La lista OMS dei farmaci essenziali: quale valore per i paesi “ricchi”?

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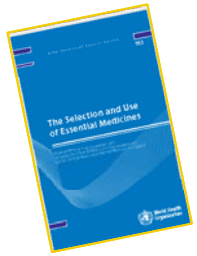
World Health Organization

Contents of the presentation

- La Essential Medicines List: un po’ di storia di una idea di successo
- Il recente update 2015
- Quali implicazioni per I Paesi ricchi?
- Conclusions

World Health Organization

Essential Medicines



Guiding principle: A limited range of carefully selected essential medicines leads to better health care, better medicines management, and lower costs

Definition: Essential medicines are those that satisfy the priority health care needs of the population

Selection: Selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness.

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Essential medicines

- In 1977, the World Health Organization (WHO) published the first Model List of Essential Medicines (Essential Medicines List, EML).
- It introduced the idea that some medicines are more important than others.
- Many later considered the first EML ‘a revolution in public health’.

‘t Hoen EFM., et al
A quiet revolution in global public health:
The World Health Organization’s Prequalification of Medicines Programme
Journal of Public Health Policy, 2014

The concept of essential medicines: lessons for rich countries

- “In 2002, WHO completed a rigorous overhaul of the process to update the Model List.
- An important change was that **affordability changed from a precondition into a consequence of the selection**.”
- Under the new definition, 12 antiretroviral medicines for HIC/AIDS were listed, irrespective of high cost. Their listing now implies that these medicines should become affordable to all those who need them.

Hogerzeil, BMJ 2004

The concept of essential medicines: lessons for rich countries

Hans V Hogerzeil

Rich countries should follow the lead of poor countries and adopt a more systematic way of controlling the cost of drugs

Conclusion

The selection of essential medicines based on sound scientific review and public health grounds, the development of evidence based national clinical guidelines and a national medicines' policy are the cornerstones of any essential medicines' programme. Although some of these components may be in place, industrialised countries would do well to consider in a more systematic way these comprehensive approaches that have proved so beneficial to developing countries.

Access to essential medicines

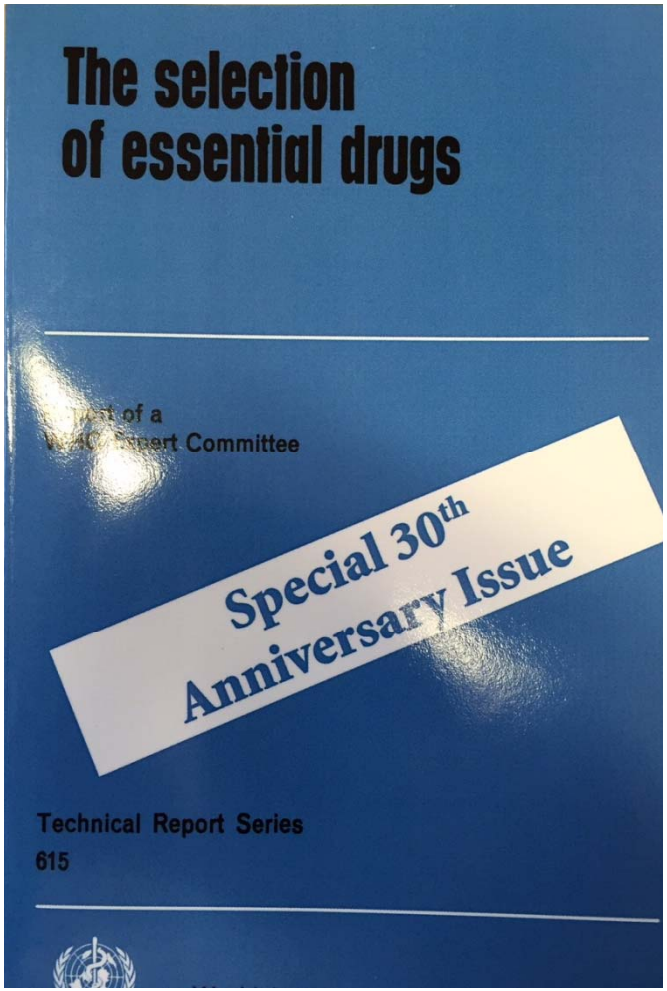
Medicines should be (4 As):

- Available
- Affordable
- Accessible
- Acceptable

The access framework:

- Rational use (EML, GL, DTCs, monitoring/DUR)
- Affordable prices
- Sustainable financing
- Reliable health and supply system

First EML: 1977



WHO EXPERT COMMITTEE ON THE SELECTION OF ESSENTIAL DRUGS

Geneva, 17–21 October 1977

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Dr G. A. Ulianova, Deputy Chairman, Pharmacological Committee, Ministry of Health of the USSR, Moscow, USSR (*Temporary Adviser*)

World Health Organization

1994: Cochrane Collaboration, EBM, EML, RCT ethics, Publication Bias

World Health Organization

EML 1977:
early evidence-based adopter

- **Important medicines for:**
  - Chronic diseases
  - Pain
  - Antibiotics
  - Neglected diseases
  - Mental health
  - Cancer
- **Concise and clear**
- **Promoting uptake of best research findings on medicines into healthcare and national policies**

No medicines for:

- Memory loss and dementia
- Hepatoprotectants
- Immunostimulants
- Osteoporosis
- Medicines of dubious efficacy and safety (as well disease mongering)

- No medicines listed that were subsequently withdrawn for unexpected risks (e.g., cox-2 inhibitors)

BMJ, January 2007
15 medical milestones during last century

- Antibiotics
- Imaging
- Tissue culture
- Anaesthesia
- Chlorpromazine
- Sanitation
- Germ theory
- Evidence based medicine
- Vaccines
- Contraceptive pill
- Computer technology
- Oral rehydration therapy
- Monoclonal antibody technology
- Smoking risks
- Structure of DNA

Increasing, not dictating, choice

Kay Dickersin, Sharon E Straus, Lisa A Bero

The systematic synthesis of evidence is the foundation of all medical discoveries and of good clinical practice

Logo of the journal *Evidence-Based Medicine*

Evidence based medicine is healthcare practice that is based on integrating knowledge gained from the best available research evidence, clinical expertise, and patients' values and circumstances. It is curious, even shocking, that the adjective "evidence based" is needed. The public must wonder on what basis medical decisions are made otherwise. Is it intuition? Magic? The public must also wonder what happens to the research evidence in which they have invested—either directly through taxes or indirectly through buying drugs and other medical products—if it is not guiding clinical practice.

