

EML at 42 (1977 – 2019)

Nicola Magrini, MD
Secretary,

WHO Expert Committee on the Selection and Use of Essential Medicines

EML at 42 (1977 – 2019)

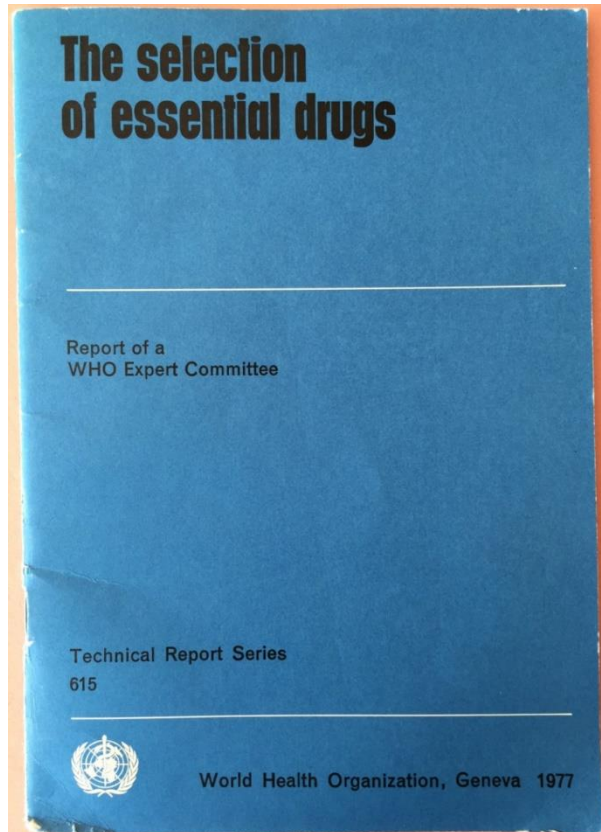
EML strategy to improve access - 2018-2023



1. **Essential medicines ... linking selection to UHC**
2. Next update 2019 and how to improve access
3. Supporting Countries to develop and implement NEMs

40 years of EML (1977 – 2017)

36 pages, 20 references



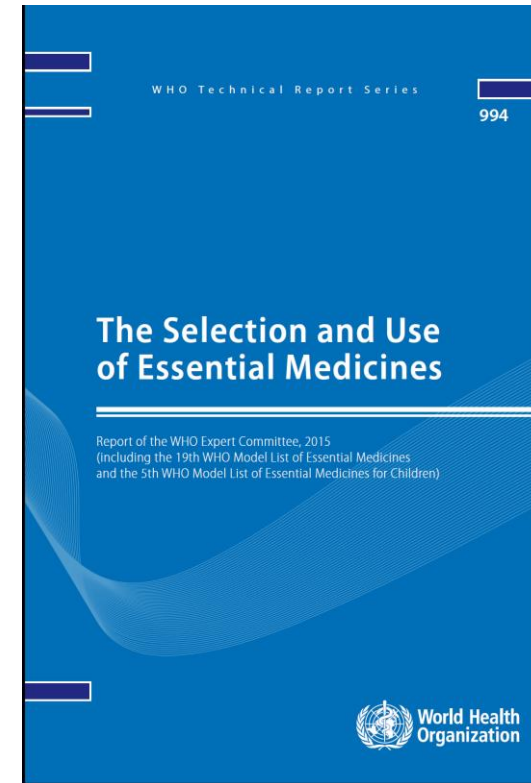
1977 1st Model list published,
approx. 200 active substances

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

Médecins sans Frontières, 2000

20th EML & 6th EMLc - 2017

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



602 pages, >800 references

eEML: database & formats

Search..



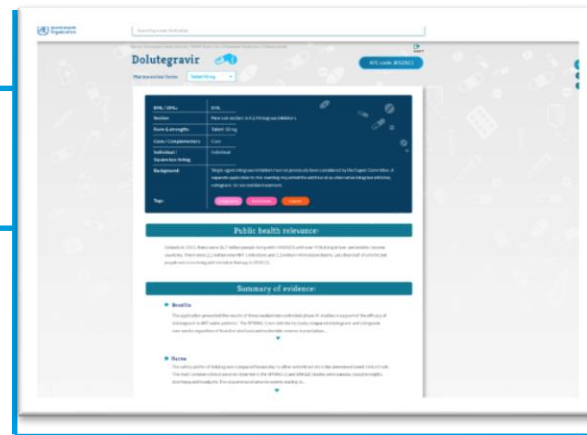
ACTIVE INGREDIENT	1st	2nd	3rd	4th	5th	6th
abacavir	0	0	0	0	0	0
abacavir + lamivudine	0	0	0	0	0	0
acetazolamide	156815 (1877)	1	1	1	1	1
acetic acid	0	0	0	0	0	0
acetylcysteine	0	0	0	0	0	0
acetylsalicylic acid	156815 (1877)	1	1	1	1	1
aclovir	0	0	0	0	0	0
adipidone trihydrochloride	156815 (1877)	1	156815(184)	050303(40)	0	0
albumin, human	0	0	0	0	0	781296(199)
alcohol-based hand rub	0	0	0	0	0	0
aluminum	0	0	0	0	0	0
allopurinol	156815 (1877)	1	1	1	1	1
all-trans retinoic acid (ATRA)	0	0	0	0	0	0
aluminum acetate	156815 (1877)	1	1	1	1	151203(40)
aluminum diacetate	0	0	0	0	0	0
aluminum hydroxide	156815 (1877)	1	1	1	1	1

