Il programma dei farmaci essenziali dell'OMS, la nuova lista marzo 2007

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WHO

Essential medicines 30 years on

Outline

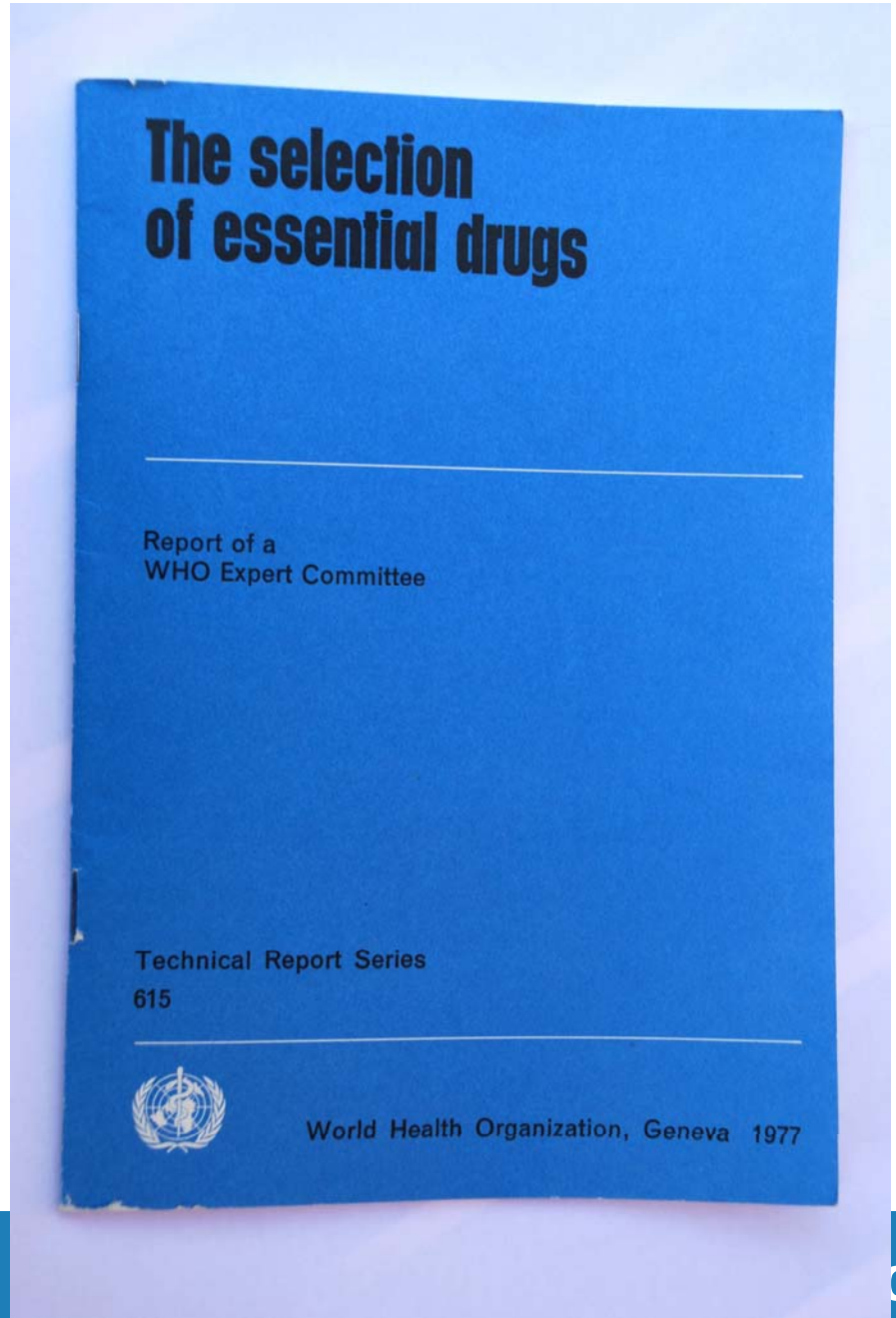
- A review of 30 years of essential medicines
- Where are we now - the 15th Model List
- Challenges in selection
- Innovation versus essential
- Where next?

1970s

International context

- National pharmaceutical policies nonexistent
- Good manufacturing practice limited to industrialised countries - generally poor quality drug regulation
- Few limited lists – selection processes generally informal
- No international criteria on ethical promotion
- Limited/no independent drug information
- Access gap
- Few prescribing standards
- Pre HIV, beginning of 'explosion' of drug development

In 1977…..


The selection of essential drugs
Report of a WHO Expert Committee
Technical Report Series
615
World Health Organization, Geneva 1977

***Lance**t 1978 - Desert island drugs*

Iodine

Codeine

Ciprofloxacin

Prednisolone

Dexamphetamine

	Total n medicines*	Total F+D	Ratio F+D per molecule
Year			
1977	186	0	..
1979	210	250	1·19
1982	216	265	1·23
1984	238	321	1·35
1987	257	375	1·5
1989	267	400	1·5
1991	277	414	1·5
1993	287	431	1·5
1995	286	435	1·52
1997	304	524	1·72
1999	308	547	1·78
2002	320	559	1·72

F+D=number of forms plus dosages. *Multiple salt forms of a drug are counted as two distinct medicines; combination drugs are not counted as distinct medicines if the single components appear on the EML.

Table 1: **Trends in WHO EML**

Laing et al, Lancet 2003;361:1723-29.

Panel 1: **History of the essential medicines concept**

1970: Tanzania made its first EML

1975: Resolution WHA28.66 called on WHO to assist member states to select and procure essential drugs of good quality and at reasonable cost

1977: First list of 205 items published. WHO criticised for attempting to restrict the right of prescribers to prescribe[7]

1978: Alma Ata conference identified provision of essential drugs as one of eight key components of primary health care

1981: First edition of *Managing Drug Supply* identified drug selection as an essential management requirement[8]

1982: Bangladesh adopted essential drugs list based on the WHO selection and banned 1700 products. World Health Assembly gave little support to the essential medicines concept

1984: The World Health Assembly resolution known as the Nordic resolution obtained support of all delegations except the USA (West Germany and Japan abstain)

1985: Nairobi conference brought together NGOs, industry, and government representatives, resulting in the WHO Revised Drug Strategy, which put emphasis beyond selection on procurement, distribution, rational use, and quality assurance for the public sector

UK introduced a restricted list of medicines

1986: Revised Drugs Strategy received unanimous support by the World Health Assembly

1991: Review of changes in the essential drug list highlighted growth of list and increase in the number of substitutable drugs. Inclusion of comparative cost information suggested. Many countries and NGOs adopted the essential drugs approach

1997: Second edition of *Managing Drug Supply* included detailed descriptions on how to select medicines based on prevalent morbidity patterns and existing standard treatment guidelines[11]

1999: Concern expressed at lack of evidence provided to justify changes. Change from experience to evidence-based submissions occupied most of 2000–01

Increasing attention paid to effect of WTO TRIPS agreement. Suggestion made at Seattle WTO meeting that drugs on the WHO essential drugs list be subject to automatic compulsory licensing to ensure universal access

2001: The WHO discussion document *Updating and Disseminating the WHO Model List of Essential Drugs: the Way Forward* attacked by USA in 35-page memorandum. Final version of the revised procedure adopted by the WHO Executive Board in January, 2002

Doha Declaration stated that the TRIPS agreement should be implemented in a manner "supportive of WTO members' right to protect public health and, in particular, to promote access to medicines for all"

2002: Several antiretroviral drugs under patent added to the list. New list published on the internet within days of the meeting; alphabetical and anatomical therapeutic chemical (ATC) classifications and translations in four languages appeared within months[18]

WHO developed a web-based Essential Medicines Library.

WHO stated at TRIPS Council meeting that "people of a country which does not have the capacity for domestic production of a needed product should be no less protected by [TRIPS safeguards than] people who happen to live in countries capable of producing the product."

The evidence revolution

Full description of essential drugs (Expert Committee Report, April 2002)

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

Selection criteria: Essential medicines are selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness

Purpose: Essential medicines are intended to be available within the context of functioning health systems at all times, in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford.