How could something so intuitively obvious to lay people not be similarly viewed by clinicians? And how could this medical milestone be so misunderstood by some? Critics of evidence based medicine worry that it dictates a single "right" way to practise, despite differences among patients; that some self appointed group of "experts" will declare only one type of study to be useful; or that healthcare decisions will be made solely on the basis of costs and cost savings.

Giving a name to evidence based medicine and, now, awarding it milestone status could help everyone to realise that it is about making decisions that are based on the best available evidence, not dictating what clinicians do.

Establishing a modern milestone

The term "evidence based medicine" was coined in 1991 by a group at McMaster University, Ontario. It arose from a confluence of events and changes in our culture. These included a growing recognition that:

- The systematic synthesis of all reliable information on a topic has greater value than traditional reviews
- Bias can explain results in many individual studies, and randomised clinical trials are now recognised as the study design that is best suited to avoiding bias in questions of intervention effectiveness, although other types of study may be better for other types of questions
- Tragedy can result from paying attention to poor quality evidence instead of good quality evidence
- Clinicians need information, and they don't get enough from the sources they typically use
- The medical literature is growing exponentially, and there is not enough time in the day to read even the good stuff, and
- Undesirable gaps and variation in practice exist.

> It is curious, even shocking, that the adjective "evidence based" is needed

Imagine a world without evidence based medicine. Most women with early breast cancer would still be undergoing mastectomy instead of lumpectomy and radiation. Now they can choose.

Many babies born prematurely would still be dying from respiratory distress syndrome, not having the advantage of a mother who took corticosteroids or of being given surfactant themselves.

Pregnant women in Boston might still be taking diethylstilbestrol to prevent miscarriage, on the enthusiastic recommendation of well respected local experts, with the result that many of their children would be developing reproductive abnormalities and cancer.

A boy with asthma might have his treatment changed every six weeks as new drug samples are dropped off at his doctor's surgery. The choice of drug to help prevent a second fracture in an elderly woman might be made on the basis of television advertisements.

Finally, without evidence based medicine, precious health resources might have been spent unnecessarily. In the United States, research into preventing and treating AIDS has cost $30bn (£16bn; 23bn) since 1981. Had the research results not been applied to practice, more than 50% of hospital beds in the US would be filled with AIDS patients, at a cost of $1.4 trillion. Similarly, without the application of cardiovascular research from 1982 to the present, the cost of treating these patients would be 35% higher.

Making the evidence accessible

What is the future for evidence based medicine? The biggest challenge will be getting all clinicians, consumers, policy makers, and other stakeholders on board. We need to help the naysayers to understand what evidence based medicine is and what it isn't. It seems obvious to say that we also need to seek evidence that it is useful. The results of evidence based medicine often clash with the agenda of special interest groups. The challenges created by rich and powerful manufacturers of drugs and devices cannot be overemphasised. Not to be left behind, the industry is developing its own systematic reviews and making them public.

We need to alert clinicians and patients to studies showing that reviews sponsored by the industry almost always favour the sponsor's product, whereas those that aren't sponsored by such companies do not. We also need to provide patients and the general public with the tools to enable them to understand and evaluate systematic reviews. Finally, it is not enough to create high quality, evidence based resources: we need to ensure global access to them.

The question has moved beyond "Why is evidence based medicine important?" to "Why is it not already a reality?" and "How can we all work together to make it a reality, quickly?" Evidence based medicine is one of our most important medical milestones because, without it, the other 14 of the *BMJ*'s milestones would not have been implemented.

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Department of Medicine, University of Calgary, Calgary, Alberta
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EML: why it is a ‘Model List'

- Model for its selection process *(“one medicine per class” approach - square box symbol - unless clinically relevant differences demonstrated*)

- Model to facilitate efforts to 'improve health' of population

  Regulation

  Quality

  (Rational) Responsible and evidence-based use

  Procurement and Supply

Evidence-based medicine term

- Historically the Critical appraisal CMAJ series: since 1981
- Coined by Gordon Guyatt (McMAster University) in 1990 in a document for teaching critical appraisal for students as form of **“enlightened skepticism” toward the application of diagnostic, therapeutic and prognostic technologies in their day-to-day management of patients**
- Firts time appearance: 1991 ACP Journal Club
- JAMA series “Users guide to the medical literature” 1993 - 2000

1994: Cochrane Collaboration, EBM, EML, RCT ethics, Publication Bias

World Health Organization

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.

The EML reform in 2002: 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 process (EB109/8 2001)

Essential medicines concept

10. During the consultation processes, most reviewers agreed with the 1999 Expert Committee's conclusion that: "essential drugs are those that satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in the appropriate dosage forms, and at a price that individuals and the community can afford".[1]

11. Some reviewers questioned the inclusion of the phrase on affordability and others wondered whether the expression "the majority of the population" is useful. There were other concerns that the needs for sustained financing for essential medicines, and for essential medicines of adequate quality, were not dealt with.

12. Taking this into account, a complete description of essential medicines might:

- first include a definition: Essential medicines are those that satisfy the priority health care needs of the population;

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
  - "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)
- WHO responsible management and oversight of CoIs
- 2008 WHO new Guideline Manual, adopting GRADE
- Other considerations: regulatory status (off-label), availability, guidelines

Contents of the presentation

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World Health Organization

EML 2015:
77 applications and a few big challenges

- Cancer drugs: a large comprehensive review was commissioned (29 applications)
- New highly effective HCV drugs (new direct antiviral, single agents and combinations, IFN free regimens)
- MDR-TB drugs (4) and 1 for TB prophylaxis
- New oral anticoagulants (NOACs), polypill, LMWH
- … a tight Agenda

EML and public health relevance
(WHO Bull April 2015)

Perspectives

Tough decisions on essential medicines in 2015

Nicola Magrini,[a] Jane Robertson,[a] Gilles Forte,[a] Bernadette Cappello,[a] Lorenzo P Moja,[a] Kees de Joncheere[a] & Marie-Paule Kieny[a]

In 1977, the World Health Organization (WHO) published its first Model List of Essential Medicines.[1] This year, the Expert Committee for the Selection and Use of Medicines will consider requests to include high-cost medicines for cancer, hepatitis C, multidrug-resistant tuberculosis and new oral anticoagulants on the model list. These applications challenge perceptions of essential medicines and raise questions about how to address issues of cost and affordability for countries when making decisions at the global level.