ONLINE SEARCH ENGINE

ELECTRONIC DATABASE

TEMPLATE

Dolutegravir	ATC code: J05ZA12
INN / ICD10:	INN
Section:	New anti-infectives: G.4.2.1 Integrase inhibitors
Dose form(s) & strength(s):	Tablet: 50 mg
Core / Complementary:	Core
Individual / Square box listing:	Individual
Background:	Single-agent integrase inhibitors had not previously been considered by the Expert Committee. A separate application to this meeting requested the addition of an alternative integrase inhibitor, dolutegravir, for second-line treatment.
Public health relevance:	Globally in 2015, there were 36.7 million people living with HIV/AIDS with over 95% being in low- and middle-income countries. There were 2.2 million new HIV-1 infections and 1.1 million HIV-related deaths, less than half of all infected people were receiving antiretroviral therapy in 2015 (1).
Summary of evidence:	The application presented the results of three randomized controlled phase 3 studies in support of the efficacy of dolutegravir in adult naive patients: the SPRING-2 non-inferiority study compared dolutegravir and raltegravir over 96 weeks in patients at baseline with low and moderate reverse transcriptase inhibitor (RTI) resistance (2), the SPRING-3 study compared dolutegravir with raltegravir in patients with HIV-1 resistance (3), and the SPRING-4 study compared dolutegravir with raltegravir in patients with HIV-1 resistance (4). The SPRING-2 study compared dolutegravir in combination with abacavir/zidovudine with dolutegravir in combination with abacavir/zidovudine plus efavirenz/tenofovir disoproxil fumarate in 833 participants who had not received previous treatment for HIV infection (5). The dolutegravir combination met the criterion for superiority with a greater proportion of patients achieving a HIV RNA level of less than 50 copies per mL at 48 weeks (88% versus 81%) (adjusted treatment difference 7%, 95% CI 2% to 12%). The dolutegravir group also had more favorable outcomes for the frequency and severity of time to viral suppression, changes in CD4+ T-cell count from baseline, safety and antiretroviral resistance. The SPRING-3 study compared dolutegravir with raltegravir in patients with low and moderate RTI resistance. At 48 weeks, the proportion of patients in each group with viral RNA less than 50 copies per mL was 75% for dolutegravir versus 64% for raltegravir (adjusted mean difference 7.4%, 95% CI 0.7% to 14.1%), and a greater mean change in CD4+ T-cell count was observed in the dolutegravir group (adjusted difference 31.3%, 95% CI 16.3 to 46.3). In the SPRING-4 study, the proportion of patients in each group with viral RNA less than 50 copies per mL was 75% for dolutegravir versus 64% for raltegravir (adjusted mean difference 7.4%, 95% CI 0.7% to 14.1%), and a greater mean change in CD4+ T-cell count was observed in the dolutegravir group (adjusted difference 31.3%, 95% CI 16.3 to 46.3). In the SPRING-3 study, the proportion of patients in each group with viral RNA less than 50 copies per mL was 75% for dolutegravir versus 64% for raltegravir (adjusted mean difference 7.4%, 95% CI 0.7% to 14.1%), and a greater mean change in CD4+ T-cell count was observed in the dolutegravir group (adjusted difference 31.3%, 95% CI 16.3 to 46.3).




LINK TO WHO GUIDELINES

EVIDENCE SYNTHESIS

Summary of findings:

Bedaquiline + background MDR-TB treatment compared to Background MDR-TB treatment alone (regimen of drugs recommended by WHO) in Multidrug-resistant tuberculosis (MDR-TB)

Patient or population: Multidrug-resistant tuberculosis (MDR-TB)

Setting: Core MDR-TB clinic

Intervention: Bedaquiline + background MDR-TB treatment

Comparison: Background MDR-TB treatment alone (regimen of drugs recommended by WHO)

Outcome	Intervention absolute effect* (95% CI)	Risk with Background MDR-TB treatment alone (regimen of drugs recommended by WHO)	Risk with Bedaquiline + background MDR-TB treatment	Relative effect (95% CI)	95% CrI (absolute)	Quality of the evidence (GRADE)	Comments
Subjects cured by end of study: 152 weeks (COB Stage 2: n=17) ^{1,2}	Study population 32 per 100 ¹	88 per 100 (42 to 74)	88 per 100 (57 to 100)	1.00 (0.28 to 2.21) ^{1,2}	152 (1 RCT) ^{1,2}	⊕○○○ Low ^{1,2}	
Serious Adverse Events during Investigational 24 week treatment (phase COB Stage 1 and 2: ITT) (assessed through clinical and laboratory results)	2 per 100	7 per 100 (1 to 27) ¹	7 per 100 (0 to 14)	0.93 (0.27 to 3.00)	227 (1 RCT) ^{1,2}	⊕○○○ Very Low ^{1,2}	
Mortality up to end of study at 152 weeks (COB Stage 2: ITT) (assessed through clinical and laboratory results)	1 per 100 ^{1,2}	11 per 100 (3 to 30) ^{1,2}	11 per 100 (8 to 14)	0.92 (0.28 to 3.01) ^{1,2}	185 (1 RCT) ^{1,2}	⊕○○○ Very Low ^{1,2}	
Time to virological suppression (COB Stage 2: ITT) (assessed with microbiological endpoints: MDR-TB)	0 per 100	Not estimable (N/A to N/A)	Not estimable	Not estimable	18 (1 RCT) ^{1,2}	⊕○○○ Low ^{1,2}	
Culture conversion at 24 weeks (COB Stage 2: ITT) (assessed with microbiological endpoints: MDR-TB)	58 per 100	78 per 100 (63 to 100) ¹	88 per 100 (83 to 100) ¹	0.87 (0.18 to 1.77) ¹	152 (1 RCT) ^{1,2}	⊕○○○ Low ^{1,2}	
Acquired resistance to Bedaquiline, isoniazid, rifampicin, or ethambutol (assessed with molecular endpoints)	Study population 52 per 100 ¹	30 per 100 (8 to 73) ¹	30 per 100 (8 to 73) ¹	0.93 (0.11 to 1.49) ²	37 (1 RCT) ^{1,2}	⊕○○○ Very Low ^{1,2}	

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 - Priority areas and how to better align EML and GLs
2. Next update 2019 and how to improve access
3. Supporting Countries to develop and implement NEMLs

Essential medicines for universal health coverage



Veronika J Wirtz*, Hans V Hogerzeil*, Andrew L Gray*, Maryam Bigdeli, Cornelis P de Joncheere, Margaret A Ewen, Martha Gyansa-Lutterodt, Sun Jing, Vera L Luiza, Regina M Mbindyo, Helene Müller, Corrina Moucheraud, Bernard Pécoul, Lembit Rago, Arash Rashidian, Dennis Ross-Degnan, Peter N Stephens, Yot Teerawattananon, Ellen F M 't Hoen, Anita K Wagner, Prashant Yadav, Michael R Reich

Executive summary

Essential medicines satisfy the priority health-care needs of the population. Essential medicines policies are crucial to promote

ment. Sustained quality and all" as a ce (UHC), and the need treatment. The rec medicines on the Ra tatives an prehensive later, The Policies c progress h be adres inform fu medicines

These five core challenges for essential medicines policies are not new. Indeed, over the past few decades the global health community has sought to address them at all levels. However, finding long-lasting sustainable solutions has proved difficult. National and global economic and political interests have strongly influenced the development and implementation of essential medicines policies, which have implications for public health, economic development, and trade. As a result, essential medicines policies are often highly contested, at both national and global levels.

contribute to the global sustainable development agenda? This report addresses these questions, with the intent to reposition essential medicines policies on the global development agenda.

inequitable and inefficient, and its reduction is a target for UHC. Furthermore, the Commission fo that the available data on pharmaceutical expenditu

confirmed that many people worldwide do not have access to even a limited basket of essential medicines. Countries should adapt the Commission's model to their national contexts to create a locally relevant estimate as a

