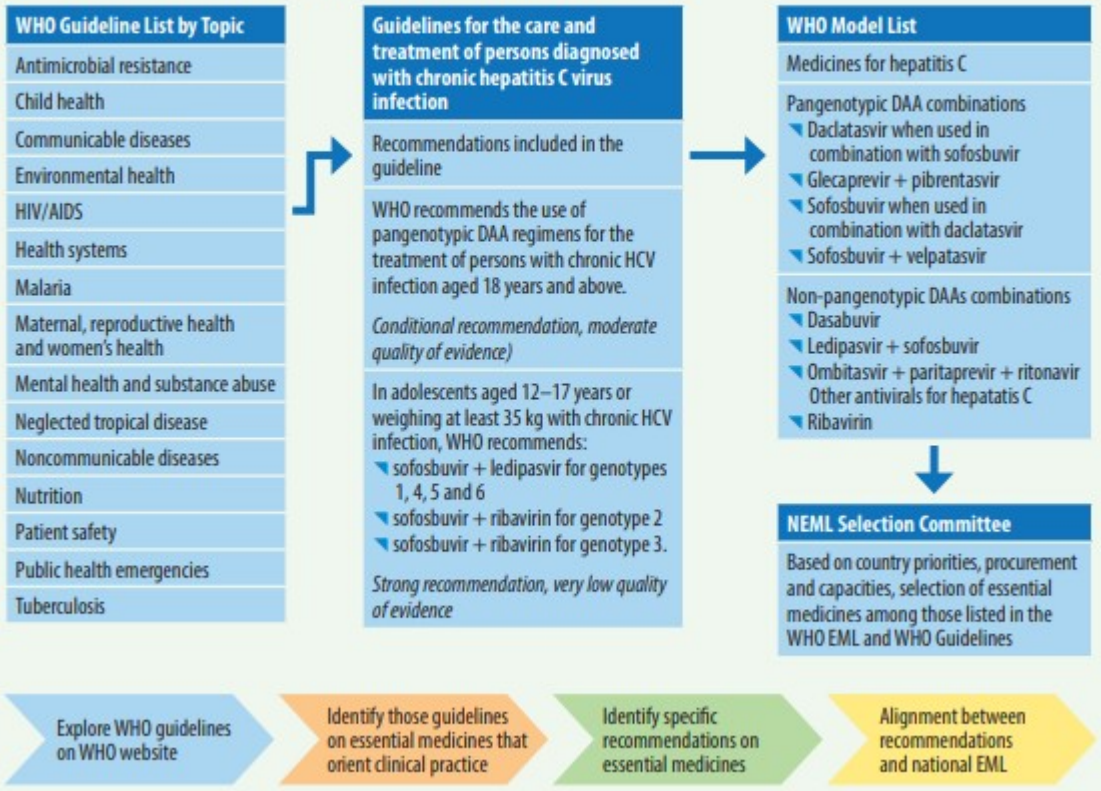
# WHO guidelines to support NEML selection

FIGURE 2. **Using WHO guidelines to support NEML selection**

Conceptual framework describing the interplay between the WHO Model List of Essential Medicines and WHO Guidelines: an example focused on direct-acting antivirals (DAAs) for hepatitis C.

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# When WHO guidelines are not available ?

E.g. cancer medicines

- Comprehensive review of cancer medicines on the WHO EML in 2015, prioritizing cancers with high incidence whose treatment results in meaningful survival benefit, and cancers (regardless of incidence) where the goal of treatment is cure/long-term remission.
- Guiding principles for inclusion of essential cancer medicines developed and adopted in 2019

→ Magnitude of clinical benefit

- Threshold for benefit of **at least 4-6 months survival gain**
- European Society of Medical Oncology Magnitude of Clinical Benefit Scale **(ESMO-MCBS) score** of A or B in the curative setting / 4 or 5 in the non-curative setting

→ **Most effective cancer medicines required to treat the most treatable cancers recommended as essential**

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# The principle of parsimony in EML selection

Markets are filled with thousands of medicines: many are similar pharmacological analogs (so-called "me-too drugs"), offering little, if any, additional clinical benefit in comparison. The expression "me-too" in the field of medicines was first introduced by Goodman in the 1950s and was popularized during the Golden Age of pharmacotherapy, when hundreds of new chemical entities were studied and eventually approved. Describing a medicine as a me-too has a double meaning, that of a "*market latecomer which often differs trivially from earlier products and that the billions of dollars spent marketing these me-too products could be spent in better ways*" (Lee, 2004) but also as medicines which "*may be useful when equivalent drugs can replace each other in the event of shortages*" (Aronson and Green, 2020).

It is thus important to have a mechanism to facilitate the selection of a limited number of essential medicines from the plethora of pharmaceuticals available on the global market. Controlling the number of medicines deemed essential will deliver both healthcare and economic advantages: to facilitate rational prescribing and use by providing more focused information, to enable better value procurement through tendering and competition leading to lower costs for individuals and health systems and to improve access (Hogerzeil, 2004).

https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2020.578000/full

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# The EML “square box” concept

- Some medicines on the EML are listed with a square box symbol (□), with specified therapeutic alternatives
- These medicines can be assumed to be therapeutically equivalent in terms of efficacy and safety
- Intended to signal to countries that they can select a medicine (or medicine(s)) from among a group of medicines to best suit local needs (based on availability and resources)
- No therapeutic advantage of one over the others → no justified price advantage ?

| | |
|---|---|
| **8. IMMUNOMODULATORS AND ANTINEOPLASTICS** | |
| **8.1 Immunomodulators for non-malignant disease** | |
| ***Complementary List*** | |
| □ *adalimumab** <br> *Therapeutic alternatives*:* <br> *- certolizumab pegol* <br> *- etanercept* <br> *- golimumab* <br> *- infliximab* <br> **including quality-assured biosimilars* | ***Injection:*** *10 mg/0.2 mL* ***[c]****; 20 mg/0.4 mL* ***[c];*** *40 mg/0.8 mL; 40 mg/0.4 mL.* |

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# Parsimony in the context of antimicrobial stewardship - AWaRe

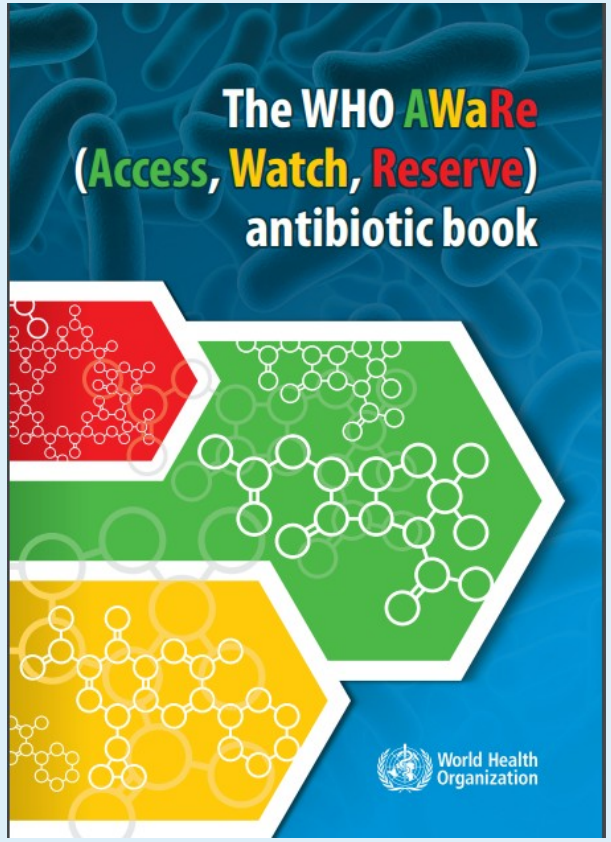
**Box 1.1 – Principles of the AWaRe framework**

- Maximizing clinical effectiveness
- Minimizing toxicity
- Minimizing unnecessary costs to patients and health care systems
- Reducing the emergence and spread of antibiotic resistance (i.e. prioritizing antibiotics that are less likely to lead to antibiotic resistance in an individual patient and the community)
- Parsimony (i.e. avoiding the inclusion of many similar antibiotics)
- Simplification (i.e. same Access antibiotic recommended for multiple indications)
- Alignment with existing WHO guidelines

WHO Access, Watch, Reserve (AWaRe) classification of antibiotics for evaluation and monitoring of use, 2023

This classification is intended to be used as a tool for countries to better support antibiotic monitoring and stewardship activities. It is not intended as model for the inclusion of antibiotics on national essential medicine lists. Antibiotics classified under AWaRe and also included on the WHO Model Lists of Essential Medicines are indicated in the worksheets.

| Antibiotic | Class | ATC code | Category | Listed on EML/EMLc 2023 |
|---|---|---|---|---|
| Cefacetrile | First-generation-cephalosporins | J01DB10 | Access | No |
| Cefadroxil | First-generation-cephalosporins | J01DB05 | Access | No |
| Cefalexin | First-generation-cephalosporins | J01DB01 | Access | Yes |
| Cefaloridine | First-generation-cephalosporins | J01DB02 | Access | No |
| Cefalotin | First-generation-cephalosporins | J01DB03 | Access | No |
| Cefapirin | First-generation-cephalosporins | J01DB08 | Access | No |
| Cefatrizine | First-generation-cephalosporins | J01DB07 | Access | No |
| Cefazedone | First-generation-cephalosporins | J01DB06 | Access | No |
| Cefazolin | First-generation-cephalosporins | J01DB04 | Access | Yes |
| Cefradine | First-generation-cephalosporins | J01DB09 | Access | No |
| Cefroxadine | First-generation-cephalosporins | J01DB11 | Access | No |
| Ceftezole | First-generation-cephalosporins | J01DB12 | Access | No |