Essential medicines are those that satisfy the priority health-care needs of

issues of budget impact or affordability of a medicine. Experience suggests that in the absence of competition, options may be limited. Other tools such as those of WHO-CHOICE (CHOosing Interventions that are Cost–Effective) may help national policy-makers decide what is a reasonable price to pay for a medicine.[4] The challenge is to provide access to effective medicines without creating ad hoc vertical programmes and, at the same time, to avoid diverting funds from other important health-care services. Regional pooled procurement mechanisms, price controls, dedicated funding for specific needs, differential

medicines for cancer, given the small gains in life expectancy offered by some new and expensive treatments. Previous expert committee decisions confirm the preference for listing treatments that offer cure or effective disease management over those that offer only marginal benefit. There have been calls for changes to regulatory assessments to ensure that only medicines offering clinically relevant improvements in cancer survival, or large clinical benefit, receive marketing approval.[8,9] The American Society of Clinical Oncology proposes minimum benefit thresholds for the design of clinical trials,[10] while

World Health Organization

EML and public health relevance
(WHO Bull April 2015)

- In 2013, the expert committee defined public health relevance to encompass overall incidence and prevalence of diseases as well as diseases that are specific to certain regions and diseases that are uncommon but for which there are effective medicines.
- This broader framework allows the committee to include medicines for comparatively rare conditions such as leukaemia.
- The committee's main criteria for inclusion in the list are the magnitude of clinical benefit and a favourable risk–benefit profile determined through systematic evidence synthesis and appraisal.

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WHO moves to improve access to lifesaving medicines for hepatitis C, drug-resistant TB and cancers

Share

News release

8 MAY 2015 | GENEVA - WHO today published the new edition of its Model List of Essential Medicines which includes ground-breaking new treatments for hepatitis C, a variety of cancers (including breast cancer and leukaemia) and multi-drug resistant tuberculosis (TB), among others. The move opens the way to improve access to innovative medicines that show clear clinical benefits and could have enormous public health impact globally.

"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," said WHO Director-General, Dr Margaret Chan. "Placing them on the WHO Essential Medicines List is a first step in that direction."

Increasingly, governments and institutions around the world are using the WHO list to guide the development of their own essential medicines lists, because they know that every medicine listed has been vetted for efficacy, safety and quality, and that there has been a comparative cost-effectiveness evaluation with other alternatives in the same class of medicines.