5 challenges for EM policies

1. Adequate financing
2. Affordability
3. Quality and safety
4. Optimal uses
5. Missing EM

new that basic and was at or onal the and d to ines ority of per sion

S0140-6736(16)31905-5.
[http://dx.doi.org/10.1016/S0140-6736\(16\)31904-3](http://dx.doi.org/10.1016/S0140-6736(16)31904-3),
[http://dx.doi.org/10.1016/S0140-6736\(16\)31903-1](http://dx.doi.org/10.1016/S0140-6736(16)31903-1), and
[http://dx.doi.org/10.1016/S0140-6736\(16\)31906-7](http://dx.doi.org/10.1016/S0140-6736(16)31906-7)

*Joint first authors and commission co-chairs

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The EML reform in 2001: more explicit criteria



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



A more transparent and evidence-based process (EB109/8 2001)

Revised procedure for updating and disseminating the Model List

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

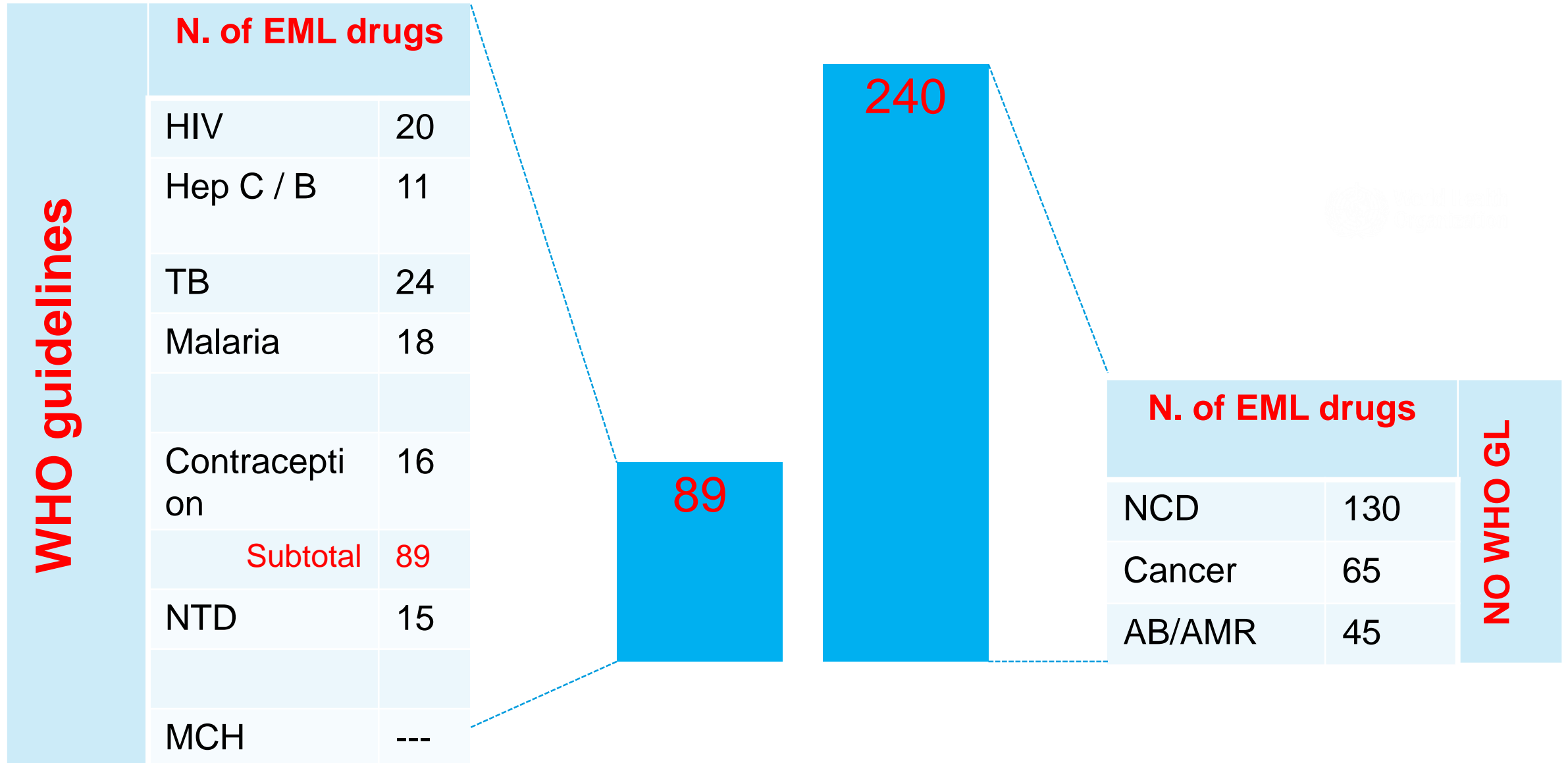


EML criteria (EB 109/8, 2001)

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



EML medicines and WHO technical Dpts GLs



Essential medicines ... linking selection to UHC

Comprehensive coordination: WHO GLs, priority areas, ...



1. Connection with relevant WHO GLs:

- HIV, HepB/C, TB and Malaria
- Reproductive Health
- Paediatric GLs – specifically on AB
- Cancer pain

2. Priority areas/chapters in need of a comprehensive update

- Cancer – EML on a leading role
- AB/AMR – EML on a leading role
- CV/Resp
- Neurology/MH
- Dialysis
- Other areas: Rheumatoid arthritis, inflammatory bowel diseases

3. Closer look at high-priced (newly approved) medicines

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EML 2017 preparatory Working Groups

AB/AWARE

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

Cancer

- Guiding principles: magnitude of benefits
- Individual drug review expanded to the group (enzalutamide and abiraterone)
- TKI inhibitors from South Asia
- Immunotherapies for cancer