The WHO AWaRe (access, watch, reserve) antibiotic book; 2022

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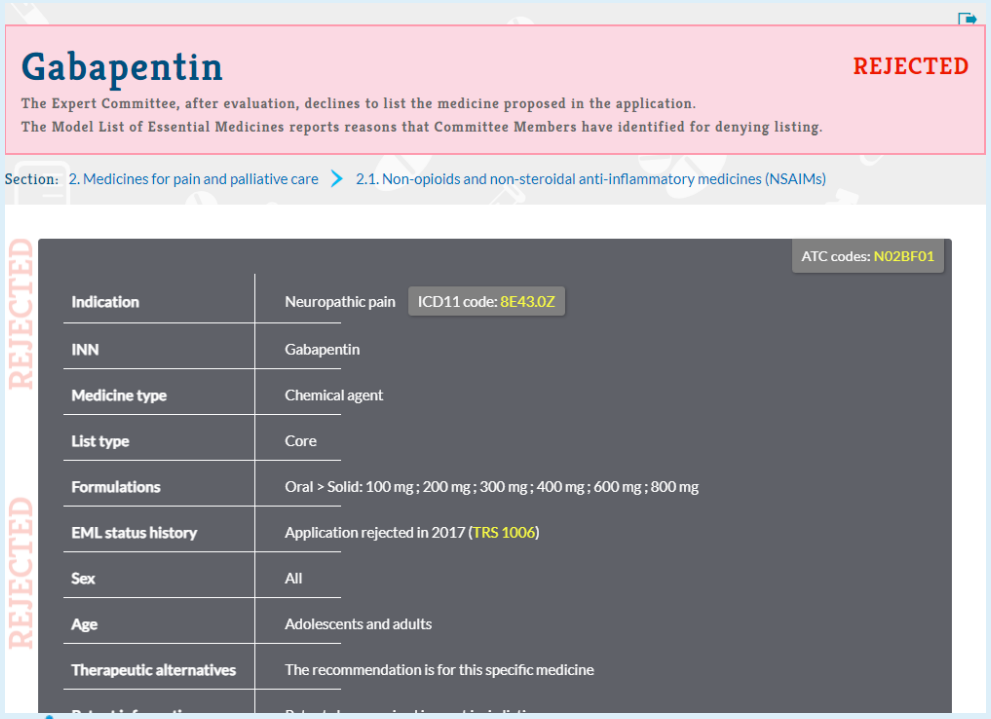
# Medicines not recommended or removed from WHO EML

- Evidence evaluated by WHO Expert Committee and determined NOT to meet the criteria of ‘essential’

**Deprioritize (or reconsider) for NEML ?**



## Gabapentin

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 2. Medicines for pain and palliative care > 2.1. Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)

REJECTED

ATC codes: N02BF01

| | |
|---|---|
| Indication | Neuropathic pain ICD11 code: 8E43.0Z |
| INN | Gabapentin |
| Medicine type | Chemical agent |
| List type | Core |
| Formulations | Oral > Solid: 100 mg ; 200 mg ; 300 mg ; 400 mg ; 600 mg ; 800 mg |
| EML status history | Application rejected in 2017 (TRS 1006) |
| Sex | All |
| Age | Adolescents and adults |
| Therapeutic alternatives | The recommendation is for this specific medicine |

REJECTED

2017: application for addition of gabapentin to the EML management of neuropathic pain (central and peripheral) in adults

Not recommended because of uncertainty in efficacy estimates as a result of publication and outcome reporting biases in the available evidence.

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# EML recommendations and improving access


THE WALL STREET JOURNAL. | PHARMALOT

$12 FOR 12 W

WSJ Pharmalot

RESEARCH & DEVELOPMENT | FDA | LITIGATION | PRICING & PATIENT ACCESS | CLINIC

11:49 am ET
May 8, 2015 CANCER

PREVIOUS
To What Extent Shoul Drug Maker be Allowe to Convey Off-Label Info?

WHO Adds Gilead Hepatitis C Drugs to its List of Essential Medicines

ARTICLE | COMMENTS (3)

SEARCH PHARMALOT

ABBVIE | CANCER | GILEAD SCIENCES | GLEEVEC | GLIVEC | HARVONI | HEPATITIS C

Email | Print | 135 | 122

By ED SILVERMAN

As the debate over the cost of prescription drugs accelerates, the World Health Organization has added several treatments for cancer and hepatitis C to its list of so-called essential medicines, which the agency believes should be made available at affordable prices.

The move comes amid growing friction between payers – both public and private – and the pharmaceutical industry over drug pricing. The addition by the WHO follows requests by consumer groups for the agency to widen its list to in latest treatments carrying high price tags.

Among the drugs added to the list are three hepatitis C treatments – Sov which are sold by Gilead Sciences , and the Viekira Pak medication sol


Health | Fri May 8, 2015 6:18am EDT

Related: HEALTH

WHO adds hepatitis C drugs to essential list, urges lower prices

LONDON

The World Health Organization (WHO) logo is pictured at the entrance of its headquarters in Geneva, January 25, 2015. REUTERS/PIERRE ALBOUY

The World Health Organization has added new curative treatments for hepatitis C to its essential medicines list, but the U.N. agency said prices needed to fall to make them accessible to patients in poorer countries.

The treatment of hepatitis C, which affects about 150 million people globally and kills around half a million each year, has been transformed by the arrival of new drugs, such as Gilead's Sovaldi.

These products can cure hepatitis C but are out of reach at Western prices to patients in

Microsoft Cloud

This cloud helps accelerate a cure for cancer.

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Home › Lifestyle › Health › 'Cancer treatment ain't just for the rich'

'Cancer treatment ain't just for the rich'

WHO added 16 new anti-cancer medicines to the model list of essential medicines (WHO EML) o

Written by Anuradha Mascarenhas
Updated: May 16, 2015, 9:34

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Written by Anuradha Mascarenhas | Updated: May 16, 2015 9:34 am

ABOUT AUTHOR

chewing – is the single most important factor which causes cancer.

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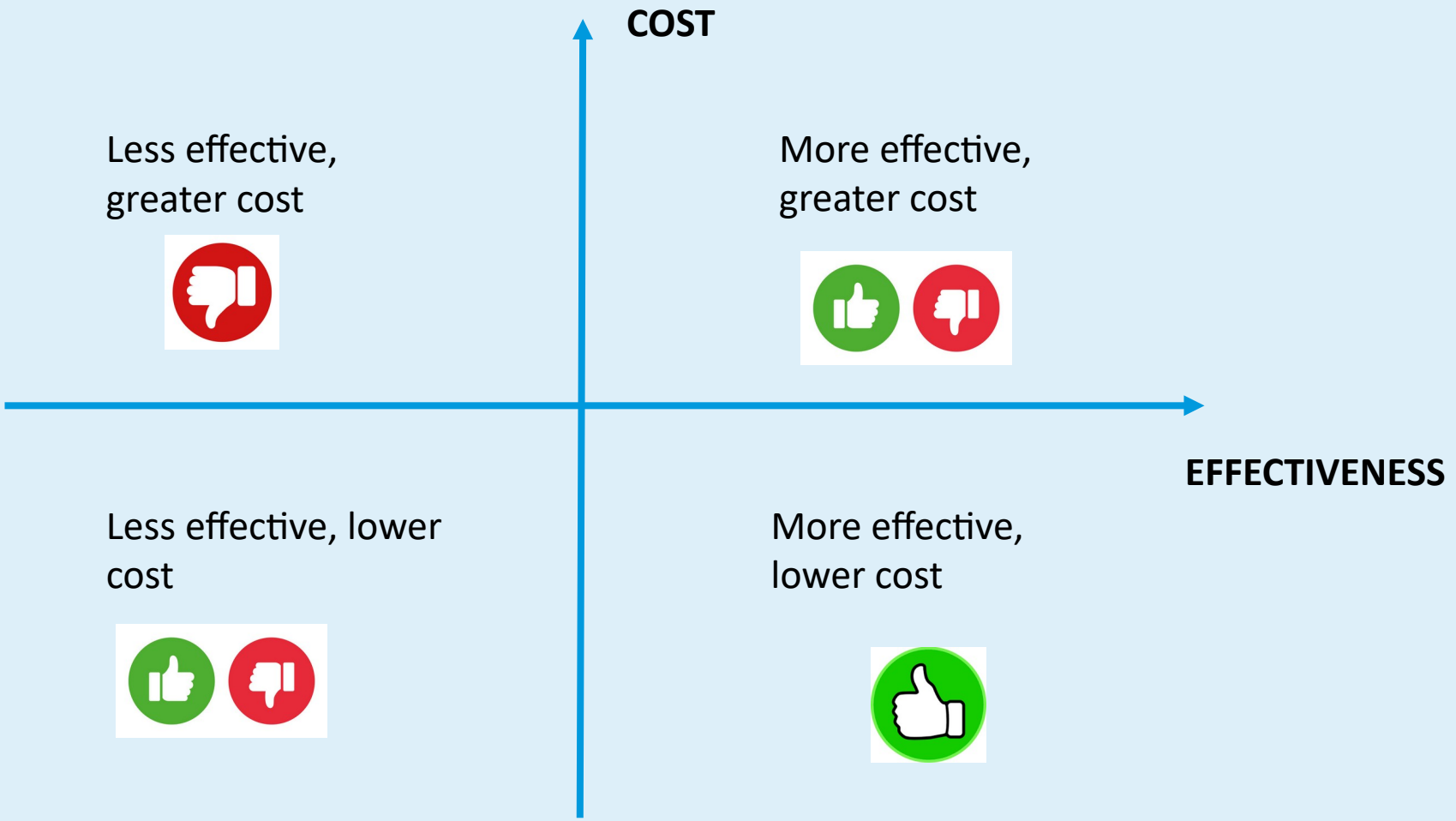
# Some decisions easier than others...

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*“When new effective medicines emerge to safely treat serious and widespread diseases, it is vital to ensure that everyone who needs them can obtain them. Placing them on the WHO Essential Medicines List is a first step in that direction.”*

*Dr Margaret Chan, former WHO Director General, May 2015*

# EML recommendations and improving access

Since the ‘first step’…..