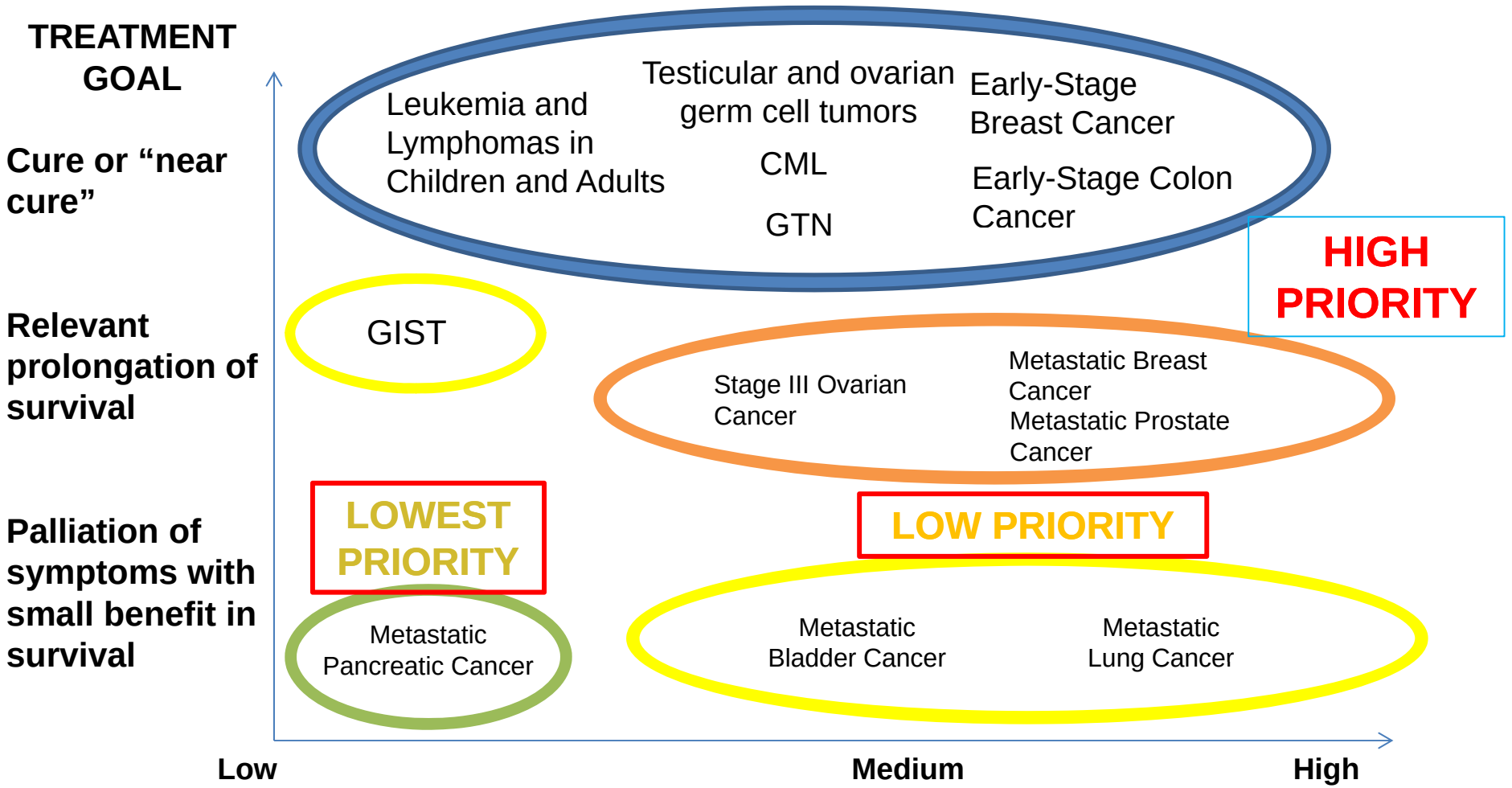
WHO EML 2015
New cancer medicines

8 May, 2015

World Health Organization

THE GUIDING PRINCIPLES

Methodology to Develop Proposal for Revisions



Slide credit: Dr. Gilberto Lopes

Diseases Addressed

ADULT CANCERS		PEDIATRIC CANCERS
AML and APL (adult+ped)	GTN	ALL
CLL	Head and neck cancer	Burkitt lymphoma
CML	Hodgkin lymphoma	Ewing sarcoma
DLBCL	Kaposi sarcoma	Hodgkin lymphoma
Early stage breast cancer	Metastatic breast cancer	Osteosarcoma
Early stage cervical cancer	Metastatic colorectal cancer	Retinoblastoma
Early stage colon cancer	Metastatic prostate cancer	Rabdomyosarcoma
Early stage rectal cancer	Nasopharyngeal cancer	Wilms tumor
Epithelial ovarian cancer	Non-small cell lung cancer	
Follicular lymphoma	Ovarian germ cell tumors (adult+ped.)	
GIST	Testicular germ cell tumors (adult+ped)	

Format of WHO cancer applications

Section	Lead Author(s) and/or Staff
Executive Summary	Lead Author(s)
Public Health Relevance	Staff
Requirements for diagnosis, treatment and monitoring	Lead Author(s)
Overview of regimens	Lead Author(s)
Review of benefits and harms (including systematic reviews)	Lead Author(s) and Staff
Recommendations	Lead Author(s)
Additions proposed for section 8.2 of EML	Lead Author(s)
Supplementary Documents	
Medicine Prices from MSH Price Indicator Guide (2014)	Staff
Costing scenarios	Staff
Regulatory information for recommended medicines	Staff
Patent status for recommended medicines	Staff
Granulocyte-Colony Stimulating Factor (G-CSF)	Lead Author(s) and Staff

The template: large B cell lymphoma

- A highly effective (inexpensive) regimen CHOP: 55% cure rates
- Adding rituximab: 70/ cure rates (15% absolute benefit)

Substantial chance for cure with drugs alone in a moderate-incidence disease: Large B-cell lymphoma is a disease that is highly curable with drugs alone. Surgery offers no chance for cure (though biopsy is necessary to establish a diagnosis). Four old, relatively inexpensive drugs (cyclophosphamide, doxorubicin, vincristine, and prednisone, or CHOP) can cure approximately 55% of patients (i.e. the cure rate increases from 0% to 55% with CHOP alone). At the same time, the addition of the newer biologic agent rituximab, when added to CHOP, can increase the cure rate to about 70% (i.e. cure rate increases from 55% to 70% with addition of rituximab), but at substantial increase in cost and difficulty of administration (the R-CHOP regimen is about 30 times more expensive than CHOP).

UICC EML Costing Scenarios

DIFFUSE LARGE B-CELL LYMPHOMA

CHOP Scenario

A patient with a body surface area of 1.8m^2 receiving R-CHOP for 6 cycles.

Essential Regimen: CHOP: Chemotherapy only, 6 cycles

	Unit Size and Cost	Units required for entire regimen	Total Cost
Cyclophosphamide	$8.75 per 500mg vial $2.89 per 1g vial	6x 500mg vials + 6x 1g vials	$ 69.83
Doxorubicin	$6.48 per 50mg vial	12 vials	$ 77.75
Vincristine	$2.61 per 1g vial	18 vials	$ 47.02
Prednisone	$0.03 per 100mg tab-cap	30 tab-caps	$ 0.81
Total Cost			**$ 195.41**

UICC EML Costing Scenarios

"Back of the Envelope" Calculations

R-CHOP Scenario

A patient with a body surface area of 1.8m^2 receiving R-CHOP for 6 cycles.

Advanced Regimen: R-CHOP: Chemotherapy plus monoclonal antibody, 6 cycles

	Unit Size and Cost	# of units necessary for a full course of treatment	Total Cost
Rituximab	$14.65 per 10mg/ml ampoule	408 ampoules	$ 5,976.38
Cyclophosphamide	$8.75 per 500mg vial $2.89 per 1g vial	6 500mg vials + 6 1g vials	$ 69.83
Doxorubicin	$6.48 per 50mg vial	12 vials	$ 77.75
Vincristine	$2.61 per 1g vial	18 vials	$ 47.02
Prednisone	$0.03 per 100mg tab-cap	30 tab-caps	$ 0.81
Total Cost			**$ 6,171.79**

EML comprehensive cancer review: methodology

- The cancer WG discussed thresholds for clinical benefits and acknowledged their importance but did not endorse an explicit threshold
- The EC discussed magnitude of benefit as the main criterion to include a medicines in EML but … was out of its mandate to define a threshold for clinical benefit

EML comprehensive cancer review: methodology

- The cancer WG discussed thresholds for clinical benefits and acknowledged their importance but did not endorse an explicit threshold
- The EC discussed the application and the importance of magnitude of benefit as the main criterion to include a medicines in EML but was out of its mandate to define a threshold for clinical benefit
- **Some medicines included in EML are cost effective AND unaffordable**: this will require actions to increase access to these essential medicines

WHO EML 2015
New Hepatitis C medicines (DAA)

An inclusive approach

World Health Organization

EML 2015 - New HepC medicines

- The Committee recommended the addition of six oral direct-acting antiviral agents for hepatitis C, including

Sofosbuvir	**ledipasvir + sofosbuvir**
Simeprevir	**Daclatasvir**
ombitasvir + paritaprevir + ritonavir ± dasabuvir	

- The recommendations for inclusions were based on the comparative efficacy, increased tolerability and the potential public health impact
- The very high cost of hepatitis C medicines was considered and the Committee recommended WHO to take actions at global level to make these medicines more accessible and affordable.

EML evidence synthesis: a good example

WHO Essential Medicines List Application

OMBITASVIR, PARITAPREVIR/RITONAVIR co-formulated tablet with or without DASABUVIR

Application prepared by Andrew Hill, Liverpool, UK

How to present all available evidence: phase 3 trials

… how to be more comparative?