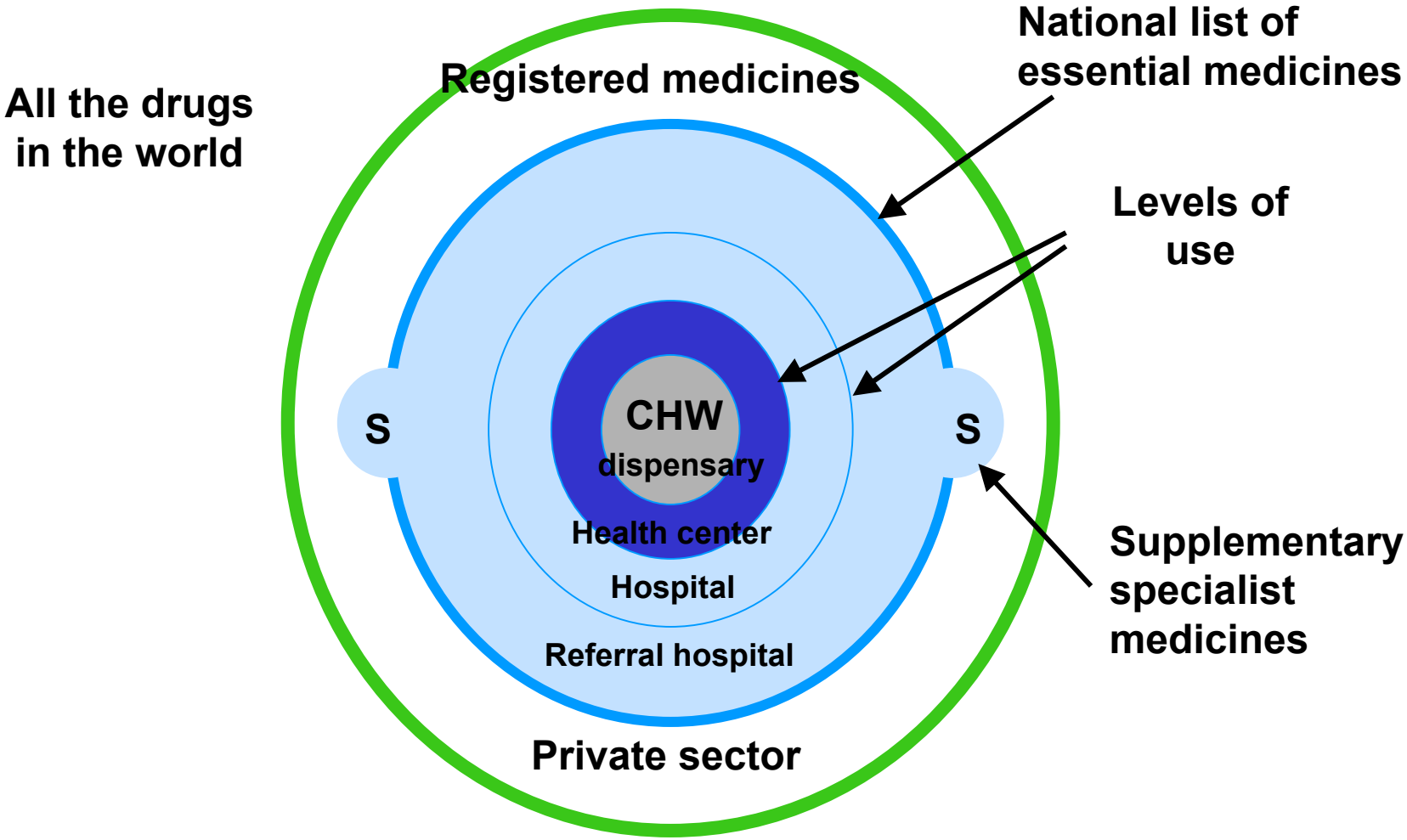
Implementation: The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility.

2002 meeting

- 12 ARVs added –
  - Patent and absolute price excluded as criteria
- List published and translated in days
  - Transparent process
- Recognition of multiple roles of global Model List
  - Purchasing, advocacy, model process

2007 - EML 15

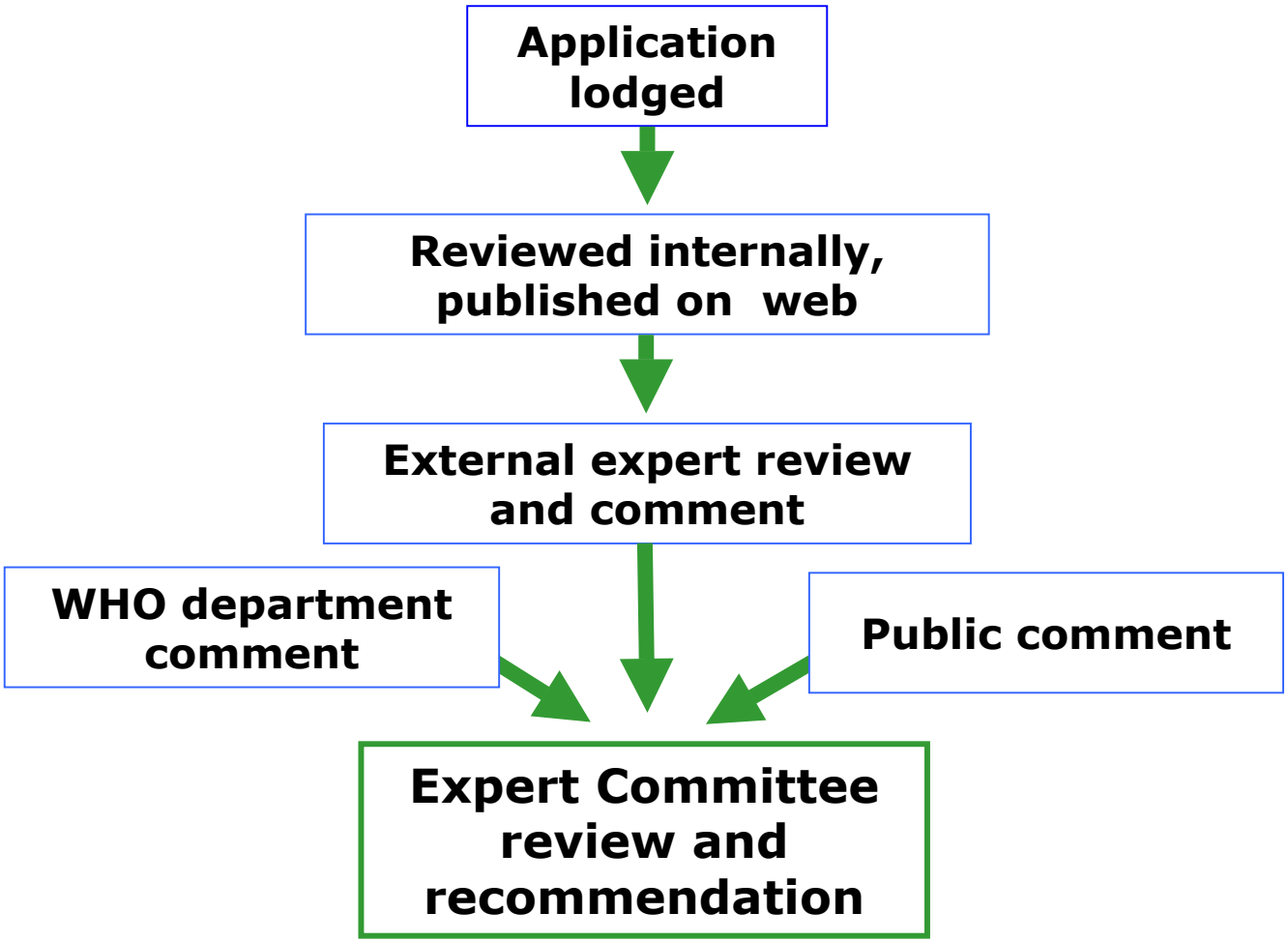
The Essential Medicines Target



Selection - the ideal

- WHO treatment guideline developed
- Treatment recommendation made
- Proposal to update list to reflect new guideline
- Potential to influence practice

Process


Application lodged
Reviewed internally, published on web
External expert review and comment
WHO department comment
Public comment
Expert Committee review and recommendation

World Health Organization

15th Expert Committee on the Selection and Use of Essential Medicines

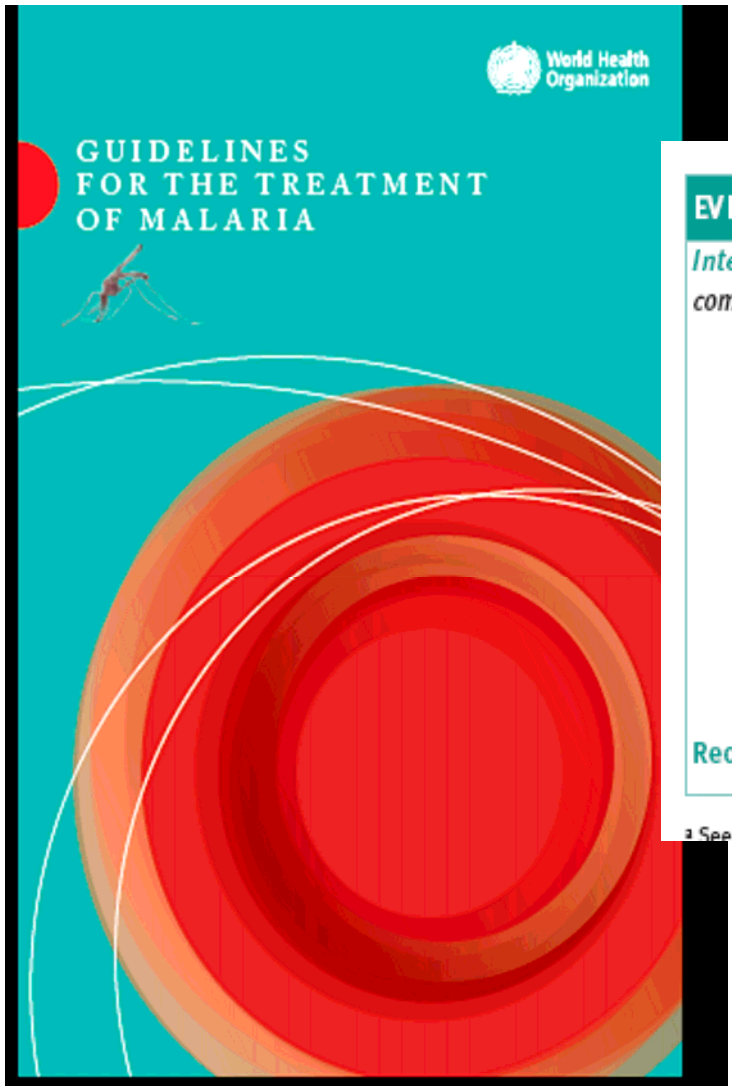
Intended applications:

Drug name	Formulation	Applicant
emtricitabine and tenofovir disoproxil fumarate fixed-dose combination	Tablet 200 mg emtricitabine and 300 mg tenofovir DF, equivalent to 245 mg of tenofovir disoproxil.	Daniel E. Kates, M.D., Director, Medical Communications, Gilead Sciences Inc.
immunoglobulin		David Watters and Helen Chapel, IPOPI
morphine	Slow release tablet	Phil Wiffen, supported by the International Association for Hospice and Palliative Care
tenofovir disoproxil fumarate (TDF)	Tablet 300 mg tenofovir disoproxil fumarate equivalent to 245 mg tenofovir disoproxil	Daniel E. Kates, M.D., Director, Medical Communications, Gilead Sciences Inc.