- ✓ Prequalification by WHO (DAAs, rituximab, trastuzumab)
- ✓ Voluntary licensing agreements with Medicines Patent Pool (DAAs) for LMICs
- ✓ Increased competition, lower prices, greater access

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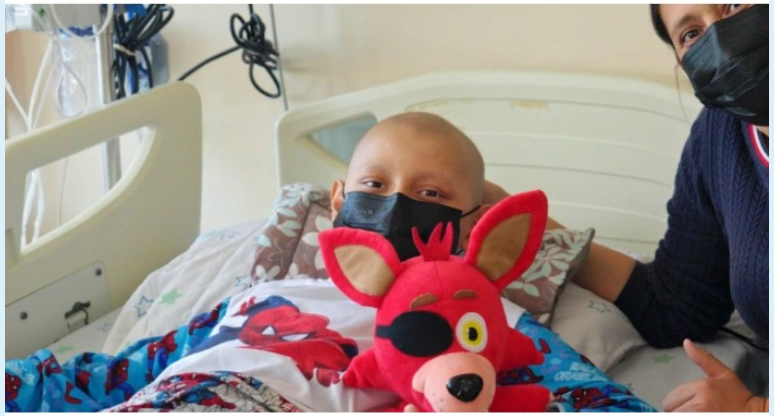
# EML recommendations and improving access

## WHO's Global platform for access to childhood cancer medicines

- Partnership with St. Jude Children's Research hospital
- Providing quality-assured **essential** cancer medicines at no cost to paediatric hospitals in low-and middle-income countries



**WHO, St. Jude launch groundbreaking international delivery of childhood cancer medicines**

11 February 2025 | News release | Geneva/Memphis |Reading time: 4 min (959 words)

The World Health Organization (WHO) and St. Jude Children's Research Hospital have commenced distribution of critically-needed childhood cancer medicines in 2 of 6 pilot countries, through the Global Platform for Access to Childhood Cancer Medicines. Currently, these medicines are being delivered to Mongolia and Uzbekistan, with next shipments planned for Ecuador, Jordan, Nepal and Zambia. The treatments are expected to reach approximately 5000 children with cancer across at least 30 hospitals in these countries within this year.

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# EML recommendations and improving access

## Medicines are listed on the EML using their International Non-proprietary Name (INN)

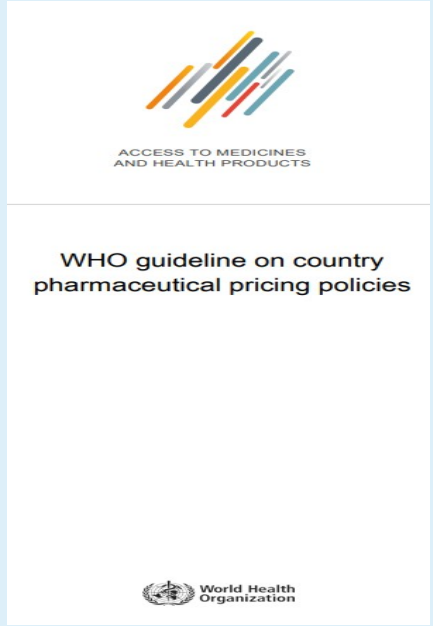
- Listing of medicines on the EML is ‘brand-agnostic’
- Quality-assured generic and biosimilar medicines should be considered acceptable for national selection

### Strong recommendation for promoting the use of quality-assured generic and biosimilar medicines

7.A. WHO recommends that countries enable early market entry of generic and biosimilar medicines through legislative and administrative measures, with a view to encouraging early submission of regulatory applications, allowing for prompt and effective review, and ensuring these products are safe, efficacious and quality-assured.

7.B. WHO recommends that countries use multiple pricing policies to achieve low prices for generic and biosimilar medicines that are informed by the cost of production. These policies may include: internal reference pricing, mark-up regulation, tendering and lower patient co-payments.

7.C. To maximize uptake of generic and biosimilar medicines WHO recommends that countries implement, and enforce as appropriate, a suite of policies, including:
- legislation to allow generic substitution by dispensers and, where applicable, biosimilar substitution;
- legislative structure and incentives for prescribers to prescribe by International Nonproprietary Name;
- dispensing fees that encourage use of low-price generic and biosimilar medicines;
- regressive mark-up structure where lower rates of mark-ups are applied for higher-priced products, and appropriate financial and non-financial incentives are applied for dispensers; and
- education programmes for consumers and professionals regarding the quality, safety, efficacy and price of generic and biosimilar medicines.




WHO guideline on country pharmaceutical pricing policies

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# Accessing EML information, applications, evidence, and recommendations…

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# Applications on WHO website:

## Applications, reviews and comments

Applications for the 24th Expert Committee

### New medicines

- A.1 Acamprosate - alcohol use disorder - EML
- A.2 Alfacalcidol and calcitriol - disorders of bone and calcium metabolism - EML and EMLc
- A.3 Anakinra - systemic onset juvenile idiopathic arthritis with macrophage activation syndrome - EML and EMLc
- A.4 Anti-Ebola virus disease monoclonal antibodies - acute Ebola virus disease - EML and EMLc
- A.5 Anti-PD-L1 immune checkpoint inhibitors - non-small cell lung cancer - EML
- A.6 Baricitinib - COVID-19 - EML and EMLc
- A.7 Bromocriptine and cabergoline - hyperprolactinaemia - EML
- A.8 CD-19-directed CAR-T cell therapy - relapsed/refractory large B-cell lymphoma - EML
- A.9 Ceftolozane + tazobactam - bacterial infections due to multidrug-resistant organisms - EML and EMLc
- A.10 Cladribine, glatiramer and rituximab - multiple sclerosis - EML
- A.11 Cryoprecipitate (pathogen-reduced) - bleeding disorders - EML and EMLc

### Applications for new indications for existing listed medicines

- I.1 Cancer medicines for children - anaplastic large cell lymphoma - EMLc
- I.2 Cancer medicines for children - Langerhans cell histocytosis - EMLc
- I.3 Ethionamide - drug-susceptible tuberculosis meningitis - EML and EMLc
- I.4 Fluoxetine - anxiety disorder - EML
- I.5 Fluoxetine - obessive-compulsive disorder - EML
- I.6 Methotrexate - psoriasis - EML and EMLc
- I.7 Mifepristone-misoprostol - intrauterine fetal demise - EML
- I.8 Rituximab - Burkitt lymphoma - EMLc
- I.9 Zoledronic acid - osteogenesis imperfecta - EML and EMLc

### Applications for new formulations/strengths of existing listed medicines

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# Applications on WHO website:

## A.10 Cladribine, glatiramer and rituximab - multiple sclerosis - EML

### Application, expert reviews and public comments

#### Application

Inclusion of Cladribine, glatiramer and rituximab - multiple sclerosis - EML

#### Expert reviews

Expert Review 1

Expert Review 2

Expert Review 3

#### Comments

Clinton Health Access Initiative

F. Hoffmann-La Roche Ltd

Institute for Clinical and Economic Review

#### WHO Department Comments

Mental Health and Substance Use

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# Applications on WHO website:

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

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**Co-applicant**:
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**Contributors**:
Application writing team: Appendix 15.1.1
Organising Committee: Appendix 15.1.2
Research team: Appendix 15.1.3
MSIF Essential Medicines Panel: Appendix 15.1.4
MSIF Off-Label Treatments Panel: Appendix 15.1.5

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

| A.10 | Cladribine, glatiramer and rituximab – multiple sclerosis – EML |
|---|---|
| Draft recommendation | ☒ Recommended<br>☐ Not recommended<br>Justification:<br>This Application refers to the inclusion of rituximab [□ listed representa<br>of square box grouping with ocrelizumab], cladribine and glatiramer ace<br>treatment of multiple sclerosis (MS).<br>This Application is supported by several international organisations repr<br>six WHO world regions, including upper-middle and lower-middle incor<br>An application to include glatiramer acetate, fingolimod, and ocrelizum<br>WHO Model List of Essential Medicines was submitted in 2019 by the M<br>Sclerosis International Federation (MSIF), also co-author of the current<br>that time, the Committee noted that there was no clear-cut superiority<br>over other MS medicines in terms of safety, efficacy, and affordability, a<br>used agents (e.g., natalizumab) and off-label medications (e.g., rituxima<br>excluded from that Application.<br>Therefore, this Reviewer carefully considered the selection of the most<br>agents among several pharmacological options available for MS (at leas<br>relapsing and remitting forms). The Application reports a robust and de<br>of selection, summarising the body of evidence and transparently repor<br>decision-making process, based on the work done by two specific initiat<br>Off-Label Treatments (MOLT) and MSIF Essential Medicines (MEMP) gui<br>with the MEMP and MOLT recommendations, rituximab, cladribine and<br>acetate emerged as effective, feasible and acceptable options for the tr<br>MS.<br>**Rituximab** is already listed on the WHO Model List of Essential Medicine<br>available and listed on many national EMLs. The magnitude of benefit w<br>large to moderate, however the certainty of evidence supporting its ben<br>profile was judged low or very low. Overall, the balance of effects, mod<br>administration (6-monthly infusions), possibility to use it without screen<br>monitoring, its availability and low cost support the inclusion in the EML<br>treatment of MS, both relapsing and progressive forms. Rituximab is co<br>during pregnancy, but may be used with careful timing of treatment. Ha<br>considered small to trivial.<br>There are no direct comparisons between ocrelizumab and rituximab, t<br>less costly, available as biosimilars, but used off label. In those setting w<br>prescribing is limited, ocrelizumab may offer an alternative to rituximab<br>this Reviewer support the inclusion of rituximab as the representative o<br>box grouping, including ocrelizumab.<br>Please, also refer to Application A28 Application for the addition of ocre<br>the WHO Model List of Essential Medicines.<br>**Cladribine** is considered the oral agent with the best benefit risk profile<br>relapsing forms of MS was judged large, while no data from RCTs are available on<br>progressive forms.<br>**Glatiramer acetate** offers several advantages in low-resourced settings, including its<br>lack of pre-test and on-therapy monitoring requirements, good safety profile without<br>risk of opportunistic infections, and safety in women of childbearing age, pregnant<br>and breastfeeding women. Its benefit was judged large in relapsing MS and moderate<br>in progressive forms. Harms were judged trivial. |