WHO EML AWaRe categories: Access, Watch and Reserve

ACCESS: EML 1st and 2nd choice AB for 23 syndromes

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

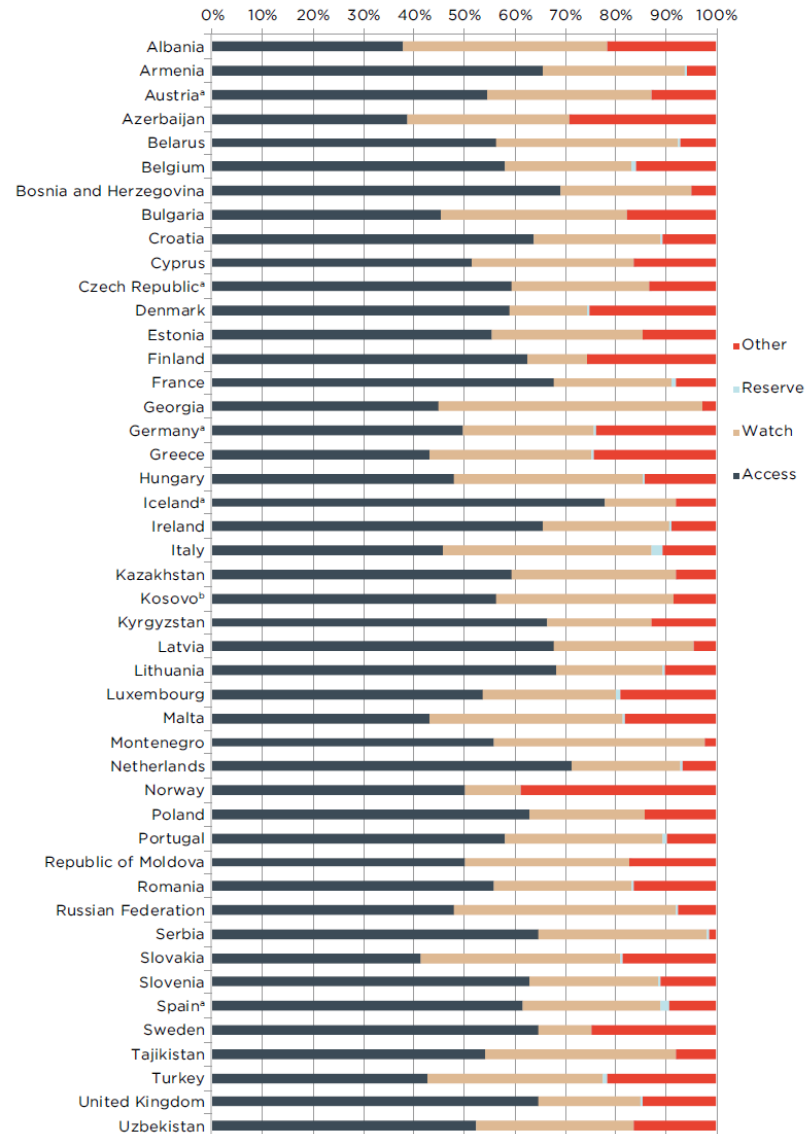
WATCH: AB classes with higher resistance potential recommended only for specific indications that should be prioritized as key targets for stewardship programs. It includes the highest priority agents on the list of **Critically Important Antimicrobials (WHO CIA)** that should not be used prophylactically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

RESERVE: last resort AB or tailored to specific patients or when other options have failed

EML AWaRe 2019: next steps

- **Additional syndromes/indications/recommendations:**
 - SAP – surgical AB prophylaxis (WHO GL)
 - Dental infections, medical prophylaxis
 - Typhoid fever
 - New antibiotics reviewed (7) and classified in AWARE
 - Dosages (paed) and optimal duration
 - Modelling on thresholds for gonorrhoea (currently 5%)
- **Guidance template (electronic) & eEML/AB platform**
 - 1st and 2nd choice AB for all syndromes/diseases
 - Algorithms when NOT to prescribe AB
- **New AWARE iteration**
- **AWARE in guidelines for implementation and stewardship**

WHO AB Global Report 2018 and AWARE



^a Only community consumption reported.
^b In accordance with Security Council Resolution 1244 (1999)

Consumption of oral antibiotic formulations for young children according to the WHO Access, Watch, Reserve (AWaRe) antibiotic groups: an analysis of sales data from 70 middle-income and high-income countries



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

Summary

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

Methods We analysed wholesale antibiotic sales in 70 middle-income and high-income countries in 2015. We identified oral antibiotic formulations appropriate for use in young children (defined as child-appropriate formulations

Lancet Infect Dis 2018

Published Online

December 3, 2018

[http://dx.doi.org/10.1016/S1473-3099\(18\)30547-4](http://dx.doi.org/10.1016/S1473-3099(18)30547-4)

See Online/ Comment

[http://dx.doi.org/10.1016/S1473-3099\(18\)30557-7](http://dx.doi.org/10.1016/S1473-3099(18)30557-7)

Paediatric Infectious Diseases

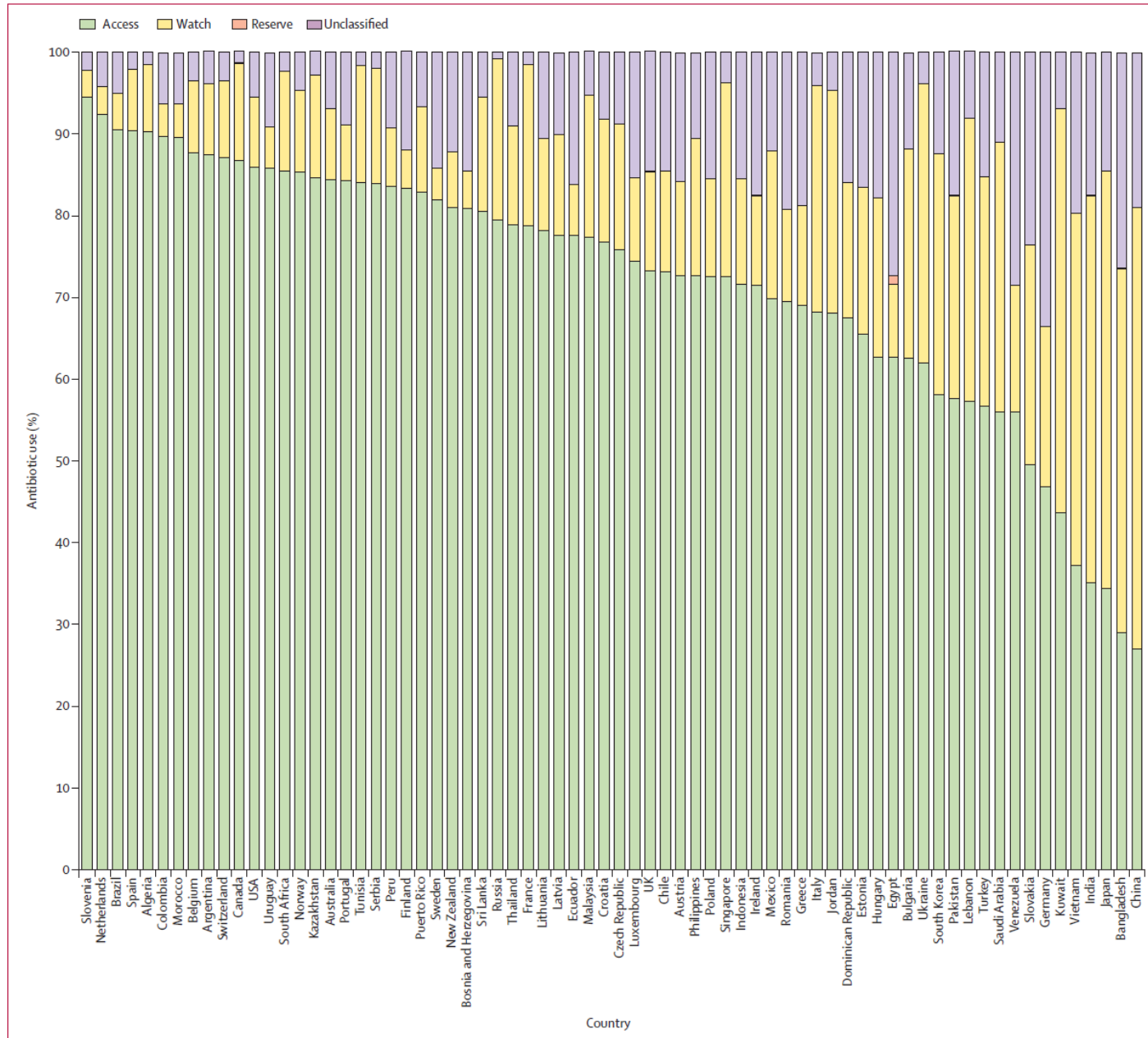


Figure 1: Percentage antibiotic use of child-appropriate oral formulations according to WHO AWaRe grouping. Only core Access antibiotics have been included in the Access group. AWaRe=Access, Watch, Reserve.