Intended applications for paediatric medicines:

Drug name	Formulation	Applicant
phenobarbitone: • application for inclusion • evidence table	Injectable 200mg/ml, 1ml	Supported by Department of Child and Adolescent Health, WHO; prepared by Dr J. Wilmshurst, South Africa

Back to the EML Expert Committee Resources Menu
See also the Essential Medicines Library



EVIDENCE: trials comparing monotherapies with ACTs[a]

Interventions: *single drug (oral AQ, MQ or SP) compared with single drug in combination with AS (both oral)*

Summary of RCTs: one meta-analysis of 11 RCTs has been conducted. This found a clear benefit of adding 3 days of AS to AQ, MQ or SP for uncomplicated malaria. The combination treatment resulted in fewer parasitological failures at day 28 and reduced gametocyte carriage compared to the baseline value. Adding AS treatment for 1 day (6 RCTs) was also associated with fewer treatment failures by day 28 but was significantly less effective than the 3-day regimen (OR: 0.34; 95% CI: 0.24–0.47; $p < 0.0001$).

Expert comment: the addition of AS to standard monotherapy significantly reduces treatment failure, recrudescence and gametocyte carriage.

Basis of decision: systematic review.

Recommendation: replace monotherapy with oral ACTs given for 3 days.

[a] See also Annex 7.1.

EVIDENCE: trials comparing ACTs[a]

Interventions: oral AL, AS+AQ, AS+MQ, AS+SP

Summary of RCTs: AL 6-dose regimen compared with 4-dose regimen; 6 doses resulted in higher cure rate in 1 trial in Thailand (RR: 0.19; 95% CI: 0.06–0.62).

AS+MQ compared with AL 6-dose regimen; systematic review including 2 small RCTs from Thailand. Higher proportion of patients with parasitaemia at day 28 with AL but difference not statistically significant. One additional RCT in Lao People's Democratic Republic also reported higher proportions of patients with parasitaemia at day 42 with AL but also not statistically significant.

AS+AQ compared with AL 6-dose regimen; 1 trial in Tanzania found a significantly higher proportion of parasitological failures on day 28 with AS+AQ.

No trials of AL compared with AS+SP.

Expert comment: the efficacy of ACTs with AQ or SP as partner medicines is insufficient where cure rates with these medicines as monotherapies is less than 80%. The efficacy of AL and AS+MQ generally exceeds 90% except at the Thai-Cambodian border, where AL failure rate was 15%.

Basis of decision: expert opinion.

Recommendations

1. Use the following ACTs: AL (6-dose regimen), AS+AQ, AS+MQ, AS+SP.
2. In areas with AQ and SP resistance exceeding 20% (PCR-corrected at day 28 of follow-up), use AS+MQ or AL.

6.5.3.1 For curative treatment	
Medicines for the treatment of *P. falciparum* malaria cases should be used in combination.	
amodiaquine*	tablet, 153 mg or 200 mg (base) * amodiaquine should preferably be used as part of combination therapy
artemether + lumefantrine*	tablet, 20 mg + 120 mg * recommended for use in areas with significant drug resistance and not in pregnancy or in children below 10 kg
chloroquine	tablet 100 mg, 150 mg (as phosphate or sulfate); syrup, 50 mg (as phosphate or sulfate)/5 ml; injection 40 mg (as hydrochloride, phosphate or sulfate)/ml in 5-ml ampoule
primaquine	tablet, 7.5 mg, 15 mg (as diphosphate)
quinine	tablet, 300 mg (as bisulfate or sulfate); injection, 300 mg (as dihydrochloride)/ml in 2-ml ampoule
Complementary List	
artemether	*injection, 80 mg/ml in 1-ml ampoule*
artesunate	*tablet, 50 mg*
doxycycline	*capsule or tablet, 100 mg (hydrochloride)* *(for use only in combination with quinine)*
mefloquine	*tablet, 250 mg (as hydrochloride)*
sulfadoxine + pyrimethamine	*tablet, 500 mg + 25 mg*

6.5.3 Antimalarial medicines	
6.5.3.1 For curative treatment	
Medicines for the treatment of *P. falciparum* malaria cases should be used in combination. The list currently recommends combinations according to treatment guidelines. The Committee recognizes that not all of these FDCs exist and encourages their development and rigorous testing. The Committee also encourages development and testing of rectal dosage formulations.	
amodiaquine*	**Tablet: 153 mg or 200 mg (base).** *to be used (a) in combination with artesunate 50 mg OR may be used alone for the treatment of *P.vivax, P.ovale and P.malariae* infections
artemether	**Injection: 80 mg/ml in 1-ml ampoule.** *For use in the management of severe malaria*
artemether + lumefantrine*	**Tablet: 20 mg + 120 mg.** * not recommended in the first trimester of pregnancy or in children below 5 kg.
artesunate*	**Tablet: 50 mg.** * to be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine **Injection:** Ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution; *For use in the management of severe malaria*
chloroquine	**Syrup: 50 mg (as phosphate or sulfate)/5 ml.** **Tablet: 100 mg; 150 mg (as phosphate or sulfate).**
Doxycycline*	**Capsule or tablet: 100 mg (hydrochloride)** *for use only in combination with quinine.
mefloquine*	**Tablet: 250 mg (as hydrochloride).** *to be used in combination with artesunate 50mg
primaquine*	**Tablet: 7.5 mg; 15 mg (as diphosphate)** *only for use to achieve radical cure of *P.vivax* and *P.ovale* infections, given for 14 days
quinine*	**Injection: 300 mg quinine dihydrochloride/ml in 2-ml ampoule.** **Tablet: 300 mg (as bisulfate or sulfate).** * for use only in the management of severe malaria, and should be used in combination with doxycycline
sulfadoxine + pyrimethamine*	**Tablet: 500 mg + 25 mg.** * only in combination with artesunate 50 mg

The challenges….

12.6 Lipid-lowering agents
The WHO Expert Committee on the Selection and Use of Essential Medicines recognizes the value of lipid-lowering drugs in treating patients with hyperlipidaemia. HMG-CoA reductase inhibitors, often referred to as "statins", are a family of potent and effective lipid-lowering drugs with a good tolerability profile. Several of these drugs have been shown to reduce the incidence of fatal and non-fatal myocardial infarction, stroke and mortality (all causes), as well as the need for coronary by-pass surgery. All remain very costly but may be cost effective for secondary prevention of cardiovascular disease as well as for primary prevention in some very high-risk patients. Since no single drug has been shown to be significantly more effective or less expensive than others in the group, none is included in the Model List; the choice of drug for use in patients at highest risk should be decided at the national level.

5.1.8 BLOOD CHOLESTEROL REDUCTION WITH A STATIN

Recommendation (see Table 4)	Levels of evidence	Strength of recommendations
Treatment with statins is recommended for all patients with established CHD. Treatment should be continued in the long term, probably lifelong. Patients at high baseline risk are particularly likely to benefit. Lowering total and LDL cholesterol using a moderate, trial-validated dose of statin (e.g. simvastatin 40 mg per day) is likely to be the best approach. Monitoring of blood cholesterol levels is not mandatory.	Ia	A
Other lipid lowering agents are not recommended, either as an alternative to statins or in addition to them.	Ia	A

RECOMMENDED DRUGS AND DOSES:

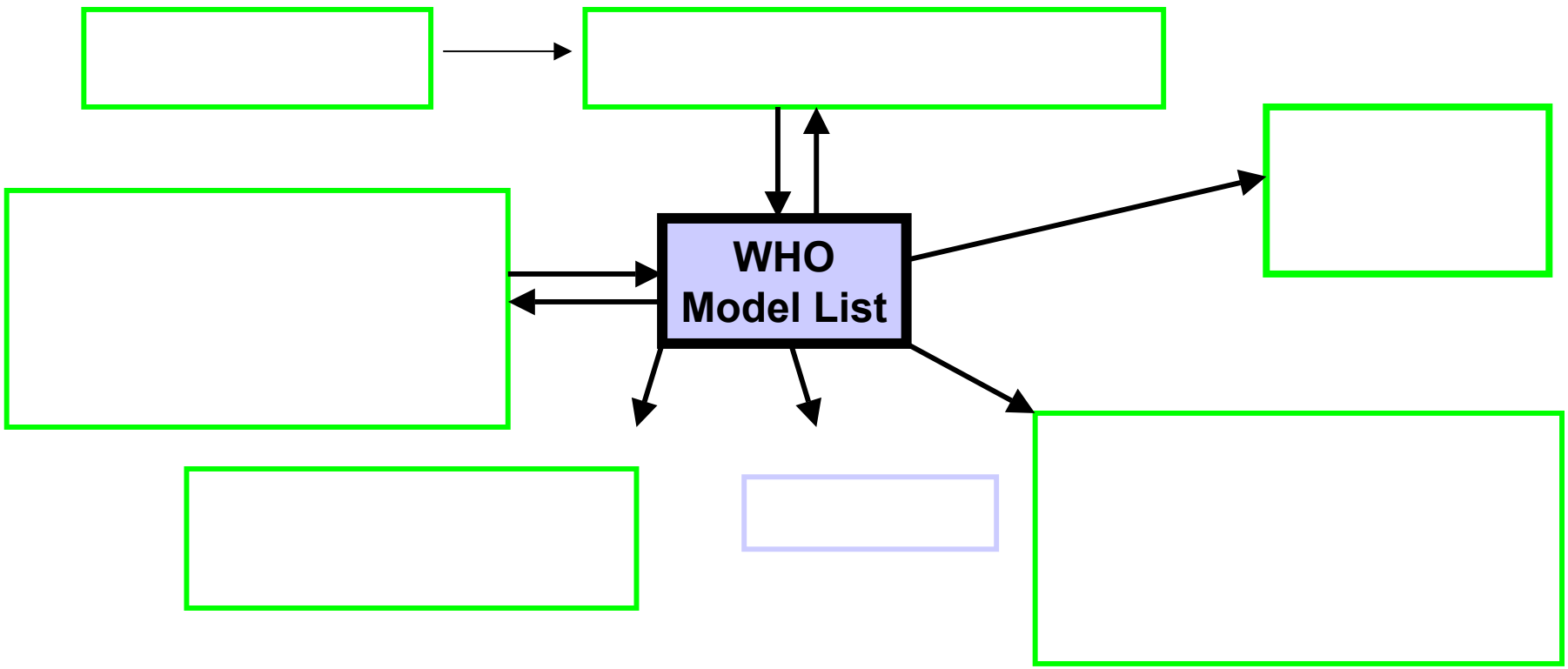
- ✔ simvastatin, initial dose 10 mg once at night, increasing to 40 mg once at night;*
- ✔ pravastatin, initial dose 10 mg once at night, increasing to 40 mg once at night.*

12.6 Lipid-lowering agents	
simvastatin*	**Tablet: 5 mg;10 mg; 20 mg and 40 mg.** * for use in high risk patients; alternatives are atorvastatin, lovastatin pravastatin, fluvastatin, depending on local availability and cost.