CLINTON HEALTH ACCESS INITIATIVE

March 14, 2023

Dear WHO Expert Committee on Essential Medicines,

Re: Application for Multiple Sclerosis Disease-Modifying Therapies to be listed on the WHO essential medicines list, A.10 Cladribine, glatiramer, and rituximab - multiple sclerosis - EML

The Clinton Health Access Initiative's (CHAI) successful approach to advancing health care worldwide has fundamentally changed how
Starting in 2002, our focus was to substantia
living with HIV by dramatically reducing th
innovator and generic companies, stringent
non-profit organizations to secure licenses t
manufacturing, and to ensure healthy and su
with ministries of health, clinicians, and cli
care. Millions of lives have been saved by th
then, we have applied similar methodologie
tuberculosis, family planning and reproduct
diseases: diabetes, cardiovascular disease, an

Since 2019, MSIF has been developing a rev
list, by systematically assessing all 30 Diseas
information below highlights the rigorous a
and glatiramer acetate for addition to the EM

The selection has been made by an indepen
with high representation from low- and mid
Centre in Evidence-Based Research Synthes
applicant contributed greatly to the work ar
systematic reviews and evidence synthesis.
was used to make recommendations with th
McMaster Centre. The three medicines were

**WHO 24th Expert Committee on the Selection and Use of Essential Medicines 2023**

**Comments from the Department of Mental Health and Substance Use**

1. ***Proposal for inclusion of multiple sclerosis disease-modifying therapies (DMTs) on the complementary WHO Model Lists of Essential Medicines (A10)***

   Applicant: Multiple Sclerosis International Federation (MSIF) and WHO Collaborating Centre in Evidence-Based Research Synthesis and Guideline Development

   and

2. ***Application for the addition of ocrelizumab on the WHO Model List of Essential Medicines for the treatment of adult patients with relapsing and primary progressive forms of multiple sclerosis (RMS and PPMS) (within the complementary list) (A28)***

   Applicant: Roche

Multiple Sclerosis International Federation (MSIF) and WHO Collaborating Centre in Evidence-Based Research Synthesis and Guideline Development have submitted an application for rituximab (infusion), ocrelizumab (square box with rituximab), cladribine (oral) and glatiramer acetate (injection). A separate application for ocrelizumab has also been submitted by Roche. This review by the WHO Brain Health Unit addresses both applications.

Early, adequate control of MS disease activity with disease modifying therapies (DMTs) can delay the

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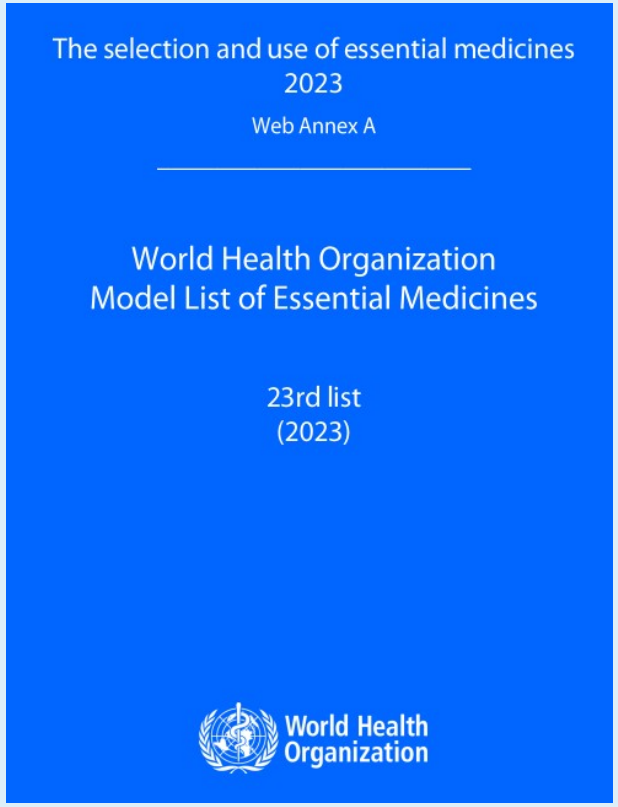
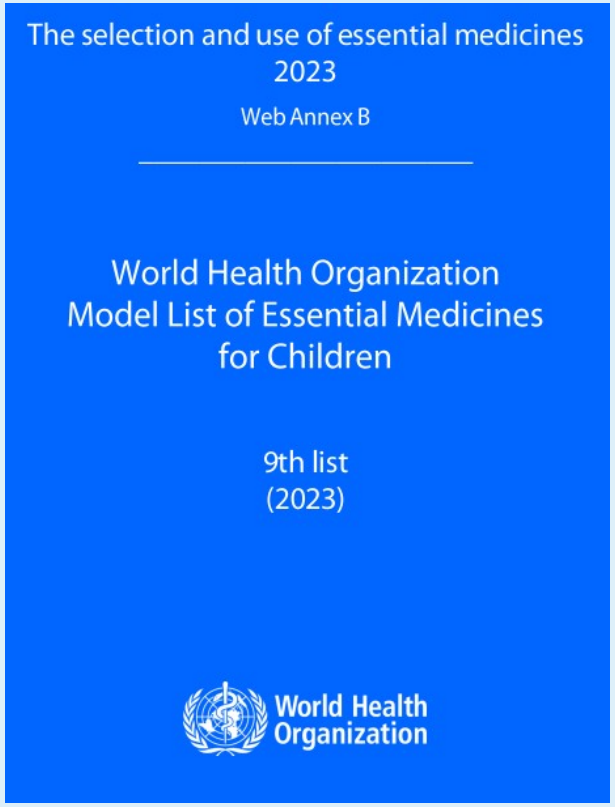
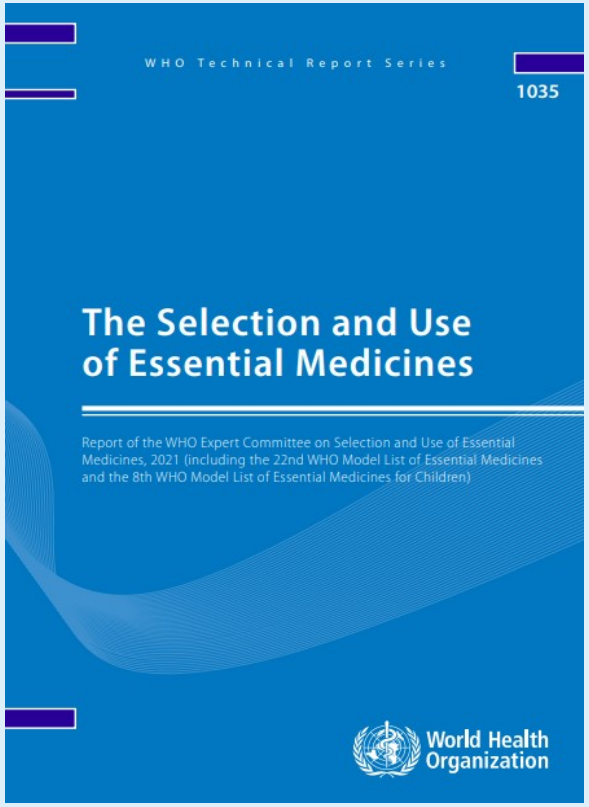
# Updated lists and Technical Report Series (TRS):

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# TRS recommendation summaries:



*Cefiderocol – addition – EML*

**Cefiderocol**

**Proposal**

Addition of cefiderocol to the co
of confirmed or suspected infect
negative organisms in adults.

**Applicant**

Shionogi & Co., Ltd. Osaka, Japa

**WHO technical department**

Comments on the application w
Coordination and Partnership
which supported the inclusion
antibiotic, particularly for use:
suspected carbapenem-resistant
based on pathogen susceptibilit
inappropriate. The technical dep
and/or strategy to ensure acces
well as the need for stewardship.

**EML/EMLc**

EML

**Section**

6.2.3 Reserve group antibiotics

**Dose form(s) & strength(s)**

Powder for injection: 1 g (as sulfa

**Core/complementary**

Complementary

**Individual/square box listing**

Individual

**Background** (if relevant, e.g. resubm

Cefiderocol has not been previo
classified under the AWaRe (Acce

**Public health relevance** (burden of disease)

Antimicrobial resistance is estimated to contribute
year globally (*1–3*). If action is not taken, it is estir
a year will be at risk from drug-resistant infection
has identified carbapenem-resistant *Acinetobacter*
resistant *Pseudomonas aeruginosa*, and carbapenem-
cephalosporin-resistant Enterobacteriaceae as critical
which new antibiotics are needed (*4*). Cefiderocol i
cephalosporin antibiotic with potent activity against
negative pathogens, including these critical priority p

In its 2018 surveillance report, the Euro
Prevention and Control reported an increase in resis
treatments across some Gram-negative pathogens b
The European Centre estimates that about 700 000 in
in the European Union and European Economic
by from multidrug-resistant bacterial infections (
in *P. aeruginosa*, *Klebsiella pneumoniae* and *Acin*
significantly to the number of estimated deaths (in t
2015, in five countries (France, Germany, Italy, Spain
prevalence of carbapenem-resistant Gram-negative
0.14 per 100 000 in the United Kingdom and 3.05 per
carbapenemases appear to vary by geographical loc
study reports an overall increase in these enzyme
carbapenem resistance has been particularly high ir
South America and Asia Pacific countries, except Jap

**Summary of evidence: benefits** (from the application)

The applicant conducted a comprehensive and syste
cefiderocol, including in vitro and in vivo studies an
comparative studies and randomized clinical trials.

*In vitro studies*

The SIDERO-WT analysis investigated the activity
comparators against carbapenem-susceptible a
pathogens (*9–11*). To date, 30 459 samples have
Gram-negative clinical isolates tested in 2014–201
10 470 in 2016–2017. Cefiderocol was effective at
concentrations (MICs) for more than 99% of isolates
latest surveillance SIDERO-WT study (2016–2017
demonstrated activity against 99.4% of Gram-negat
4 microgram/mL compared with 90.2% for ceftazidi
ceftolozane + tazobactam and 95.5% for colistin.