Table 5. Phase 3 clinical trials in genotype 1 infected patients with ombitasvir/paritaprevir/r and dasabuvir, with or without ribavirin (intent-to-treat analyses)

Study reference	Study design	Patient characteristics	Intervention	SVR12, n(%)	VF or relapse, n(%)	D/C due to AE, n(%)
SAPPHIRE-I (Feld et al. 2014)	Multicentre, randomised, double-blind, placebo-controlled, Phase 3	TN (GT1a and GT1b), no cirrhosis (n=631)	3D + RBV 12wks (n=473)	GT1a: 307/322 (95.3%) GT1b: 148/151 (98.0%)	GT1a: 7/322 (2.2%) GT1b: 1/151 (0.7%)	3/473 (0.6%)
PEARL-III (Ferenci et al. 2014)	Multicentre, randomised, double-blind, placebo-controlled, Phase 3	TN (GT1b), no cirrhosis (n=419)	3D + RBV 12wks (n=210)	209/210 (99.5%)	1/210 (0.5%)	0
			3D alone 12wks (n=209)	207/209 (99.0%)	0	0
PEARL-IV (Ferenci et al. 2014)	Multicentre, randomised, double-blind, placebo-controlled, Phase 3	TN (GT1a), no cirrhosis (n=305)	3D + RBV 12wks (n=100)	97/100 (97.0%)	2/100 (2.0%)	0
			3D alone 12wks (n=205)	185/205 (90.2%)	16/205 (7.8%)	2/205 (1.0%)
TURQUOISE-II (Poordad et al. 2014)	Multicentre, randomised, open-label, Phase 3	TN & TE (GT1), cirrhotic (TN: n=160; TE: n=220)	3D + RBV 12wks (TN: n=86; TE: n=122)	TN: GT1a: 59/64 (92.2%) GT1b: 22/22 (100.0%) TE: GT1a: 65/76 (85.5%) GT1b: 45/46 (97.8%)	13/208 (6.2%)	4/208 (1.9%)
			3D + RBV 24wks (TN: n=74; TE: n=98)	TN: GT1a: 52/56 (92.9%) GT1b: 18/18 (100.0%) TE: GT1a: 62/65 (95.4%) GT1b: 33/33 (100.0%)	4/172 (2.3%)	4/172 (2.3%)
SAPPHIRE-II (Zeuzem et al. 2014)	Multicentre, randomised, double-blind, placebo-controlled, Phase 3	TE (GT1a and GT1b), no cirrhosis (n=394)	3D + RBV 12wks (n=297)	GT1a: 166/173 (96.0%) GT1b: 119/123 (96.7%)	GT1a: 5/173 (2.9%) GT1b: 2/123 (1.6%) All PT-relapse	3/297 (1.0%)
PEARL-II (Andreone et al. 2014)	Multicentre, open-label, Phase 3	TE (GT1b), no cirrhosis (n=179)	3D + RBV 12wks (n=88)	85/88 (96.6%)	0	2/88 (2.3%)
			3D alone 12wks (n=91)	91/91 (100.0%)	0	0

Abbreviations: TN. Treatment-navie; TE, treatment-experienced; GT, genotype; 3D, ombitasvir/paritaprevir/ritonavir and dasabuvir; RBV, ribavirin; VF, virologic failure; D/C, discontinued; AE, adverse events

What evidence synthesis and overall appraisal do we really need?