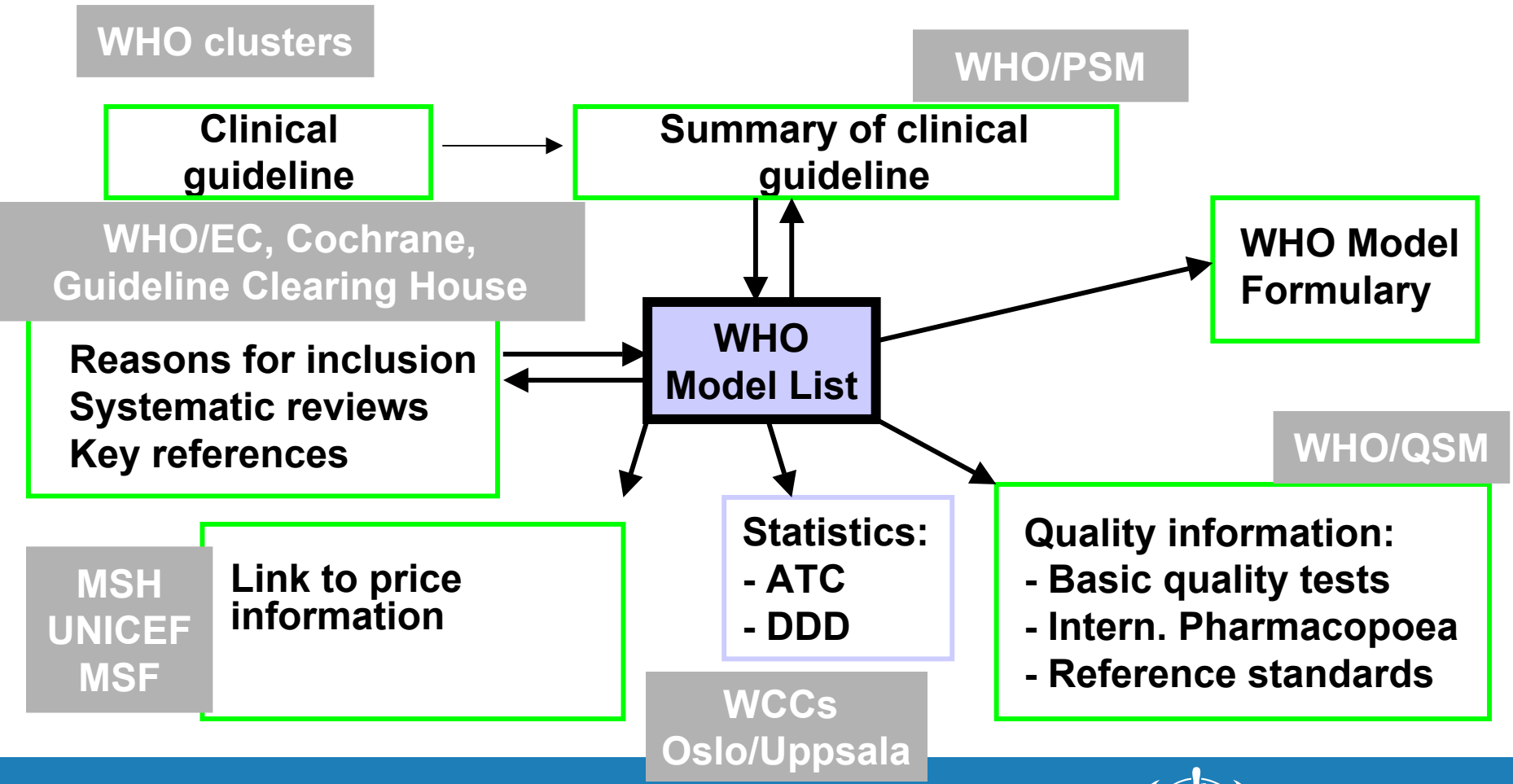
WHO Model List (revised March 2007)

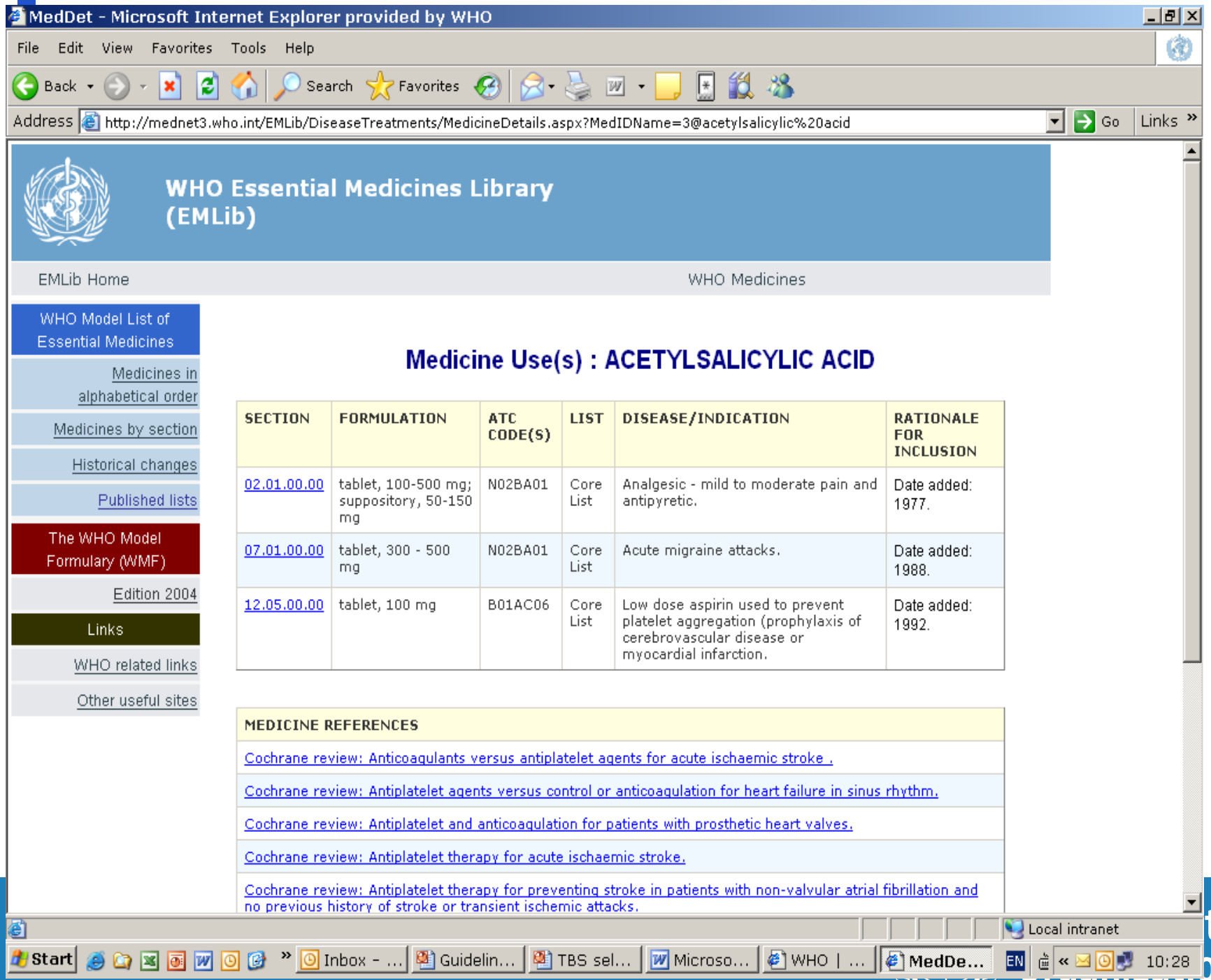
Additions, new medicines	Additions, new dosage forms	Deletes	Rejections	Defer
cefazolin injection	Acyclovir ointment	Levofloxacin ciprofloxacin for TB	Antivenom Fab Fragments	Rectal artesunate
Emtricitabine	Artesunate injection	Idoxuridine	Cefalexin	
Fluoxetine	Efavirenz 600mg tab	Chloroquine injection	Sumatriptan	
Immunoglobulin (complementary)	Morphine SR	Pentamidine 300mg injection (fro trypanosomiasis)	Artemeter /lumefantrine Suspension	
Levonorgestrel implant	Phenobarb injection	Chlormethine		
Medroxyprogesterone + estradiol injection	FDCs for HIV: Efavirenz/emtricitabine/tenofovir Lamivudine/stavudine/nevirapine Lamivudine/zidovudine/nevirapine Lamivudine/zidovudine Emtricitabine/tenofovir	Levamisole (for cancer)		
Paromomycin	FDC for TB: Rifampicin/isoniazid/ethambutol	Iopanoic acid, Tablet, 500mg		
Ribavirin	Carbamazepine (children)	Propyliodone, Oily suspension		
Simvastatin	Isoniazid (children)			
Tenofovir	Phenytoin (children)			
Caffeine citrate (children)	Pyrazinamide (children)			
	Valproic acid (children)			
	Retinol 50000, 100000 (children)			