In an analysis of difficult-to-treat resistant pathogens, cefiderocol
demonstrated activity against 94.5% of difficult-to-tre
99.8% of *P. aeruginosa* and 98.3% of Enterobacterales;
susceptible to other available treatments. In additio
non-susceptible Enterobacteriaceae, and 96.4% of car
non-fermenters were sensitive cefiderocol at a MIC of

The SIDERO-CR study collected carbapene
multidrug-resistant non-fermenter isolates from Euro
America and the Asia Pacific region (*9, 13*). Cefiderocol
activity against all of these pathogens, as well as act
previously characterized resistance factors (*13*).

*In vivo studies*

APEKS-cUTI was a phase II, multicentre (multi
randomized, active-controlled, parallel-group non-in
in 452 hospitalized adults with complicated urina
or without pyelonephritis or acute uncomplicated
Gram-negative pathogens (*14*). This study assessed
intravenous cefiderocol (2 g every 8 hours) compare
dose imipenem + cilastatin (2 g every 8 hours). The
was the composite of clinical outcome and microbiol
cure. The response rate for the primary efficacy endpo
the cefiderocol group and 55% (65/119) in the comp
met the criteria to demonstrate non-inferiority vers
with a prespecified 20% margin. At follow-up, su
was higher in the cefiderocol group than the compar
72.3%), with an adjusted treatment difference of
interval (CI) –0.37% to 18.41%). The microbiologic
modified intention-to-treat population was significa
in the cefiderocol group than the comparator group
adjusted treatment difference in favour of cefideroco
to 27.58%) was statistically significant.

APEKS-NP was a multicentre, double-blind
clinical study comparing cefiderocol with high-
meropenem for the treatment of hospital acquir
ventilator-associated bacterial pneumonia or health
pneumonia caused by Gram-negative pathogens (*15*
the modified intention-to-treat population, 251 (86%)
Gram-negative pathogen, including 92 (32%) with
with *P. aeruginosa*, 47 (16%) with *A. baumannii* and
*coli*. The all-cause mortality rate at day 14 was 12.4%
and 11.6% for the high-dose meropenem group (t

95% CI –6.7% to 8.2%, demonstrating th
upper limit of the 95% CI was < 12.5%. F
and microbiological eradication at test
treatment groups. Clinical cure rates we
66.7% in the high-dose meropenem grou
–12.7% to 9.0%); microbiological eradic
group and 48.0% for high-dose meropene
95% CI –12.1% to 10.5%).

The CREDIBLE-CR study wa
observational study to evaluate the effic
therapy in patients with confirmed carbap
pneumonia, bloodstream infections or
infections) (*16*). No formal or inferential a
to detect differences between the treatme
outcomes were similar between treatment
and causative carbapenem-resistant patho

The quality of the randomized st
The analysis concluded that the APEKS
risk of bias and the CREDIBLE-CR study

Case reports of cefiderocol use
expanded access programmes have also
A case series of cefiderocol treatment
ventilated and with carbapenem-resistan
carbapenem-resistant Gram-negative bac
30 days, with 70% of patients experiencin

**Summary of evidence: harms** (from the appli

In total, across the APEKS-cUTI, APE
serious adverse events were reported: 22
103 in patients treated with meropenem,
cilastatin and 40 in patients treated with b

In the total sample, 56/549 (10.
experienced treatment-related adverse ev
comparator treatments experienced treatment-related adverse events. Overall,
there were fewer treatment-emergent adverse events with cefiderocol (344/549;
62.7%) than with comparator treatments (252/347; 72.6%). The most common
adverse reactions for cefiderocol were diarrhoea (8.2%), constipation (4.6%),
pyrexia (4.0%) and urinary tract infection (4.7%).

In total, 22 serious adverse reactions were reported: eight in patients
treated with cefiderocol, six in patients treated with meropenem, one in a
patient treated with imipenem + cilastatin and seven in patients treated with
best available therapy.

**WHO guidelines**

Cefiderocol is a newly approved antimicrobial so is not yet inclu
formal clinical guidelines. However, its usefulness against sever
resistant pathogens has been recognized by both WHO and th
Diseases Society of America (*36, 37*).

In the 2019 WHO report on antibacterial agents in clinical
cefiderocol was identified as a siderophore cephalosporin that is a
many WHO priority pathogens, including extended spectrum bet
producing Enterobacterales, *K. pneumoniae* carbapenemase and oxa
producing Enterobacterales (*36*).

**Costs/cost–effectiveness**

Cefiderocol is appropriate for treating infections caused by ae
negative organisms in adults who have limited treatment option
options may be limited because of multidrug-resistant or carbaper
pathogens, which are associated with higher mortality rates and incr
and economic burden.

Without definitive evidence that an infection is resistant
treatment, empiric therapy may be used, and appropriate treatn
delayed. A recent systematic review examined the effect of delay
therapy in patients with severe bacterial infections. It concluded th
was significantly lower in patients who did not experience a delay
the appropriate therapy (*38*). Several systematic reviews have e
effect of antimicrobial resistance and multidrug-resistant infectio
care costs, and all found an association between increased costs a
(*39–41*). As a result, antibiotics that can effectively treat multid
infections can potentially provide health benefits and health care sa

The wholesale acquisition of cefiderocol (10 vials) in the Uni
and the USA was reported in the application as £ 1319.00 and
respectively. Length of treatment varies from patient to patient, d
infection site and underlying patient conditions. The dose of cefid
with renal function, but for a normal renal function, the standard
infusion every 8 hours. This represents a daily dose of six vials a da
£ 791.40 a day in the United Kingdom and US$ 1100 a day in the U

A cost–effectiveness analysis compared cefiderocol with c
regimens to treat complicated urinary tract infections and hosp
and ventilator-associated pneumonia caused by confirmed
resistant pathogens (*42*). It concluded that cefiderocol was a
option compared with the colistin-based treatment, with an incre
effectiveness ratio of US$ 14 616 per quality-adjusted life year.

**Availability**

Cefiderocol is manufactured by Shionogi
approval from the US Food and Dru
Medicines Agency. It is currently availa
USA. Reimbursement and health-technol
European countries.

**Other considerations**

Not applicable

**Committee Recommendations**

The Expert Committee noted that antir
health threat and that effective antibiot
negative organisms, such as carbapenen
priority pathogen on WHO's priority path

The Committee further noted
available to treat Gram-negative org
lactamases, which are highly endemic in
activity against some of the critical and hi
negative pathogens, including those prod
which other antibiotics listed on the EM
Committee also accepted that cefideroc
other beta-lactams.

The Expert Committee noted
(APEKS-cUTI and APEKS-NP) on wh
cefiderocol is based applied a non-infe
antibiotic trials. Both trials demonstrate
carbapenems with regard to microbiologi
despite large non-inferiority margins bei
infection caused by multidrug-resistant o
in these trials. In addition, the pathogen-
comparing cefiderocol with best available therapy showed similar clinical cure
for treatment of infections caused by carbapenem-resistant Gram-negative
bacteria. However, there was a higher mortality at the end of the study in the
subset of patients infected with *Acinetobacter* spp.

The Committee therefore recommended the inclusion of cefiderocol in
the complementary list of the EML as a Reserve group antibiotic, based on an
acceptable benefit-to-risk profile and high public health need. The increased
mortality observed in the CREDIBLE-CR study was a major concern and
deserves further, careful study. Therefore, the Expert Committee did not
recommend cefiderocol for treatment of proven *Acinetobacter* spp. infections
at this time.

Given the nature of cefiderocol as a last-resort Reserve antibiotic, the Committee stressed that special attention should be given to antibiotic stewardship measures to avoid inappropriate use. Strategies and policies to ensure access to this high-cost antibiotic in low-resource settings also need to be defined.

**References**


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# TRS recomm


https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines

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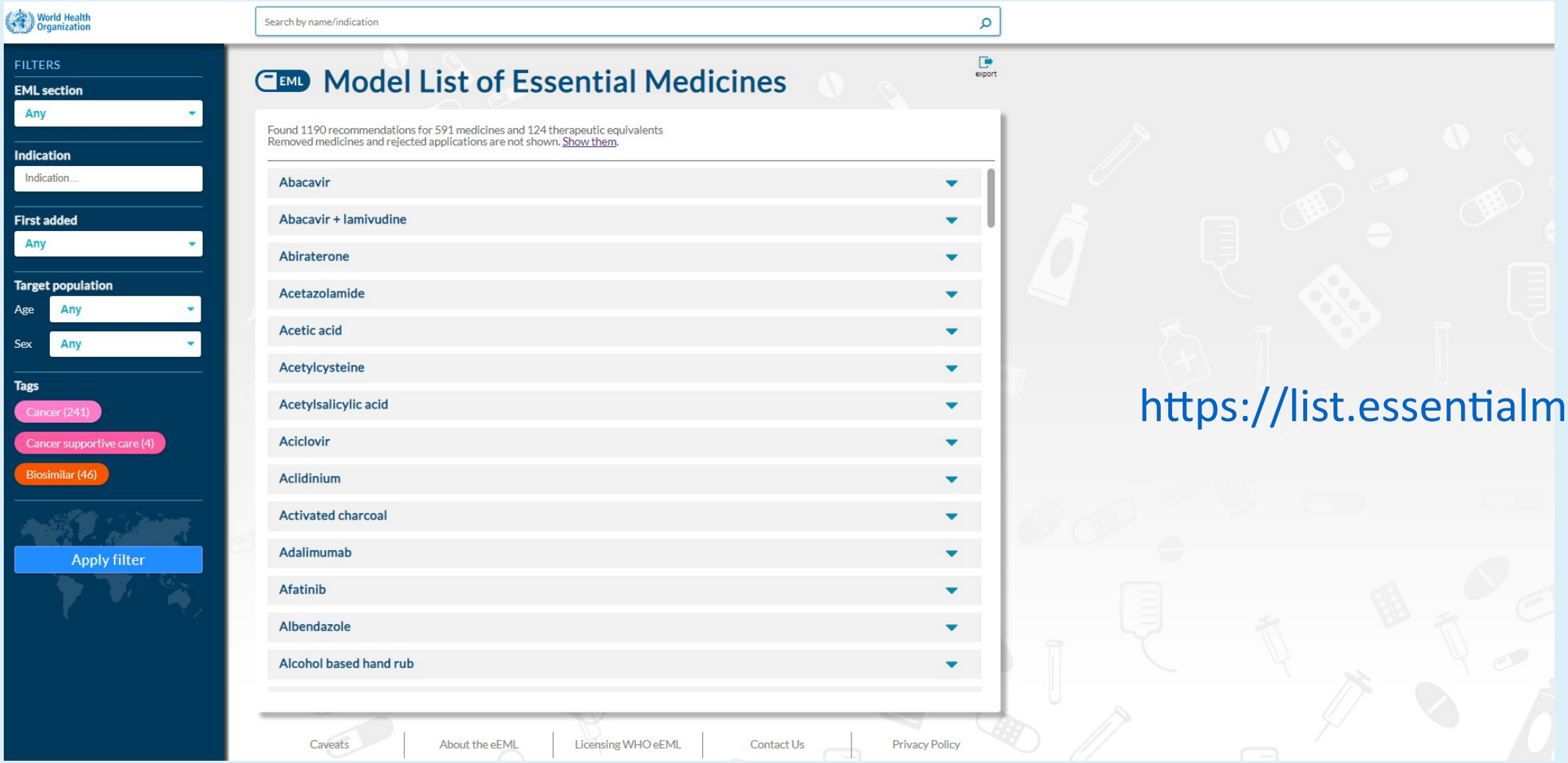
# The electronic EML - eEML