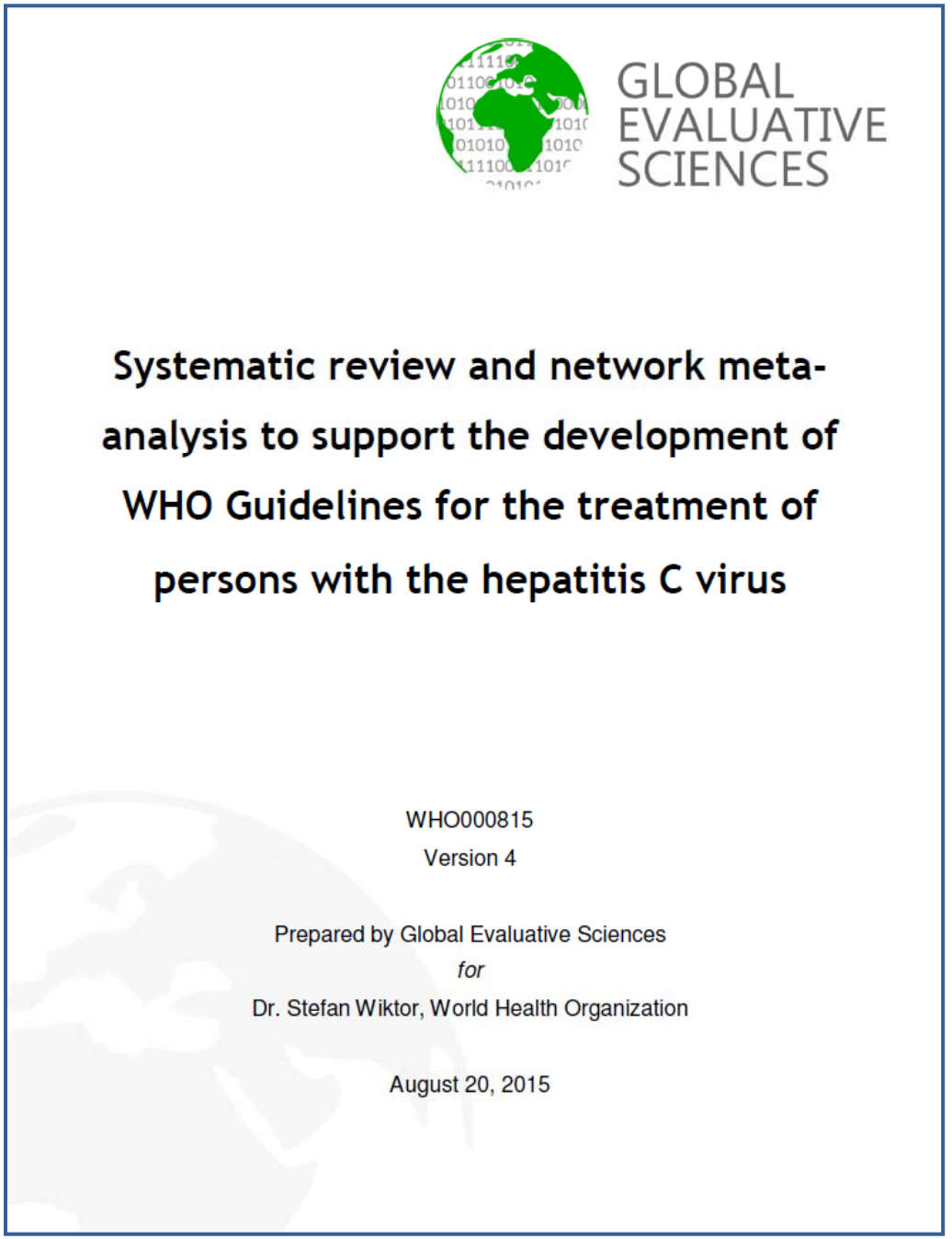
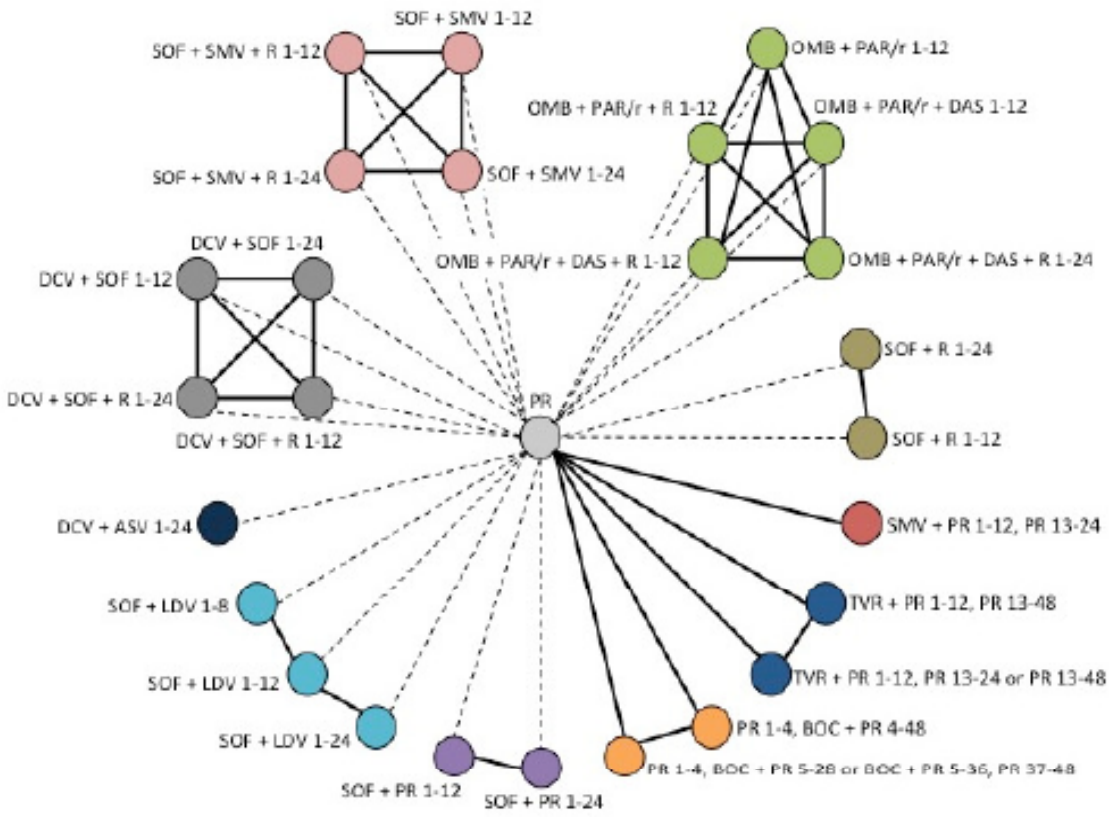


Table 3: Summary of comparative estimates of sustained virological response for treatment-naïve hepatitis C genotypes 1 and 4

Comparison	No. patients (No. arms)	Pooled proportion of SVR, % *(95% confidence interval)*	Difference in SVR, % *(95% confidence interval)*	Network meta-analysis, *relative risk (95% credible interval)*	Risk of Bias	Incon-sisten-cy	Indire-ness	Impre-cision	Magni-tude of effect	Public-ation Bias	GRADE
SMV + SOF vs.	40 (4)	97.32 (90.35, 100.00)									
PR	1564 (16)	46.86 (41.87, 51.86)	50.45 (41.88, 59.02)	**2.05 (1.68, 2.25)**	-1[a]	0	-1[b]	0	+1[d]	0	⊕⊕⊕
TVR + PR	641 (7)	76.47 (70.21, 82.74)	20.84 (11.47, 30.21)	**1.24 (1.00, 1.54)**	-1[a]	0	-1[b]	0	+1[d]	0	⊕⊕⊕
BOC + PR	901 (4)	66.43 (61.81, 71.05)	30.89 (22.53, 39.25)	1.23 (0.98, 1.59)	-1[a]	0	-1[b]	-1[c]	+1[d]	0	⊕⊕
SMV + PR	686 (5)	80.51 (77.54, 83.47)	16.81 (9.24, 24.38)	**1.23 (1.00, 1.45)**	-1[a]	0	-1[b]	0	+1[d]	0	⊕⊕⊕
SOF + PR	464 (3)	90.18 (87.48, 92.89)	7.14 (-0.33, 14.61)	1.04 (0.85, 1.17)	-1[a]	0	-1[b]	0	0	0	⊕⊕
SOF + R	390 (9)	77.26 (67.98, 86.54)	20.06 (8.46, 31.66)	**1.31 (1.02, 1.79)**	-1[a]	0	-1[b]	0	+1[d]	0	⊕⊕⊕
SOF + LDV	1028 (8)	97.65 (96.03, 99.26)	-0.33 (-7.48, 6.82)	0.98 (0.81, 1.04)	-1[a]	0	-1[b]	0	0	0	⊕⊕
DCV + SOF	195 (5)	98.35 (96.14, 100.00)	-1.03 (-8.34, 6.27)	0.97 (0.80, 1.05)	-1[a]	0	-1[b]	0	0	0	⊕⊕
DCV + ASV	265 (2)	83.07 (75.99, 90.15)	14.24 (4.31, 24.17)	1.10 (0.89, 1.47)	-1[a]	0	-1[b]	-1[c]	+1[d]	0	⊕⊕
OMB + PAR/r	1399 (8)	96.99 (95.19, 98.78)	0.33 (-6.86, 7.52)	0.99 (0.81, 1.04)	-1[a]	0	-1[b]	0	0	0	⊕⊕

Figure 2: Network diagram of the individual treatments informing comparative estimates for the treatment-naïve genotypes 1 and 4 population



Legend: Circles (nodes) represent individual treatments; the colours of the circles represent like treatments according to the groupings. Solid lines represent direct head-to-head comparisons; dashed lines represent simulated comparisons.