The WHO Essential Medicines Library:



The WHO Essential Medicines Library, status 2005




MedDet - Microsoft Internet Explorer provided by WHO
File Edit View Favorites Tools Help
Back Search Favorites
Address http://mednet3.who.int/EMLib/DiseaseTreatments/MedicineDetails.aspx?MedIDName=3@acetylsalicylic%20acid
Go Links
WHO Essential Medicines Library (EMLib)
EMLib Home
WHO Medicines
WHO Model List of Essential Medicines
Medicines in alphabetical order
Medicines by section
Historical changes
Published lists
The WHO Model Formulary (WMF)
Edition 2004
Links
WHO related links
Other useful sites
Medicine Use(s) : ACETYLSALICYLIC ACID
SECTION
FORMULATION
ATC CODE(S)
LIST
DISEASE/INDICATION
RATIONALE FOR INCLUSION
02.01.00.00
tablet, 100-500 mg; suppository, 50-150 mg
N02BA01
Core List
Analgesic - mild to moderate pain and antipyretic.
Date added: 1977.
07.01.00.00
tablet, 300 - 500 mg
N02BA01
Core List
Acute migraine attacks.
Date added: 1988.
12.05.00.00
tablet, 100 mg
B01AC06
Core List
Low dose aspirin used to prevent platelet aggregation (prophylaxis of cerebrovascular disease or myocardial infarction.
Date added: 1992.
MEDICINE REFERENCES
Cochrane review: Anticoagulants versus antiplatelet agents for acute ischaemic stroke .
Cochrane review: Antiplatelet agents versus control or anticoagulation for heart failure in sinus rhythm.
Cochrane review: Antiplatelet and anticoagulation for patients with prosthetic heart valves.
Cochrane review: Antiplatelet therapy for acute ischaemic stroke.
Cochrane review: Antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks.
Local intranet
Start
Inbox - ...
Guidelin...
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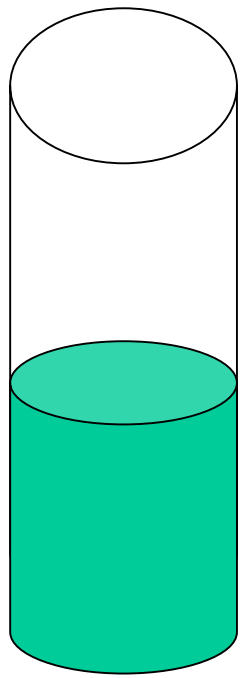
10:28

Cochrane reviews

- **Over 50% of medicines on the 14th list have a relevant Cochrane review**
- **Useful source of information**
- **Some reviews raise questions over inclusion on the list e.g. antacids, allopurinol**

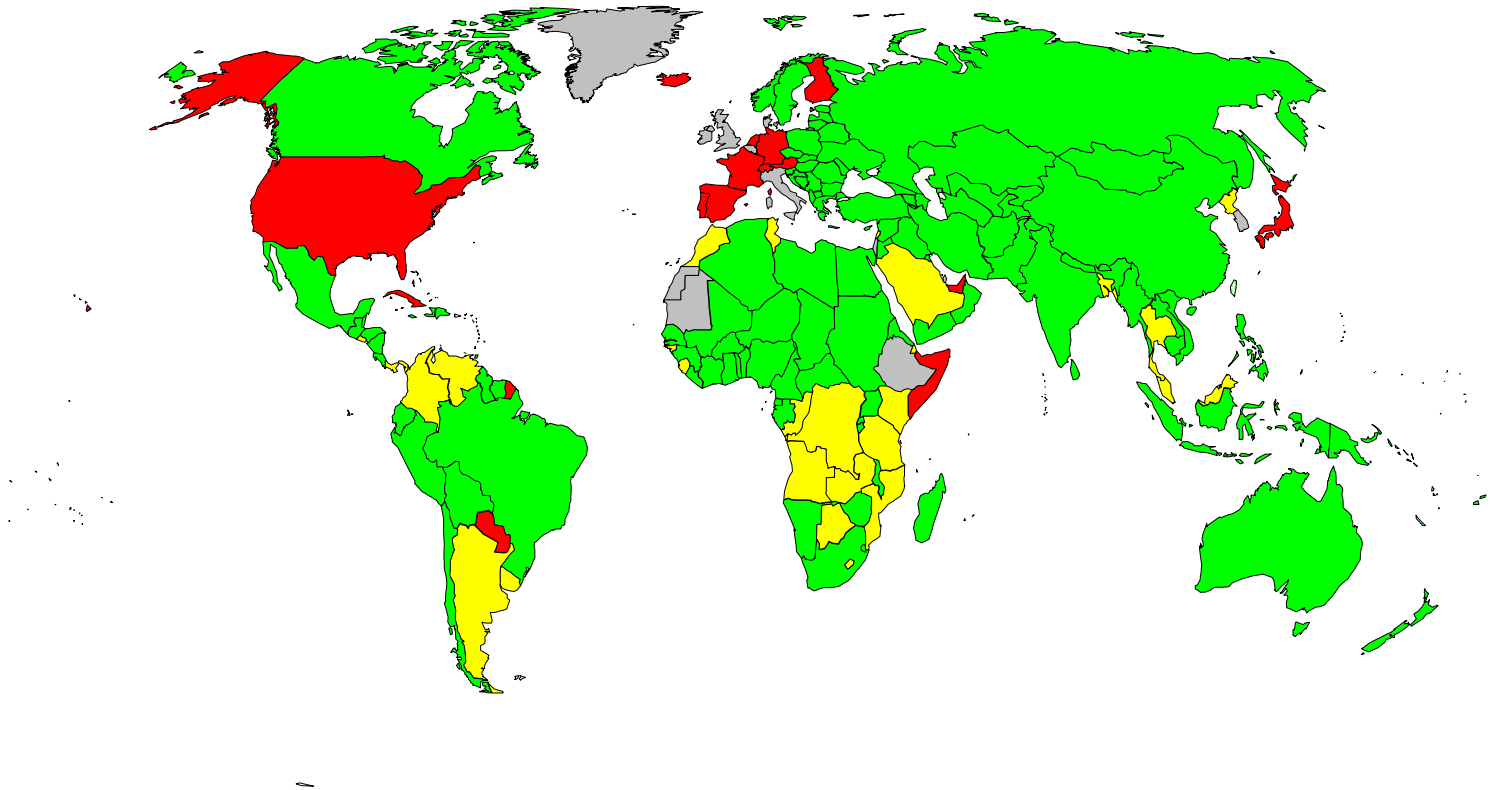


implementation

Treatment guidelines and formulary manuals put the essential drugs concept into clinical practice

World Health Organization

2003 Level 1 indicators – countries with EML or equivalent lists



Countries with an official selective list for training, supply, reimbursement or related health objectives.
Some countries have selective state/provincial lists instead of or in addition to national lists.

WHO/PSM/PAR/2006.4

World Health Organization

Ecumenical Pharmaceutical Network

ICRC

IDA FOUNDATION

International Federation of Red Cross and Red Crescent Societies

IOM • OIM International Organization for Migration

Médecins Sans Frontières

merlin

UNFPA United Nations Population Fund

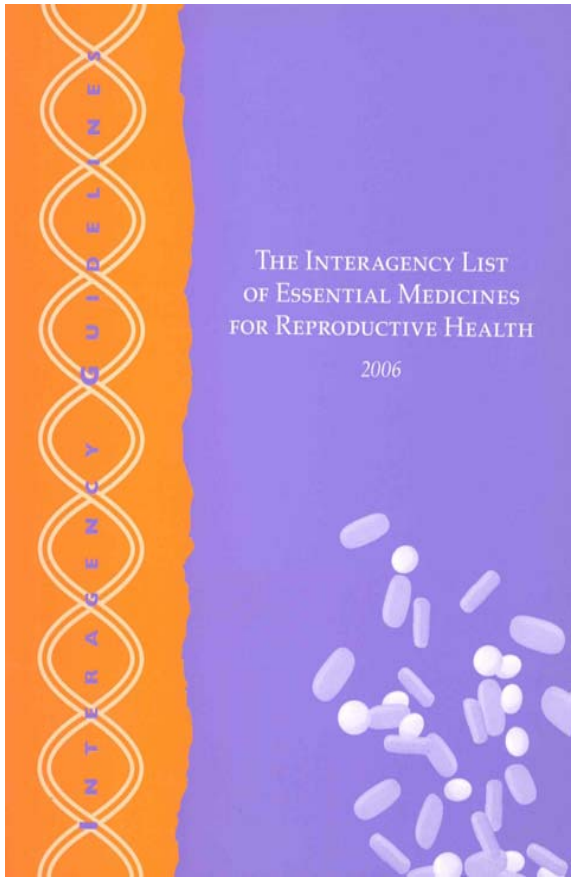
UNHCR

unicef

The Interagency Emergency Health Kit 2006

Medicines and medical devices for 10,000 people for approximately 3 months

An interagency document



World Health Organization

World Health Organization

So what?