https://list.essentialmeds.org/

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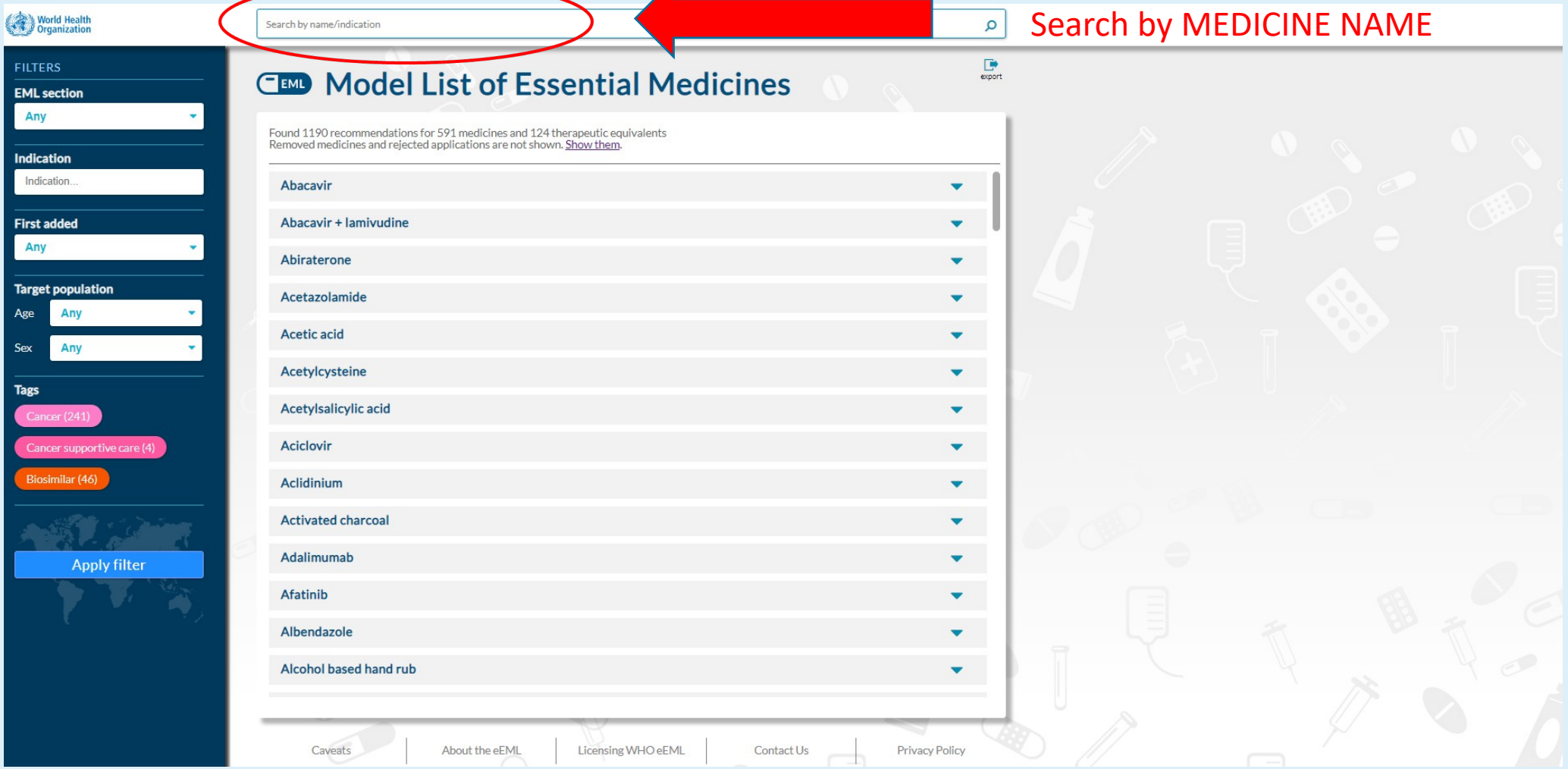


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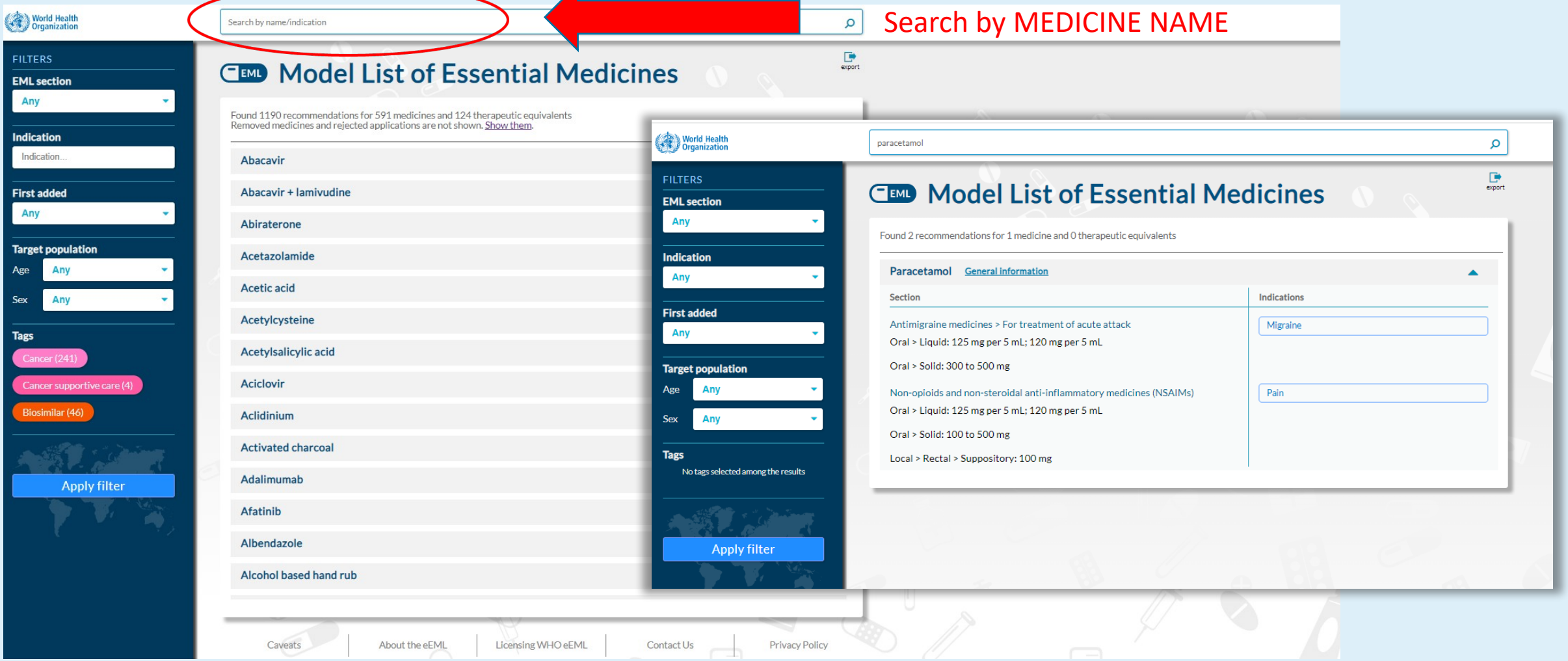