Proposing Essential Medicines to Treat Cancer: Methodologies, Processes, and Outcomes

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

Lawrence N. Shulman and Claire M. Wagner, Dana-Farber Cancer Institute; Lawrence N. Shulman, Partners In Health, Boston, MA; Claire M. Wagner and Julie Torode, Union for International Cancer Control; Jane Robertson, Gilles Forte, and Nicola Magrini, World Health Organization, Geneva, Switzerland; Ronald Barr, McMaster University, Hamilton, Ontario, Canada; Gilberto Lopes, Centro Paulista de Oncologia e Hcor Onco, São Paulo, Brazil; Gilberto Lopes, Johns Hopkins University, Baltimore, MD; and Giuseppe Longo, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy.

A B S T R A C T

Purpose

A great proportion of the world's cancer burden resides in low- and middle-income countries where cancer care infrastructure is often weak or absent. Although treatment of cancer is multidisciplinary, involving surgery, radiation, systemic therapies, pathology, radiology, and other

specialties, selection of essential medicines is challenging in resource-poor settings. The International Cancer Control Consortium (ICCC) has identified 29 cancer medicines to be included in the WHO Model Lists for Children, as well as a list of 16 medicines to be included in the WHO Model Lists for Adults.

Methods

Experts identified 29 cancer medicines to be included in the WHO Model Lists for Children, as well as a list of 16 medicines to be included in the WHO Model Lists for Adults.

Results

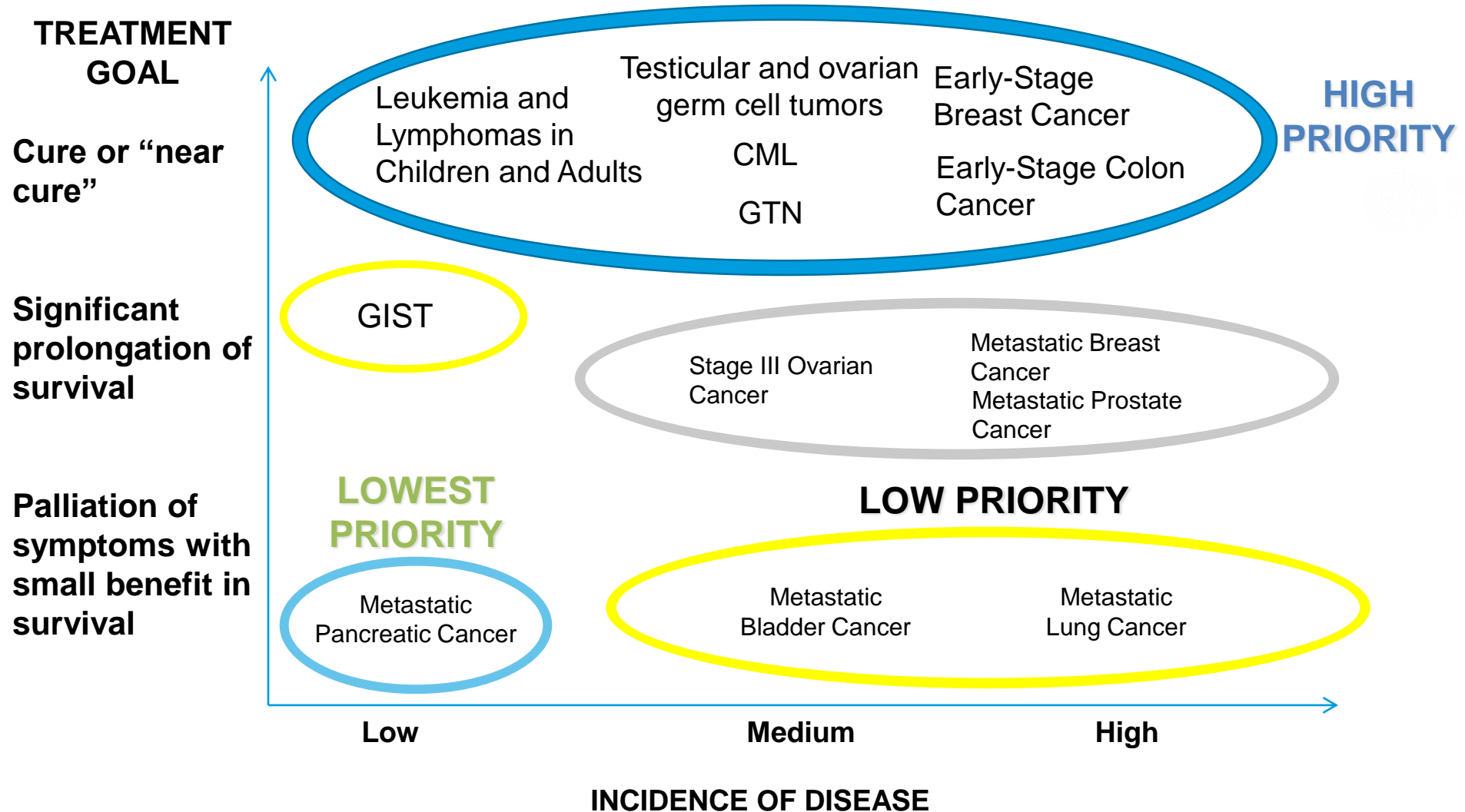
Briefing documents were created for each disease, along with associated standard treatment regimens, resulting in a list of 52 cancer medicines. A comprehensive application was submitted as a revision to the existing cancer medicines on the WHO Model Lists. In May 2015, the WHO announced the addition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

Conclusion

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

J Clin Oncol 34:69-75. © 2015 by American Society of Clinical Oncology

Methodology to Develop Proposal for Revisions



Slide credit: Dr. Gilberto Lopes

New EML cancer medicines main criterion: magnitude of absolute benefit



Imatinib: vast majority of patients in remission at 7 yrs

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

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

Same approach (using absolute efficacy estimates) applied to all proposed regimens

EML 2017

Cancer & cancer pain



Recommendations

Dasatinib (*CML*)
Nilotinib (*CML*)
Zoledronic acid (*bone metastases*)

Fentanyl (transdermal)
Methadone (*already listed for substitution treatment*)

Rejections/standby

Enzalutamide (standby)
Trastuzumab emtansine (standby)

TKIs, crizotinib (standby)

Tramadol (cancer pain)

WHO EML 2017

Cancer medicines



- The Committee did not recommend listing for:
 - enzalutamide for metastatic prostate cancer;
 - tyrosine kinase inhibitors (erlotinib, gefitinib and afatinib) and ALK inhibitor (crizotinib) for non-small cell lung cancer;
 - trastuzumab emtansine for metastatic breast cancer.
- The Committee considered that listing of these medicines was premature and recommended the establishment of an EML cancer medicines working group to coordinate comprehensive evaluation of cancer medicines for the EML.