- **Evidence of impact – health outcomes**
  - **Delhi state improved availability of supply**
  - **studies of *lack* of essential medicines**
- **Evidence of impact – policy, advocacy**
  - **Indirect evidence through impact of listing ARVs**
  - **Linkage with pricing policies**
  - **Linkage with import policies**
- **Evidence of change?**
  - **Analysis underway**

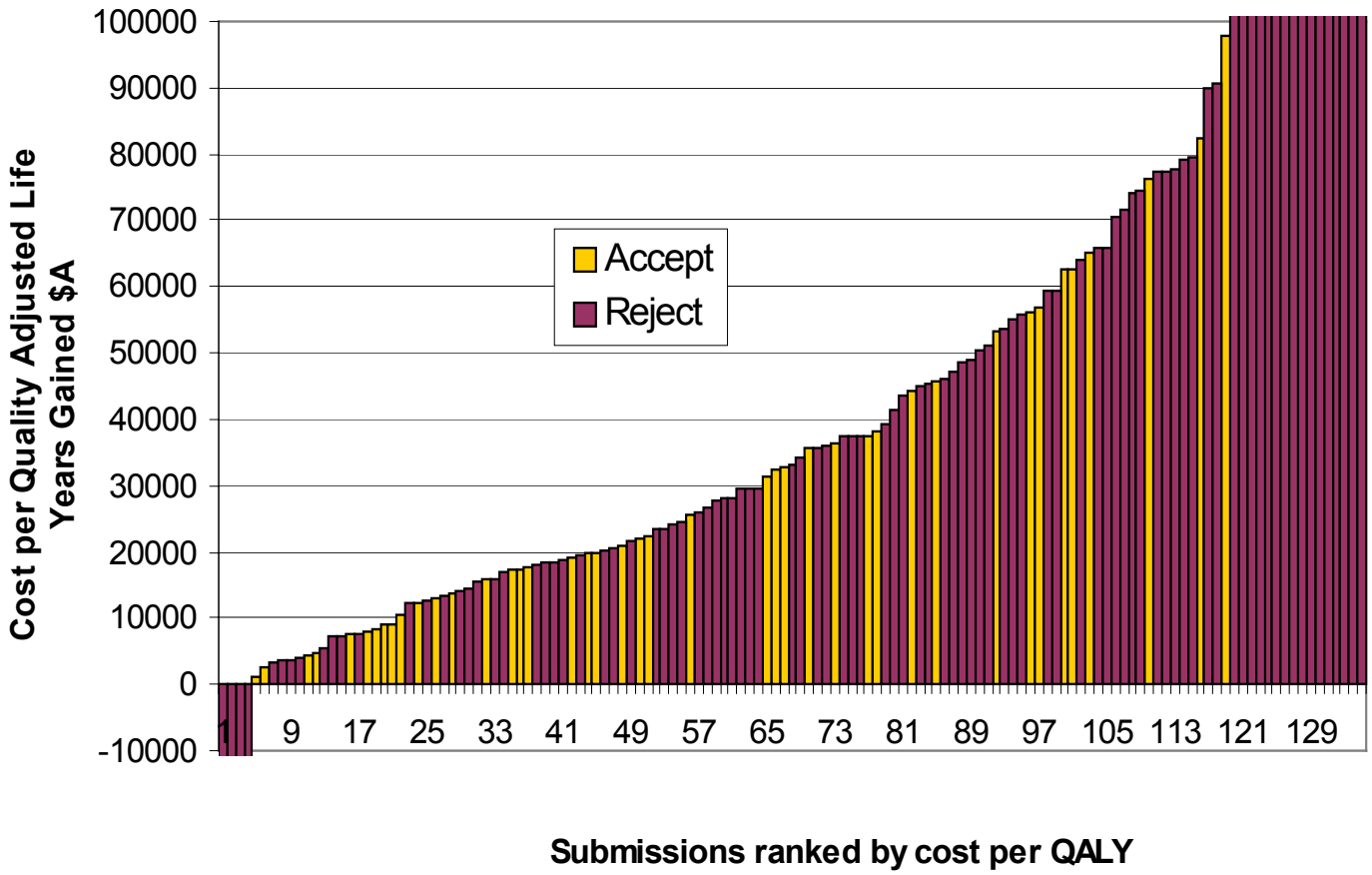
Challenges in selection

- Post-regulatory process versus early access
  - New fixed dose combination medicines
- Need for public access to evidence
  - Early proposal for amodiaquine/artesunate
- Evidence for old medicines
- Pressure for treatments for rare diseases
- (Patents are not a consideration)

What about cost-effectiveness?

- And thresholds?

Recommendations by PBAC 1993-2003 based on Cost per Life year gained



Innovation versus essential

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http://www.innovation.org/index.cfm/nonav/Great_Moments_in_Innovation

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innovation.org

discovering new medicines for better lives and a brighter future

Innovation **TODAY** | **IMPACT** of innovation | **FUTURE** of innovation | **STORIES** of innovation | **INSIDE** drug discovery | **NEWS** center | **TOOLS & RESOURCES**

Great Moments in Innovation

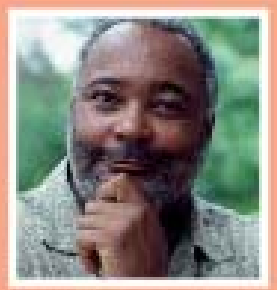
[1900] [1910] [1920] [1930] [1940] [1950] [1960] [1970] [1980] [1990] [2000]

1996 Another weapon against HIV/AIDS

The introduction of non-nucleoside reverse transcriptase inhibitors the second class of drugs that interfere with the transcriptase enzyme that plays a key role in the life cycle of HIV. This new drug binds to the enzyme so it can't copy itself.

Now: Partly Cloudy, 21° C Thu: 28° C Fri: 27° C

VALUE OF MEDICINES



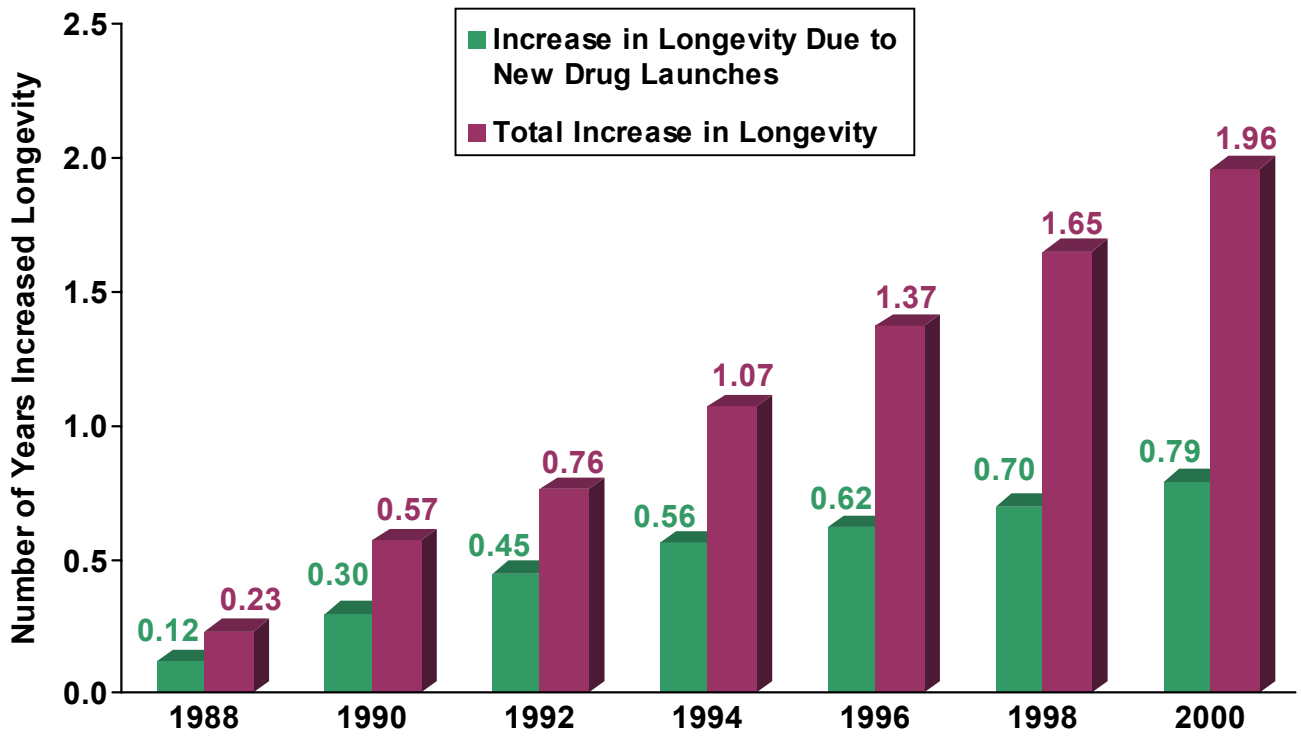


Facts and Figures 2006

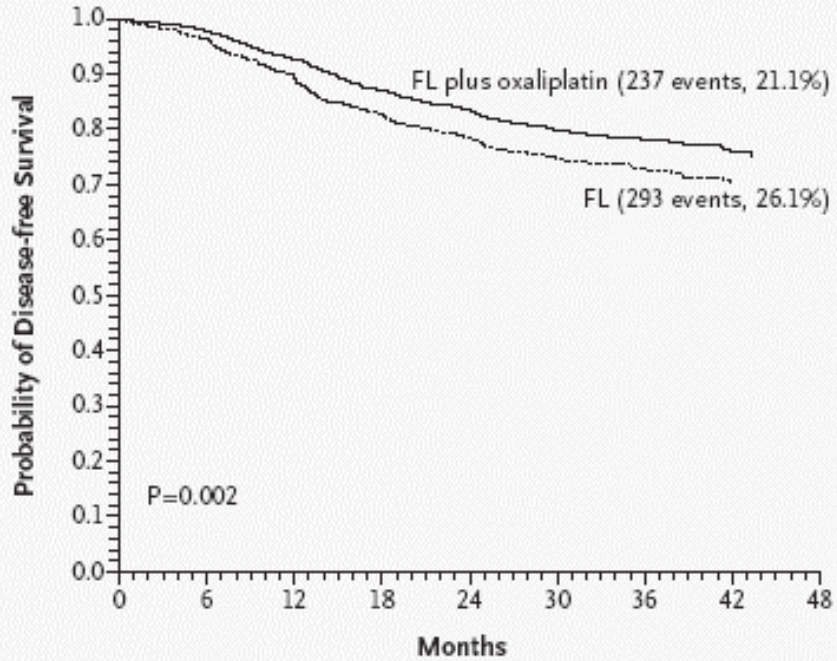
PhRMA

New Medicines Increase Longevity

They Account for 40% of Increase in Life Expectancy



Data source: Lichtenberg[8]



No. at Risk							
FL+oxaliplatin	1123	1086	1023	959	888	663	395
FL	1123	1066	981	903	817	619	356

Figure 1. Kaplan–Meier Estimates of Disease-free Survival in the Group Given Fluorouracil and Leucovorin (FL) and the Group Given FL plus Oxaliplatin, According to the Intention to Treat.