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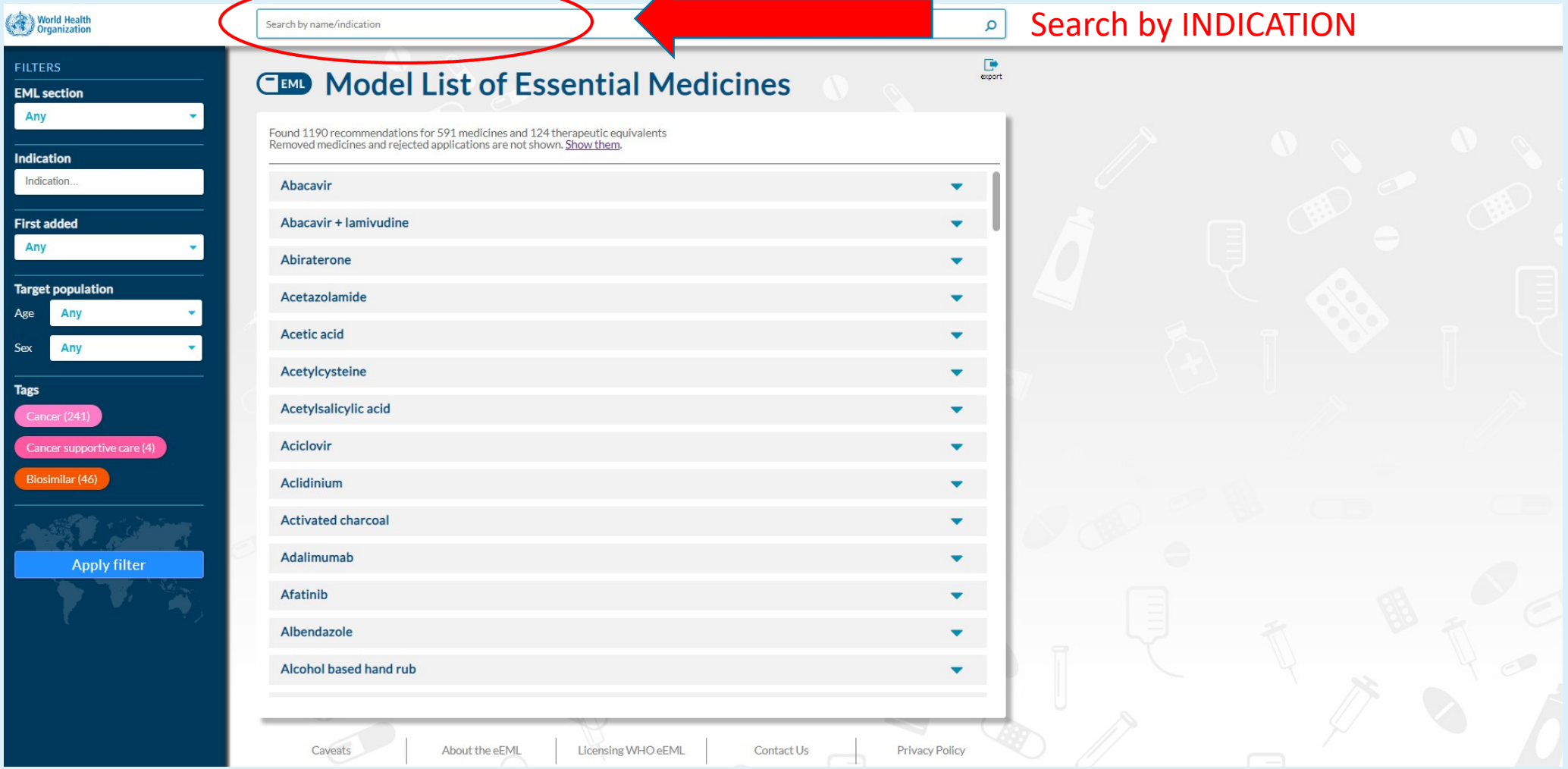


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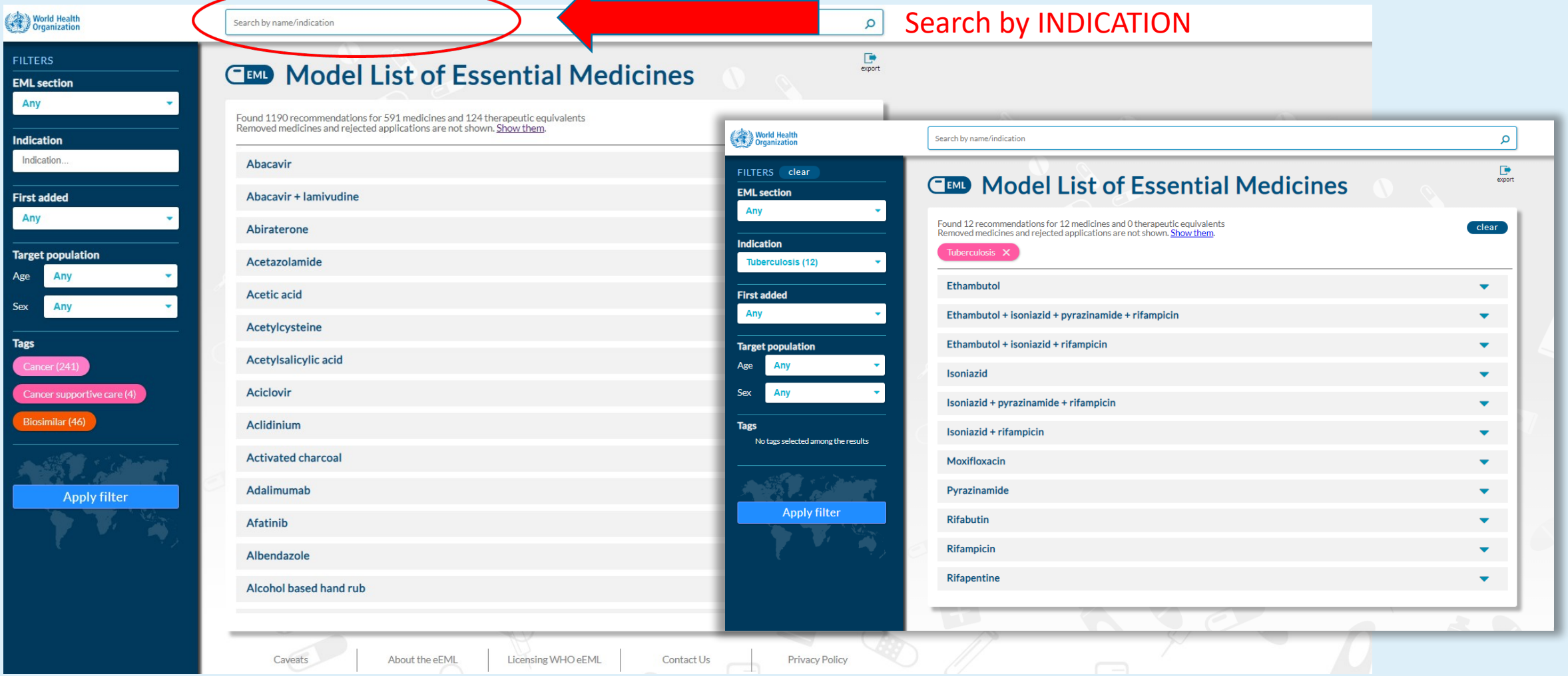

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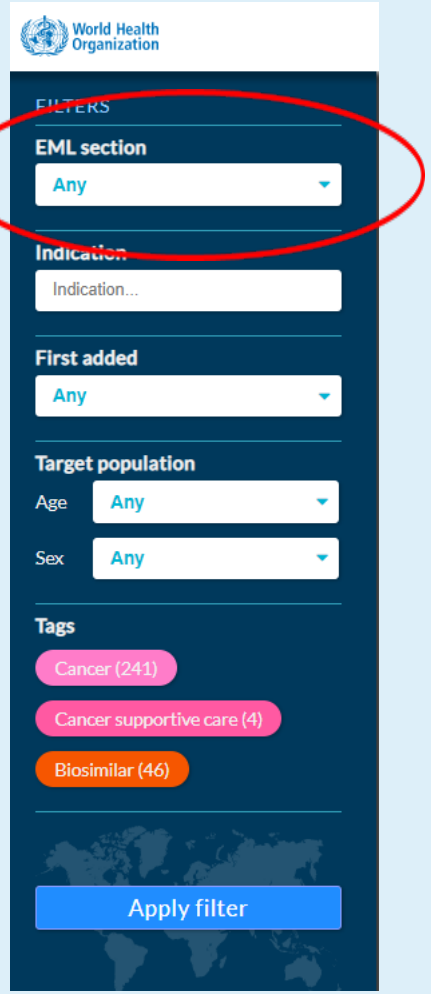