WHO EML 2019

Cancer medicines



The Expert Committee recommended the establishment of an EML cancer medicines working group to coordinate **comprehensive evaluation of available treatment options, across treatment lines** and including recently approved medicines.

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

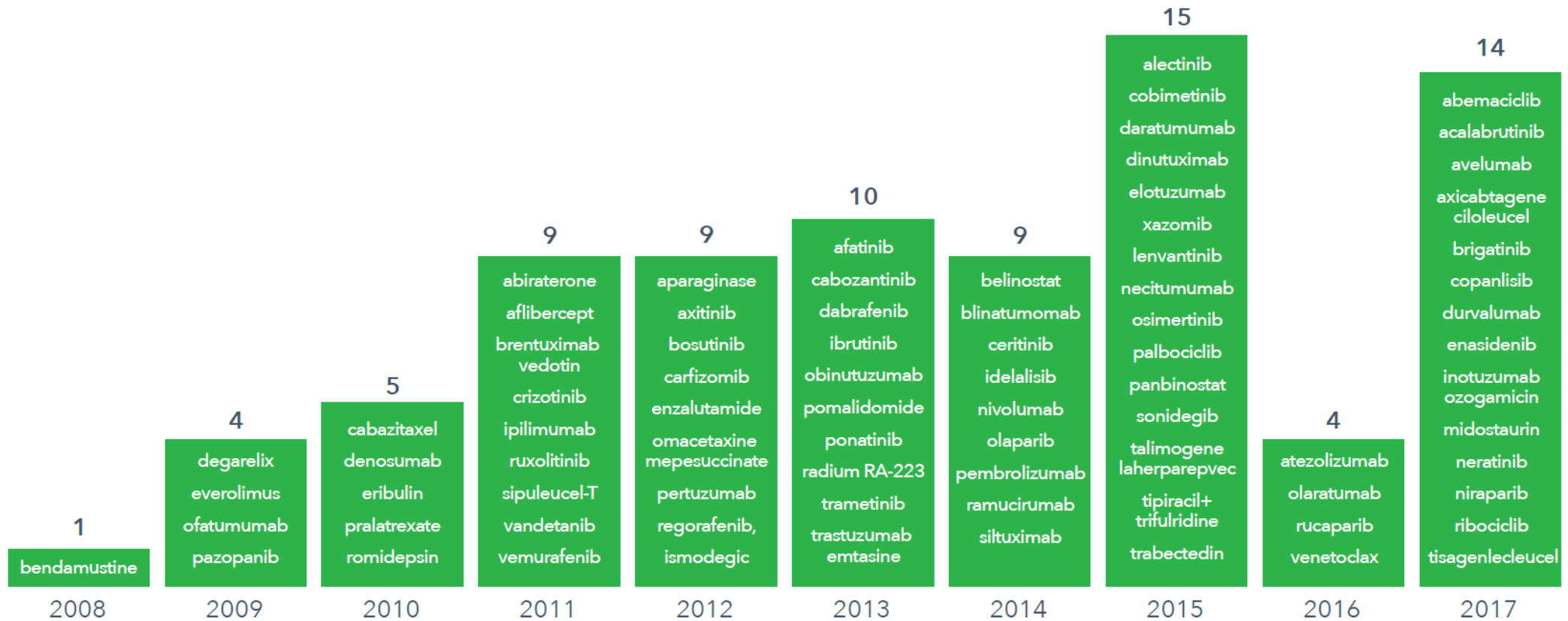
APRIL 2018

Medicine Use and Spending in the U.S.

A Review of 2017 and Outlook to 2022

There have been 52 new cancer medicines launched in the past five years including 33 in the past three years

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



WHO EML Cancer Medicines Working Group (CMWG)

Report of the meeting 22 – 23 March 2018

Geneva, Switzerland

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

- There was agreement on the usefulness and relevance of current magnitude of benefit scales for cancer medicines (ASCO-VF and ESMO-MCBS): these two scales have promoted the involvement of the oncology community (clinicians, researchers) and cancer patients in discussing the value of new cancer medicines and have fostered better understanding of what it is meant by relevant clinical benefit.
- The discussion on what is a clinically relevant magnitude of benefit was examined comparing ASCO-VF and ESMO-MCBS scales. Data from recent cancer trials were used to evaluate medicines recently approved by FDA and EMA using both scales: only a minority of newly approved medicines provide data on survival and quality of life. Indeed clinically relevant data are often lacking at the registration phase.
- It was noted that for the vast majority (i.e. 75%) of cancer medicines approved over the last 15-20 years, there has been a lack of definitive evidence of substantial clinical benefit for patients at registration.

- The CMWG recommended WHO endorse the need to have overall survival as the main eligibility criterion of a medicine proposed for EML listing. Further the CMWG recommended endorsement of an interval for overall survival of at least 4-6 months for first-line treatments as a general guiding principle.
- Among the considerations that supported the 4-6 months overall survival interval were:
 - a strong clinical and ethical conviction that for OS less than 3 months, the benefits seem weak, marginal or not relevant (depending on cancer types);
 - a 3-month survival threshold has been endorsed by both ASCO and ESMO scales, with different implications in their respective scales;
 - clinical trials estimates tend to overestimate the benefits because of patient selection, risk of bias and spurious findings. Patients included in clinical trials often differ from those seen in real life settings: benefits in patients seen in everyday practice might be less convincing as compared to those selected in trials. Trials often have important methodological limitations, leading to biased estimates of intervention effectiveness. Single studies are often exposed to type I error. Finally interventions studied in trials might not be directly transferable in LMICs as capacity of centers to deliver essential medicines and manage related toxicity might be diminished.

EML 2019: cancer medicines

- EGFR tyrosine kinase inhibitors: erlotinib, gefitinib, afatinib
- Medicines for metastatic prostate cancer
- Anti PD-1 immune-checkpoint inhibitors: Pembrolizumab, Nivolumab, Atezolizumab
- Pertuzumab
- Trastuzumab emtansine
- Medicines for Children with Cancer
- Aprepitant
- Arsenic trioxide
- Pegaspargase
- Rituximab and Trastuzumab sc

«Late papers» contributing to EML discussion



21 March 2019

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

Dear Dr. Simão,

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

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

The strategy of listing medicines based on the magnitude of their OS benefit in clinical trials should be put into context. Many treatments offer clinical benefits beyond OS, detectable and measurable on the level of novel clinical endpoints (reflecting the specificities of innovative treatments), including, very importantly, patient reported quality of life¹. Nonetheless, as explained below in point 2, many of these results will in fact be translated into real clinical benefit when used in a clinical setting and given the necessary time to generate data.