Important: ongoing trials

Important for the EC to have the "big picture" for its final recommendations, …

including the status of independent research and of head-to-head comparisons

Table 7. Ongoing trials of ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin

Trial identifier	Location	Population	Geno-type	Treatment regimen (duration)	Expected completion
Phase 2					
CORAL-I (NCT01782495)	US, Australia, Europe	TN, liver or renal transplant recipient, with or without cirrhosis (on immunosuppressant regimen)	GT1	Ombitasvir/paritaprevir/r + dasabuvir ± RBV (12/24 weeks)	Mar 2017
NIAID (NCT02194998)	US, Puerto Rico	TN, with or without cirrhosis, with HIV-1 co-infection	GT1	Ombitasvir/paritaprevir/r + dasabuvir + RBV (12/24 weeks)	Jan 2016
Phase 3					
GIFT-I (NCT02023099)	Japan	TN/TE with or without compensated cirrhosis	GT1b	Ombitasvir/paritaprevir/r (12 weeks)	Oct 2015
GIFT-II (NCT02023112)	Japan	TN/TE with or without compensated cirrhosis	GT2	Ombitasvir/paritaprevir/r + RBV (12/16 weeks)	Sept 2015
QAQISH (NCT02247401)	Egypt	TN/TE, with or without cirrhosis	GT4	Ombitasvir/paritaprevir/r + RBV (12/24 weeks)	Aug 2016
TURQUOISE-III (NCT02219503)	US, Canada, Belgium	Compensated cirrhosis	GT1b	Ombitasvir/paritaprevir/r + dasabuvir (12 weeks)	Nov 2015
TURQUOISE-IV (NCT02216422)	Russia, Belarus	Compensated cirrhosis	GT1b	Ombitasvir/paritaprevir/r + dasabuvir + RBV (12 weeks)	Dec 2015
TURQUOISE-CPB (NCT02219477)	US, Canada, Germany	TN/TE with decompensated cirrhosis	GT1	Ombitasvir/paritaprevir/r + dasabuvir + RBV (12/24 weeks)	Oct 2016
RUBY-I (NCT02207088)	US	TN with renal impairment, with or without cirrhosis	GT1	Ombitasvir/paritaprevir/r + dasabuvir ± RBV (12/24 weeks)	Mar 2016
AGATE-I (NCT02265237)	US, Canada, Europe	TN/TE with compensated cirrhosis (inc. DAA experienced)	GT4	Ombitasvir/paritaprevir/r + RBV (12/16/24 weeks)	Jan 2017
TOPAZ-I (NCT02219490)	Canada, Europe, Israel	TN/TE, with or without cirrhosis; long-term outcomes	GT1	Ombitasvir/paritaprevir/r + dasabuvir ± RBV (12/24 weeks)	Dec 2020
TOPAZ-II (NCT02167945)	US	TN/TE, with or without cirrhosis; long-term outcomes	GT1	Ombitasvir/paritaprevir/r + dasabuvir ± RBV (12/24 weeks)	Mar 2020
MALACHITE-I (NCT01854697)	Canada, Europe, Australia, South America	TN, non-cirrhotic; randomised against telaprevir-based therapy	GT1	Ombitasvir/paritaprevir/r + dasabuvir ± RBV (12weeks)	Jul 2015
MALACHITE-II (NCT01854528)	South America, Europe	TE; randomised against telaprevir-based therapy	GT1	Ombitasvir/paritaprevir/r + dasabuvir + RBV (12 weeks)	Jul 2015
Follow-up (NCT01773070)	US, Canada, Europe, Australia, NZ, Puerto Rico,	Follow-up study of prior AbbVie Phase 2/3 studies	Mainly GT1	Follow-up only	Oct 2016

EML 2015: what's specific about HepC drugs?

- "Inclusion on the EML of **all DAAs** proposed in the applications aims at
  - **promoting competition** among available alternatives and
  - **allowing for the selection of optimal combination treatment regimens**, which may or may not be existing fixed-dose combinations."

- Given the challenges of using existing diagnostic tests, highly effective, pan-genotypic treatment strategies should become the focus of a global approach **and a priority for independent research, with clinical trials directly comparing various DAA combinations**.

- The Committee also recommended that WHO continue to work on existing approaches to managing prices and evaluate alternative strategies to improve affordability and access

EML 2015: some rejections

- Polypill for secondary CV prevention *(lack of meaningful benefits, not clear if we were recommending a product or a concept and what were the combinations and the recommended doses)*
- NOACs *(marginal benefits over warfarin, lack of antidote, doubts on monitoring)*
- Ranibizumab intravitreal for age-related macular degeneration and diabetic macular edema *(substantial overlapping with bevacizumab and risk of reducing access to the inexpensive off label bevacizumab)*

Contents of the presentation

- La Essential Medicines List: un po’ di storia di una idea di successo
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- EML 2015: quali implicazioni per I Paesi ricchi?
- Conclusions

Clinical trials and access to medicines

WHO Bull October, 2015

Availability and affordability of new medicines in Latin American countries where pivotal clinical trials were conducted

Núria Homedes[a] & Antonio Ugalde[b]

- Many pharmaceutical products tested in Latin America are unavailable and/or unaffordable to most of the population and add little therapeutic value compared to existing treatments.
- There is an urgent need to determine the public-sector affordability thresholds for new pharmaceutical products,
- The products included in this study did not respond to the most pressing medical needs of people in the region and may have diverted scientific resources from addressing issues of higher relevance

EML 2015 update: implications

- The Expert Committee recommended an engagement with all stakeholders to discuss thresholds for a relevant clinical benefit and for cost-effectiveness
- Existing policy options do not seem to be sufficient to ensure global access to Essential Medicines
- The implementation of the List at country level is now a more complex task (for both LMIC and HIC)

PLOS ONE

RESEARCH ARTICLE

Essential Medicines in a High Income Country: Essential to Whom?