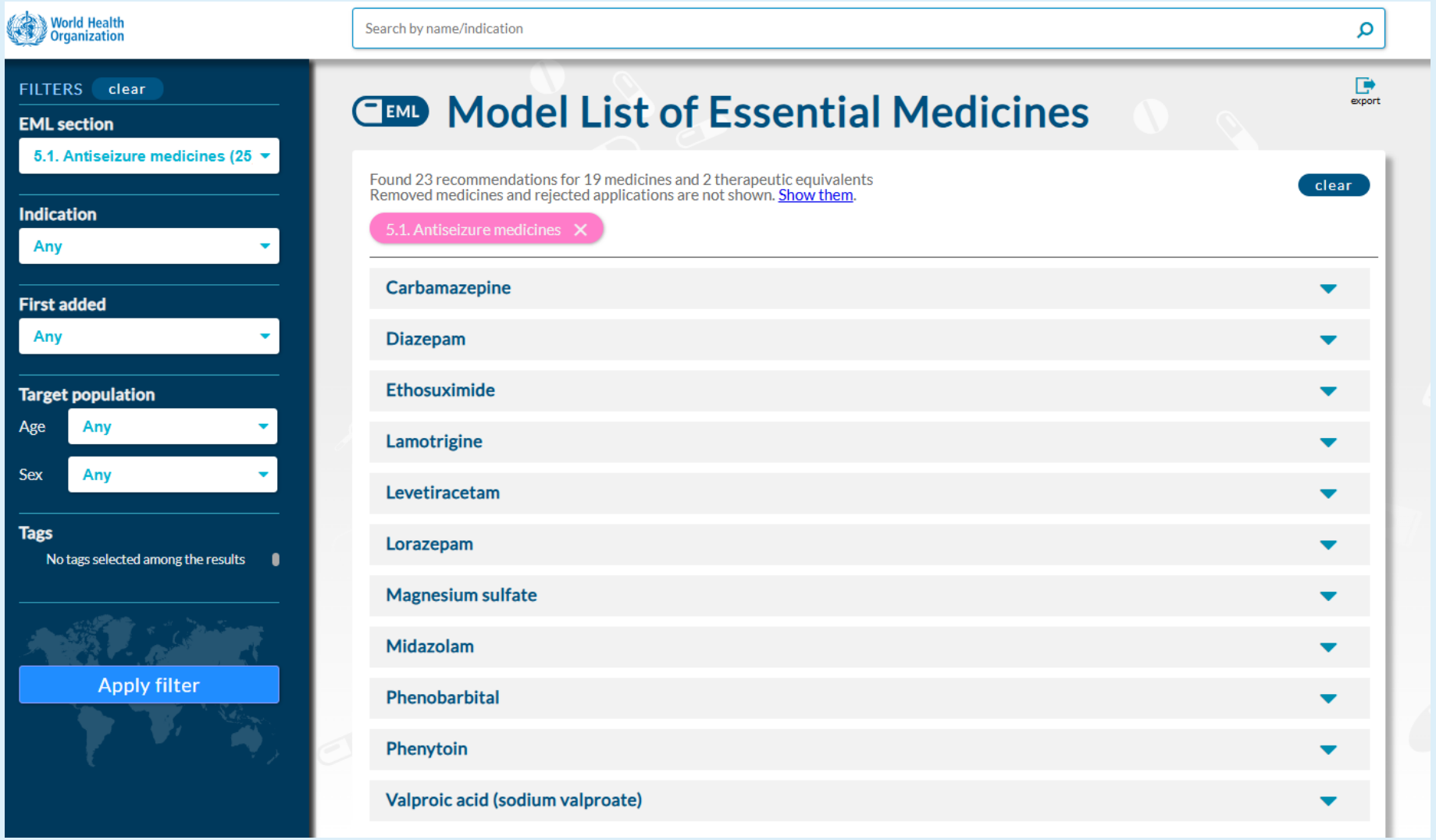


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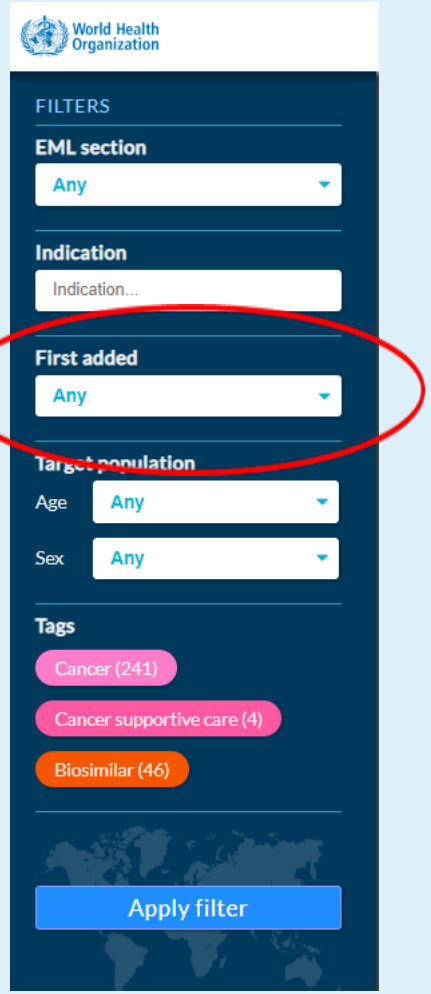


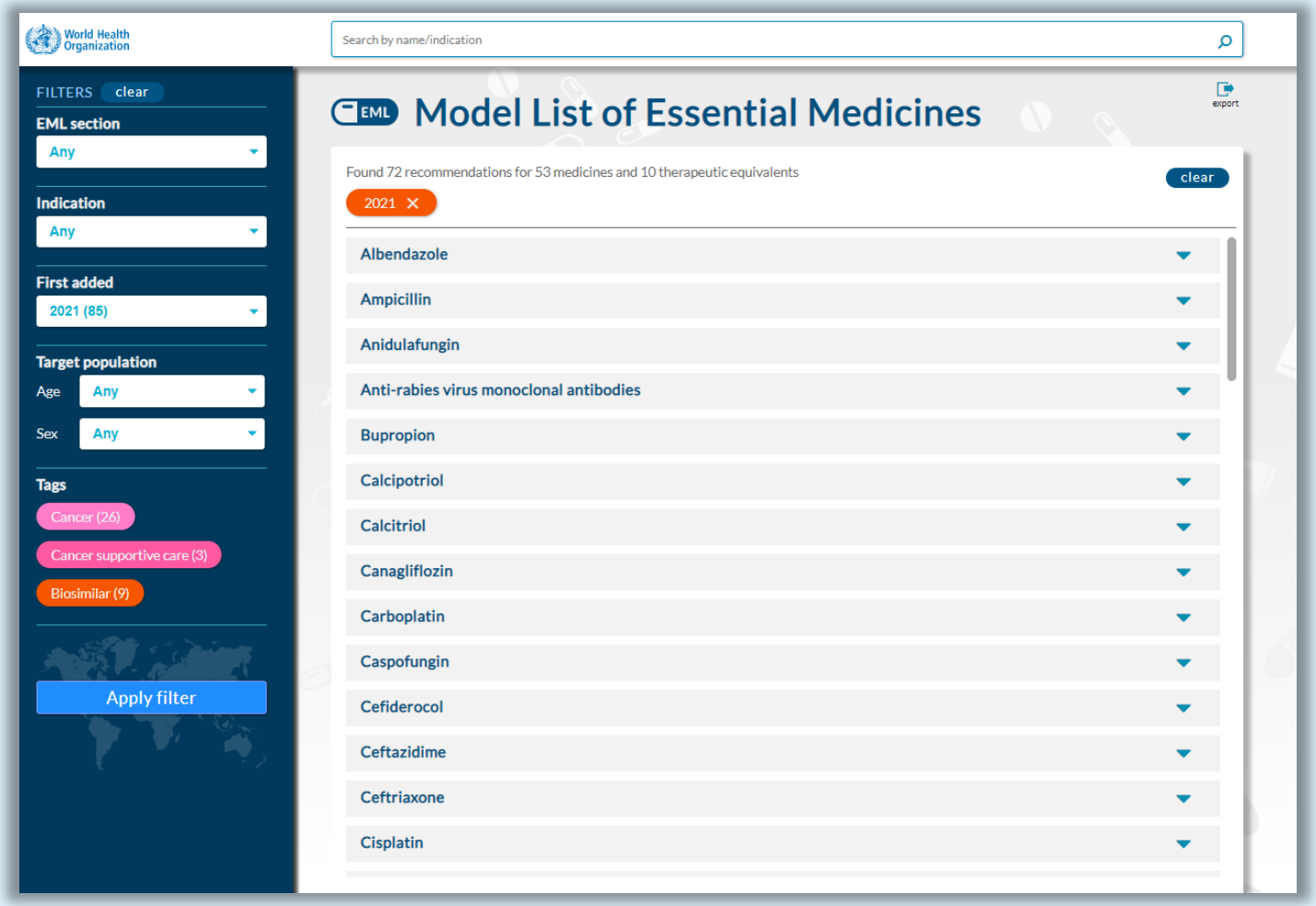


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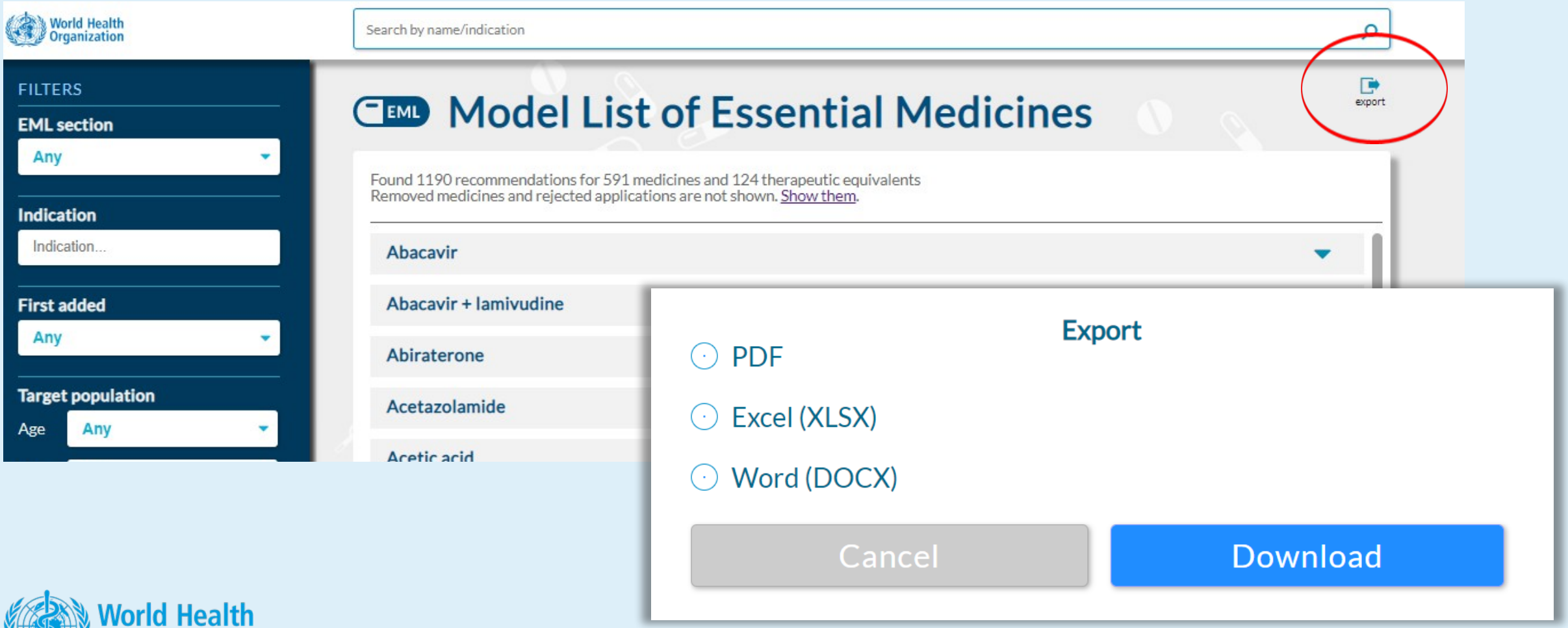

# Useful resources

Add… ?

# Thank you

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