The hazard ratio for recurrence in the group given FL plus oxaliplatin, as compared with the FL group, was 0.77 (95 percent confidence interval, 0.65 to 0.91; P=0.002).

N Engl J Med 2004;350:2343-51.

World Health Organization

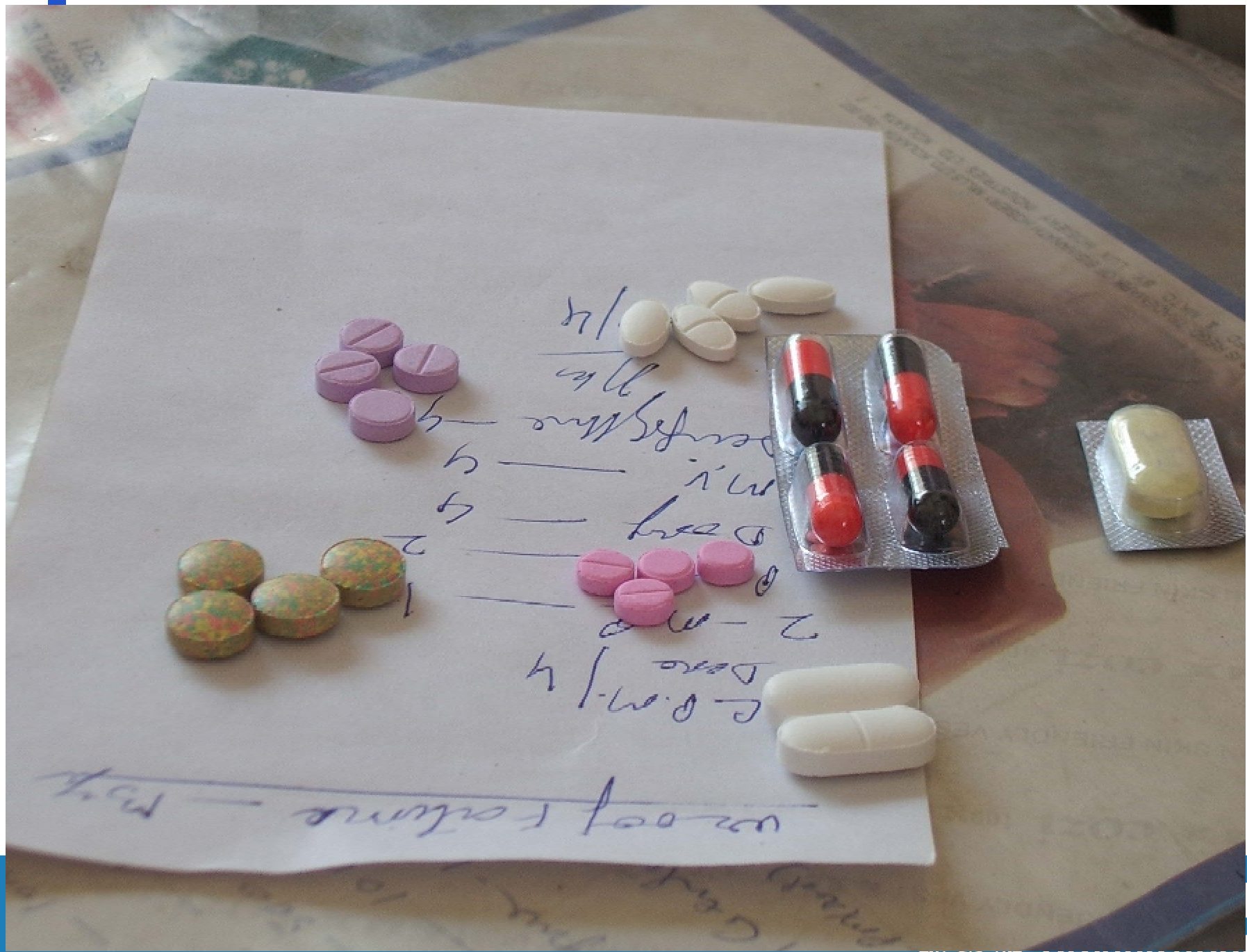
BUSINESS WIRE : OneWorld Health's First Approved Drug Added to WHO Essential Medicines List
May 22, 2007 06:00 AM Eastern Daylight Time
Paromomycin IM Injection Treatment for Deadly Kala-Azar Approved by Expert Committee
SAN FRANCISCO & NEW DELHI, India--(BUSINESS WIRE)--The Institute for OneWorld Health, a US-based non-profit pharmaceutical company, today announced that its first approved drug product, Paromomycin IM Injection, was designated by the World Health Organization (WHO) for inclusion on its Model List for Essential Medicines.

Where next?

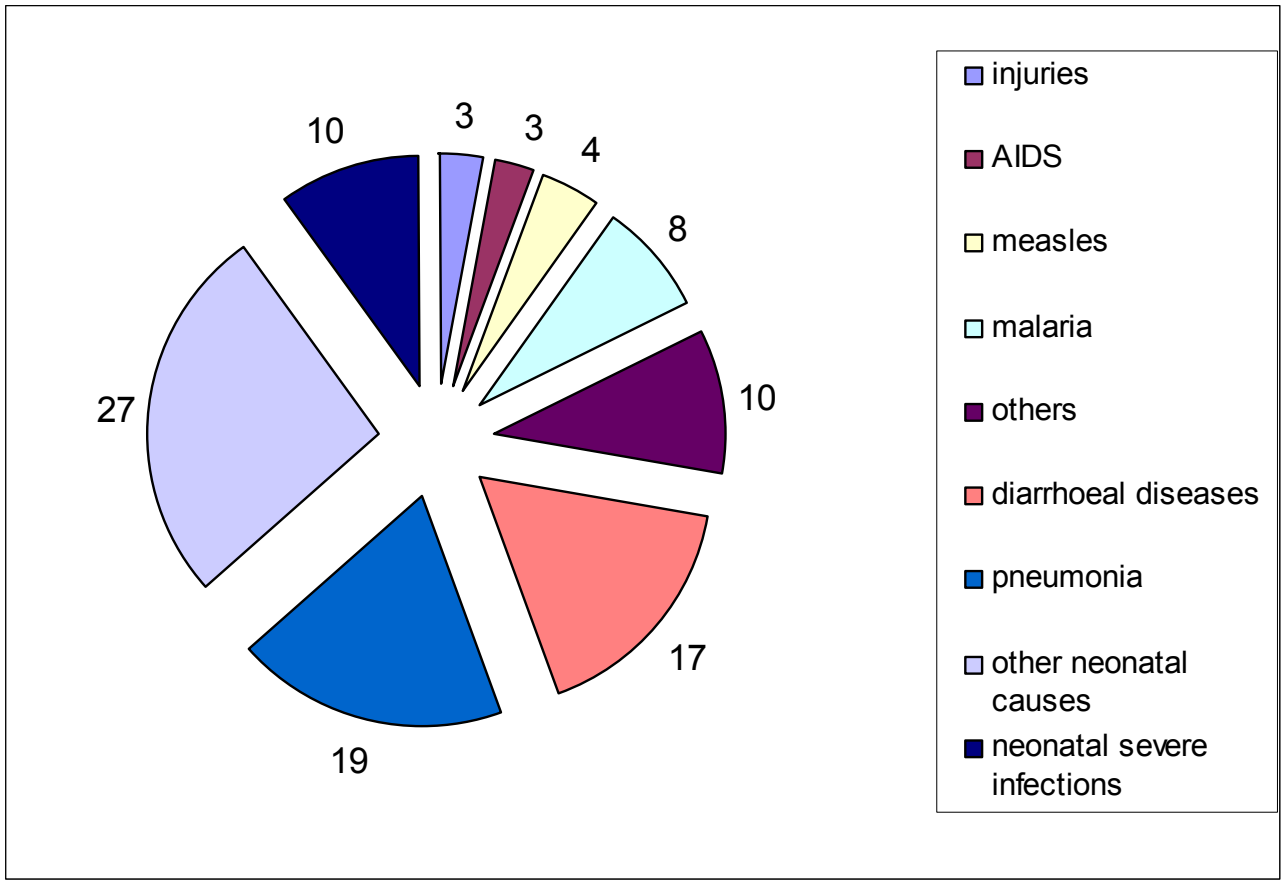
The changing policy environment

- Increasing cost of new products
- Development of trade agreements, restrictions
- Pipeline drying up for multinationals
- Patents
- Vertical funding programs and donors
- Increasing transparency about prices
- Increasing health insurance
- Increasing access gap especially for HIV
- Neglected populations and diseases