How to prioritize essential medicines for cancer

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

Background

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

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

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

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- Impact of standing Working Groups: AB/AWARE and Cancer

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- Priority areas (WGs and GLs)
- EML rejections and prioritisation

3. Supporting Countries to develop and implement NEMLs

- DB of NEMLs and eEML (and e-AWARE)
- Reimbursement and procurement
- Inputs from countries & drug utilisation
- Other priorities: insulins and ...

eEML: database & formats

Search..



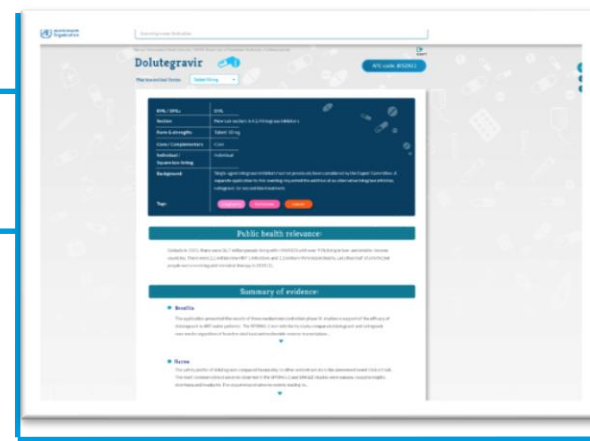
ACTIVE INGREDIENT	1st	2nd	3rd	4th	5th	6th
abacavir	0	0	0	0	0	0
abacavir + lamivudine	156815					
acetazolamide	182771	1	1	1	1	1
acetic acid	0	0	0	0	0	0
acetylcysteine	0	0	0	0	0	0
acetylsalicylic acid	156815	1	1	1	1	1
aclovir	182771	0	0	0	0	0
adjuvanted intralipid	156815	1	156815/1983	05/03/1993		
albuterol	182771	1	1	1	1	1
albumin, human	0	0	785685/1983	1	1	1
alcohol-based hand rub	0	0	0	0	0	0
aluminum	0	0	0	0	0	0
allopurinol	156815	1	1	1	1	1
all-trans retinoic acid (ATRA)	182771	0	0	0	0	0
aluminum acetate	156815	1	1	1	1	1
aluminum diacetate	182771	0	0	0	0	0
aluminum hydroxide	156815	1	1	1	1	1

ONLINE SEARCH ENGINE

ELECTRONIC DATABASE

TEMPLATE

Dolutegravir	ATC code: J05ZA12
INN / ICD10:	J05ZA12
Section:	Anti-infectives: G.4.2.1 Integrase inhibitors
Dose form(s) & strength(s):	Tablet: 50 mg
Core / Complementary:	Core
Individual / Square box:	Individual
Background:	Single-agent integrase inhibitors had not previously been considered by the Expert Committee. A separate application to this meeting requested the addition of an alternative integrase inhibitor, raltegravir, for second-line treatment.
Public health relevance:	Globally in 2015, there were 36.7 million people living with HIV/AIDS with over 95% being in low- and middle-income countries. There were 2.2 million new HIV-1 infections and 1.1 million HIV-related deaths, less than half of all infected people were receiving antiretroviral therapy in 2015 (1).
Summary of evidence:	The application presented the results of three randomized controlled phase 3 studies in support of the efficacy of dolutegravir in adult naive patients: the SPRING-2 non-inferiority study compared dolutegravir and raltegravir over 96 weeks in patients of baseline viral load and nucleoside reverse transcriptase inhibitor (NRTI) backbone (2), the SPRING-3 study compared dolutegravir to raltegravir in patients with HIV-1 RNA less than 50 copies per mL compared with 70% in the raltegravir group (adjusted mean difference -4.2%, 95% CI -1.1% to 10%). The SPRING-3 study compared dolutegravir in combination with abacavir/lamivudine with emtricitabine/efavirenz/emtricitabine/efavirenz fumarate in 833 participants who had not received previous treatment for HIV infection (3). The dolutegravir combination met the criterion for superiority with a greater proportion of patients achieving a HIV RNA level of less than 50 copies per mL at 48 weeks (88% versus 81%) (adjusted treatment difference 7%, 95% CI 2% to 12%). The dolutegravir group also had more favorable outcomes for the frequency and severity of time to viral suppression, changes in CD4+ T-cell count from baseline, safety and antiretroviral resistance. The SPRING-2 study compared dolutegravir with raltegravir-based treatment, each dosed with two NRTIs (4). At 96 weeks, a statistically significantly greater proportion of the dolutegravir group had HIV-1 RNA less than 50 copies per mL (adjusted mean difference 12.4%, 95% CI 7.7% to 17.2%) (p < 0.0001). The application also presented the results of two phase 3 studies of dolutegravir in ART treatment-experienced adult patients. The SPRING-4 study compared dolutegravir with raltegravir (with background therapy). The proportion of patients with treatment-emergent integrase-inhibitor resistance was a pre-specified secondary endpoint. At 48 weeks, the proportion of patients in each group with any integrase-inhibitor resistance was 17% for dolutegravir versus 64% for raltegravir (adjusted mean difference 7.4%, 95% CI 0.7% to 14.1%), and a secondary endpoint was met. In addition, significantly fewer patients in the dolutegravir group had treatment failure due to treatment-emergent resistance (4.8% versus 17.8% in the raltegravir group) (adjusted mean difference -13.0% CI -8.3% to -17.7%). In the SPRING-5 3-year study, twice-daily dolutegravir in combination with other ART was demonstrated to be effective in ART-experienced patients demonstrating integrase-inhibitor resistance with 68% of patients with prior virologic failure and



LINK TO WHO GUIDELINES

EVIDENCE SYNTHESIS

Summary of findings:

Bedaquiline + background MDR-TB treatment compared to Background MDR-TB treatment alone (regimen of drugs recommended by WHO) in Multidrug-resistant tuberculosis (MDR-TB)

Patent or population: Multidrug-resistant tuberculosis (MDR-TB)
 Setting: Core: MDR-TB clinic
 Intervention: Bedaquiline + background MDR-TB treatment
 Comparison: Background MDR-TB treatment (regimen of drugs recommended by WHO)