Mai Duong*, Rebekah J. Moles, Betty Chaar, Timothy F. Chen, World Hospital Pharmacy Research Consortium (WHoPReC)¶

Discipline of Pharmacy Practice, Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia

Conclusions

This study showed that decision-making in Australia around reimbursement of medicines has strayed from the fundamental utilitarian concept of essential medicines. Many stakeholders involved in medicine reimbursement decisions and management of the supply chain did not consider the EML concept in their approach. The wide range of views of what stakeholders considered were essential medicines, challenges whether the EML concept is out-dated or underutilised in high income countries.

EML concept relevance in HIC Plos1 paper (9th Dec)

- The EML concept is simple, idealistic, and has been widely received. However, this study showed that the notion of “essential” is not implicit.
- Although beneficial in theory, Australian stakeholders struggled to identify how the EML concept functioned in practice.
- In Australia, decision making around reimbursement of medicines has strayed from the fundamental utilitarian concept of essential medicines. Instead, focus is on cost-effectiveness of new technologies and meeting unmet individual needs through expansive reimbursement

EML concept relevance in HIC Plos1 paper (9th Dec)

- The EML concept is simple, idealistic, and has been widely received. However, this study showed that the notion of "essential" is not implicit.
  - True, not completely explicit …
  - Essential for WHO means "what meets the priority of health care need of the population".
  - the WHO EC on the Selection and Use of EM has to decide based on:
    - Public health burden of the disease and relevance
    - Systematic review of benefits and harms
      - Other considerations

EML concept relevance in HIC Plos1 paper (9th Dec)

- The EML concept is simple, idealistic, and has been widely received. However, this study showed that the notion of "essential" is not implicit.
- Although beneficial in theory, Australian stakeholders struggled to identify how the EML concept functioned in practice.
  - WHO has a very consolidated history for its Model List
  - The recent large update was done applying existing rules (not different ones)
  - is an effort towards better alignment with WHO guidelines
  - Support better access and offer countries stronger support in the implementation of the List

A digression on EML italian roots

Introduction

The concept of "essential medicines" dates back to military tradition, in which therapeutic supplies (such as penicillin) were essential to be carried by soldiers, field medics, and camp infirmaries, into combat zones. This was also applied to the rationalising of therapeutic restrictions necessary during wartime economy [1]. Ensuring access to essential medicines has been considered a basic human right, in line with access to food, water, shelter and education [2]. The Essential Medicines List (EML) was introduced by the World Health Organization (WHO) in 1977, as a core list of 186 pharmaceuticals deemed necessary to manage the disease burden and basic health needs of a population (Box 1) [1,3]. Today, the WHO's Model List of Essential Medicines (WHO EML) includes 409 active substances, is updated every two years, includes low and high cost medicines, and is applied to all income settings in 156 countries [4–6].

A digression on EML italian roots

- EML in 1975 … Fattorusso (WHO, DAP) & Garattini
- La lista del Prontuario degli Ospedali di Milano
- Quindi non una semplice lista ambulatoriale …

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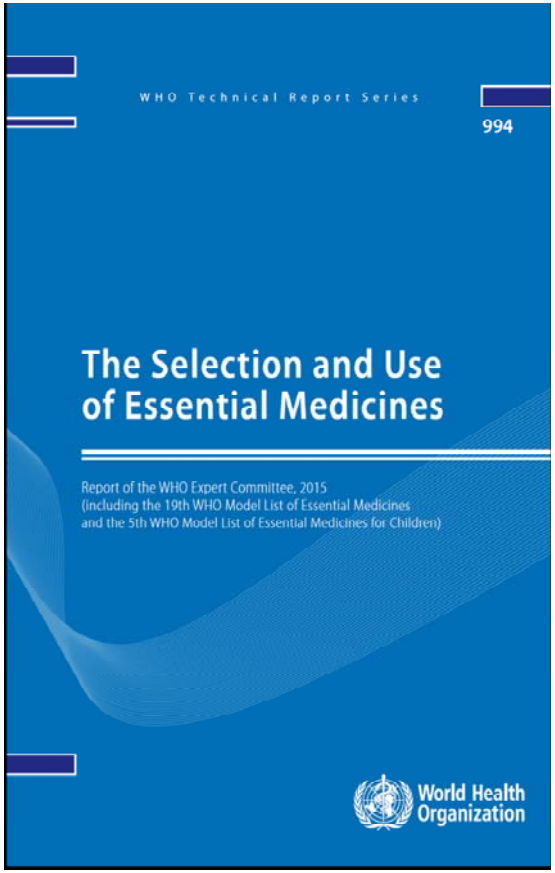
19th EML & 5th EMLc - 2015

- 19th EML: **409** medicines
- 5th EMLc (children): **294** medicines



(TRS 994: 586 pages, 1082 references)

World Health Organization

Lancet 24 Oct 2015

Essential medicines are still essential

On Oct 21, WHO published the full report of the 20th Expert Committee on the Selection and Use of Essential Medicines,[1] with its new WHO Model List of Essential Medicines (EML).[2] The new list includes recently developed medicines for drug-resistant tuberculosis (bedaquiline and delamanid), a number of new cancer treatments (such as imatinib, rituximab, and trastuzumab), and, perhaps most controversially, new direct-acting antiviral drugs (DAA) for the treatment of hepatitis C (sofosbuvir, simeprevir, daclatasvir, ledipasvir, and ombitasvir). Several of these medicines are very expensive. For example, the new medicines to treat hepatitis C are priced up to US$95 000 per 12-week course of treatment, and their primary patents will only

For many years, the WHO Model List has been viewed by some as applicable only to resource-constrained settings, and was assumed to include only the most basic medicines. This is a profound misunderstanding. The same principle of a limited list of cost-effective services underpins the logic of managed care institutions, hospital formularies, and reimbursement lists. The idea of selecting a limited list of essential medicines applies in all countries and in a variety of settings.[9]

We therefore believe that the inclusion of the newly listed cancer treatments, as well as the much-needed options for drug-resistant tuberculosis, is consistent with the definition of essential medicines. In 2002,

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- As medicine expenditures continue to rise worldwide and global drug shortages remain frequent and problematic, the EML concept can potentially play a role in managing health resources.
- Therefore, further investigation is required to address innovative ways to apply EML concepts in HICs to support population wide access to prioritised medicines, while strengthening collaborations between pharmaceutical supply chain stakeholders.
- Transitioning the EML concept from policy to practice continues to be a work in progress.

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.

Margaret Chan, WHO Director General

WHO EML Press release, 8 May 2015

World Health Organization