Essential medicines for children



Causes of death in under 5s



… effective medicines exist for many of these but are not available in children's forms or affordable……

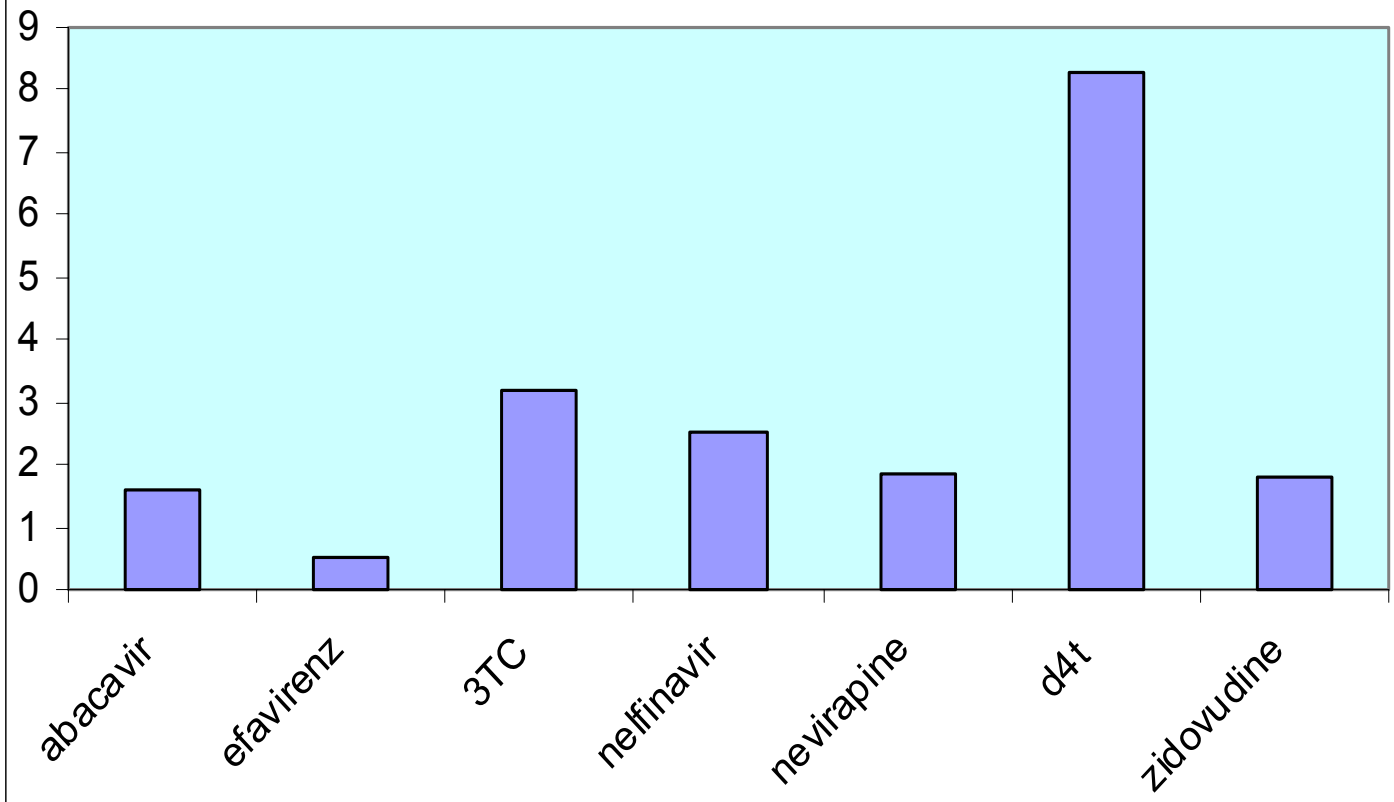
Survey of 29 countries: Problems with Children's Medicines for Malaria, TB and HIV

- Lack of appropriate paediatric formulations
  - Artemisinin derivatives in tablet form only
  - No paediatric dose forms available for isoniazid, pyrazinamide, ethambutol, rifampicin
  - Many countries no paediatric HIV medicines
- Cost of medicines
  - ARV syrup formulations, artemisinin combinations
- Need for standard methods for adapting adult medicines for use in children
- Costs of special storage conditions for unstable products

Survey of 29 countries: Problems identified for other acute and chronic illnesses in childhood

- Availability of suitable formulations
  - Vitamins & minerals, some antibiotics and anti-infectives, anti-epileptic medicines, cardiovascular medicines, cytotoxic drugs
- Costs of medicines
  - Anti-infective agents, cytotoxic drugs, insulin pens, steroid inhalers for asthma, vaccines
- Other issues
  - Lack of standardised dosing measures, breaks in cold chain for vaccines, storage costs for drugs, lack of paediatric guidelines and formulary

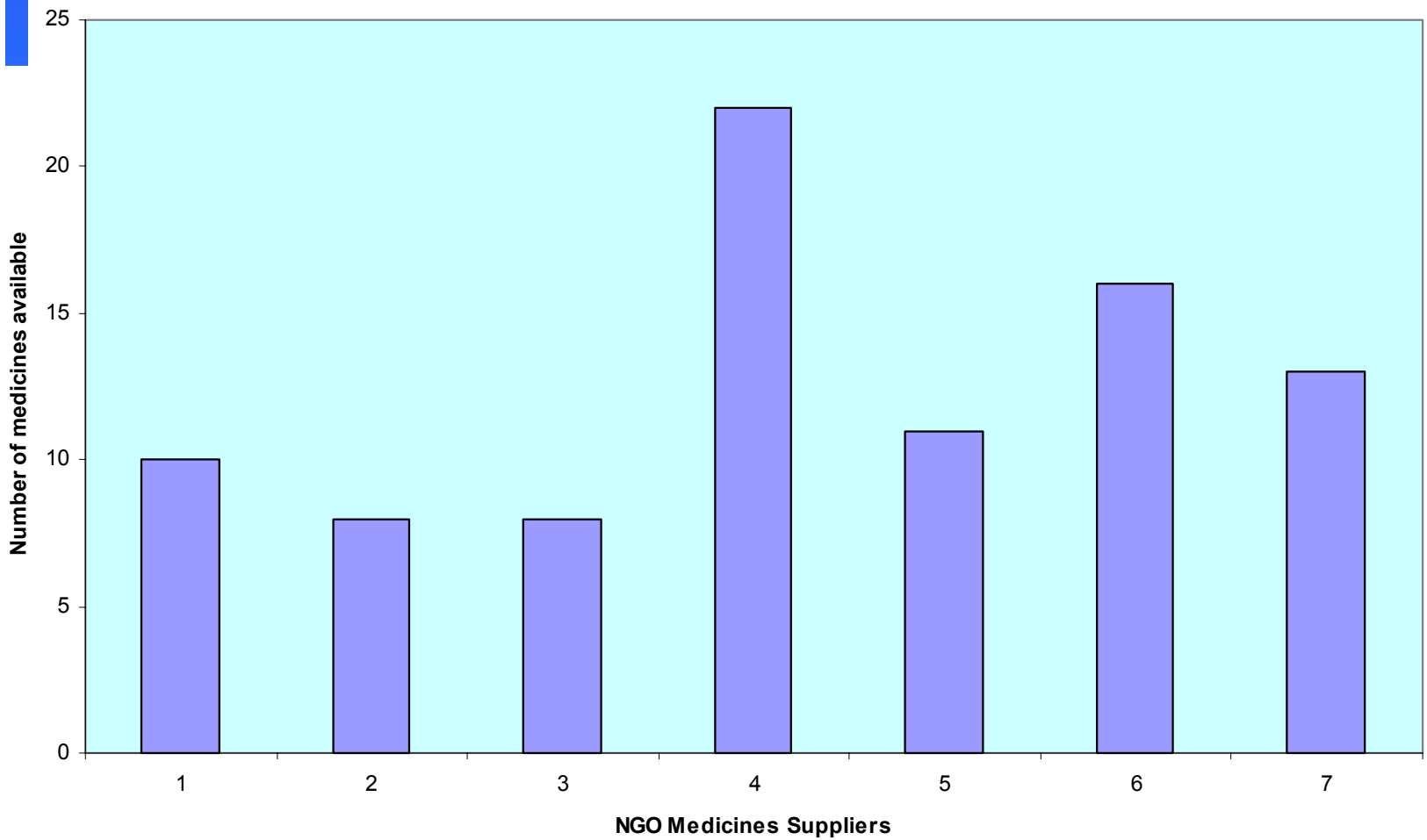
Ratio of liquid/solid dosage form prices for sample of ARVS



Source: International Drug Price Indicator Guide, 2005; median price

World Health Organization

Availability of 22 medicines for children from International NGO Medicine Suppliers



World Health Organization

EML 2005	Core	Complementary	Total
Total No of medication listings	284	84	368
Listings not assessed	129	45	174
Listings assessed	155	39	194
PF indicated	119	28	148
PF not indicated	36	11	46
PF indicated and on the list	52	3	55
PF indicated and not on the list	67	25	93
PF indicated, not on the list, duplicate listings removed	**59**	**23**	**83**
PF indicated, not on list and available*	29	2	30
PF indicated, not on list and not available*	30	21	53

http://mednet3.who.int/EML/expcom/CHILDREN/WEB_draft_list_april.pdf

First DRAFT:

WHO Model List of Essential Medicines for Children

2007

draft for consultation

World Health Organization

And…

- Guidelines and evidence
- Needs of middle income countries
- Advice on costs
- Faster process
- Better information

Conclusion

- Can a global 'essential' medicines list meet multiple needs?
- Counterweight to 'innovation'?
- Contribute to driving relevant development?
- Restore true market?

Thank you

www.who.int/medicines


World Health
Organization