Outcome	Intervention absolute effect* (95% CI)	Risk with Background MDR-TB treatment alone (regimen of drugs recommended by WHO)	Risk with Bedaquiline + background MDR-TB treatment	Relative effect (95% CI)	No. of patients (95% CI)	Quality of the evidence (GRADE)	Comments
Subjects cured by end of study: 152 weeks (COB Stage 2: n=17) ^{1,2}	Study population: 32 per 100 ¹	88 per 100 (42 to 144)	88 per 100 (57 to 100)	1.01 (0.28 to 2.21) ^{1,2}	152 (118 to 186) ^{1,2}	⊕⊕○○ Low ^{1,2}	
Serious Adverse Events during Investigational 24 week treatment (phase COB Stage 1 and 2: ITT) (assessed through clinical and laboratory results)	2 per 100	7 per 100 (1 to 21) ¹	7 per 100 (3 to 10)	0.93 (0.28 to 3.00)	227 (182 to 282) ^{1,2}	⊕○○○ Very Low ^{1,2}	
Mortality up to end of study at 152 weeks (COB Stage 2: ITT) (assessed through clinical and laboratory results)	1 per 100 ^{1,2}	11 per 100 (5 to 16) ^{1,2}	11 per 100 (8 to 14) ^{1,2}	0.92 (0.28 to 3.00) ^{1,2}	185 (140 to 240) ^{1,2}	⊕○○○ Very Low ^{1,2}	
Time to virologic suppression over 24 weeks (COB Stage 2: ITT) (assessed with microbiological endpoints: MDR-TB)	0 per 100	Not estimable	Not estimable	NA	185 (140 to 240) ^{1,2}	⊕○○○ Low ^{1,2}	
Culture conversion at 24 weeks (COB Stage 2: ITT) (assessed with microbiological endpoints: MDR-TB)	58 per 100	78 per 100 (63 to 100) ¹	78 per 100 (63 to 100) ¹	0.97 (0.18 to 1.77) ¹	152 (118 to 186) ^{1,2}	⊕○○○ Low ^{1,2}	
Acquired resistance to Bedaquiline, isoniazid, rifampicin, or ethambutol at 12 weeks (COB Stage 2: ITT) (assessed with microbiological endpoints)	Study population: 52 per 100 ¹	30 per 100 (8 to 73) ¹	30 per 100 (8 to 73) ¹	0.93 (0.11 to 1.49) ²	37 (29 to 45) ^{1,2}	⊕○○○ Very Low ^{1,2}	

Essential medicines ... linking selection to UHC (2/2)

EML and reimbursement/coverage, EML and DU, eEML



1. EML as a guide to procurement:

- Square box examples (qualified therapeutic equivalence)



Erythropoiesis-stimulating agents

Complementary List

*erythropoiesis-stimulating agents**

Injection: pre-filled syringe

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

** the square box applies to epoetin alfa, beta and theta,
darbepoetin alfa, and their respective biosimilars*

EML consultation with countries: objectives

(end of January 2019)



- There is a need to facilitate feed-backs and **inputs from** countries
- Countries should propose priorities and hot topics (for which they request WHO EML to respond or take a position on)
- WHO EML to propose a simple/facilitated process for countries (in parallel with the standard application process)

Support to countries: access to EM



EML: other priorities

Insulins

Migrants

Why **insulin** access is a global priority



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

Evidence-based clinical guidelines for immigrants and refugees



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

Competing interests: See end of document for competing interests.

Coauthors of the Canadian Collaboration for Immigrant and Refugee Health:

Deborah Assayag, Elizabeth Barnett, Jennifer Blake, Beverly Brockest, Giovanni Burgos, Glenn Campbell, Andrea Chambers, Angie Chan, Maryann Cheetham, Walter Delpero, Marc Deschenes, Shafik Dharamsi, Ann Duggan, Nancy Durand, Allison Eyre, Jennifer Grant, Doug Gruner, Sinclair Harris, Stewart B. Harris, Elizabeth Harvey, Jenny Heathcote, Christine Heidebrecht, William Hodge, Danielle Hone, Charles Hui, Susan Hum, Praseedha Janakiram, Khairun Jivani, Tomas Jurcik, Jay Keystone, Ian Kitai, Srinivasan Krishnamurthy, Susan Kuhn, Stan Kutcher, Robert Laroche, Carmen Logie, Michelle Martin, Dominique Elie Massenat, Debora Matthews, Barry Maze, Dick Menzies, Marie Munoz, Félicité Murangira, Amy Nolen, Pierre Plourde, Hélène Rousseau, Andrew G. Ryder, Amelia Sandoe, Kevin Schwartzman, Jennifer Sears, William Stauffer, Brett D. Thombs, Patricia Topp, Andrew Toren, Sara Torres, Ahsan Ullah, Sunil Varghese, Bilkis Vissandjee, Michel Welt, Wendy Wobeser, David Wong, Phyllis Zelkowitz, Jianwei Zhong, Stanley Zlotkin.

Editor's note: See Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.090313/-/DC1, for affiliations and contributions of coauthors.

This document has been peer reviewed.

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CMAJ 2011. DOI:10.1503/cmaj.090313

KEY POINTS

- Clinical preventive care should be informed by the person's region or country of origin and migration history (e.g., forced versus voluntary migration).
- Forced migration, low income and limited proficiency in English or French increase the risk of a decline in health and should be considered in the assessment and delivery of preventive care.
- Vaccination (against measles, mumps, rubella, diphtheria, tetanus, pertussis, polio, varicella, hepatitis B and human papillomavirus) and screening (for hepatitis B, tuberculosis, HIV, hepatitis C, intestinal parasites, iron deficiency, dental pain, loss of vision and cervical cancer) should be routinely provided to at-risk immigrants.
- Detecting and addressing malaria, depression, post-traumatic stress disorder, child maltreatment, intimate partner violence, diabetes mellitus and unmet contraceptive needs should be individualized to improve detection, adherence and treatment outcomes.

Consider also the WHO EML in our approach to immigrants and refugees health

VIEWPOINT

Cost, Effectiveness, and Value

How to Judge?

**Michael D. Rawlins,
MD**

London School of
Hygiene and Tropical
Medicine, London,
England.

Universal health coverage is a global aspiration supported by both the World Health Organization¹ and the United Nations.² The World Health Organization has defined universal health coverage as ensuring that “all people obtain the health services they need without suffering

confidential discounts that payers in many developed countries negotiate and are often substantially less than the list price. In developing countries, payers should similarly negotiate for lower prices for products from developed countries.

The costs of an intervention are, in theory, easy to define.

...

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

an intervention
authorities, for
ce of clinical ef-
nts before they

The resources available to finance health care in in-

are marketed. But, again, there are difficulties.

**We need less research, better research,
and research done for the right reason**

Doug Altman, BMJ 1994

[Essential medicines selection](#)

[Essential Medicines List and Formulary](#)

[Pharmacoeconomics](#)

[Selection of medicines in emergencies](#)

[WHO Expert Committees](#)

[Links](#)

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22nd Expert Committee on the Selection and Use of Essential Medicines– applications for:



Additional medicines

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