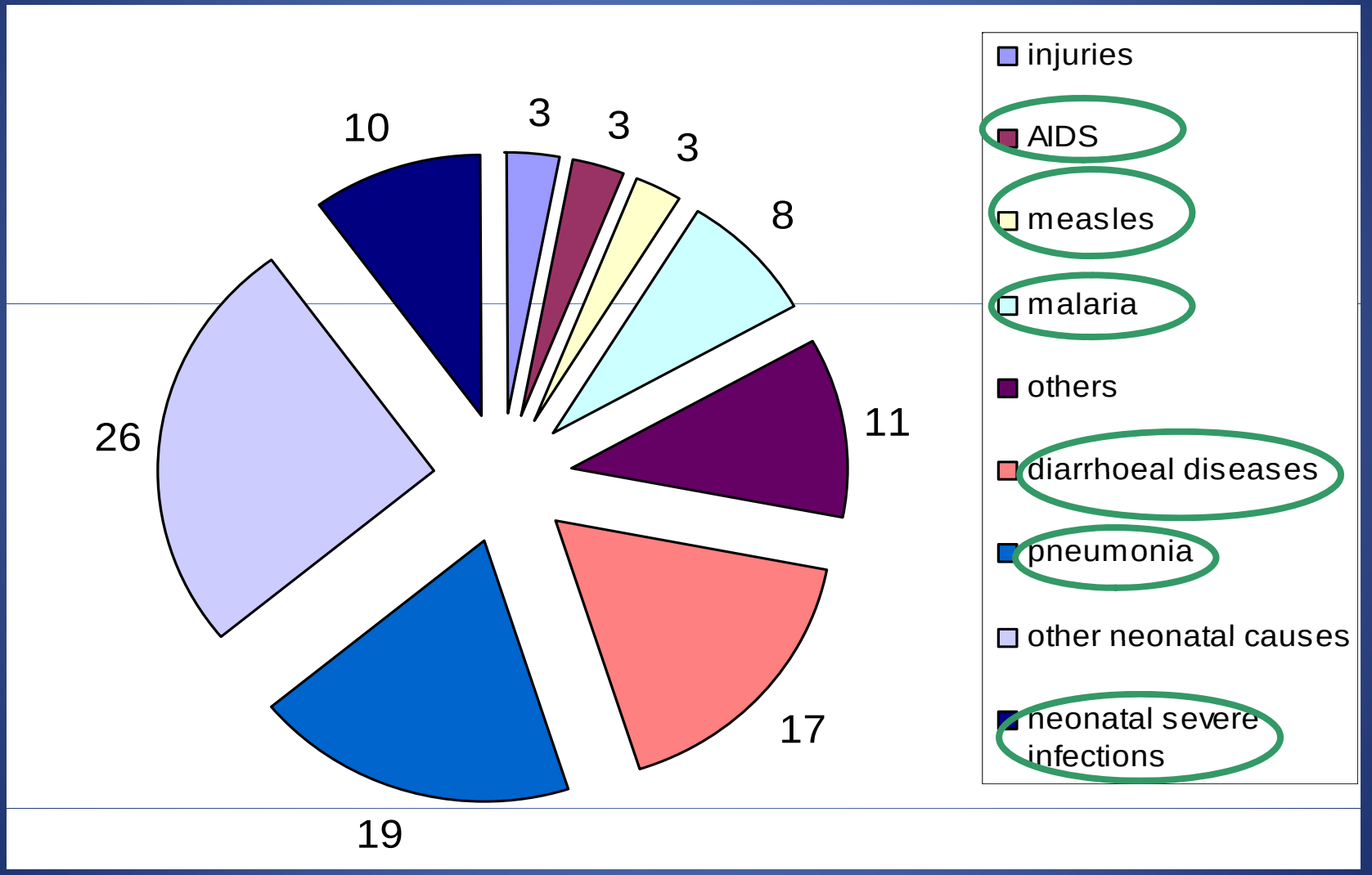
make medicines Child Size

Make Medicines Child Size: WHO Better Medicines for Children Project

Lisa Bero
University of California, San Francisco

Causes of death in children under 5



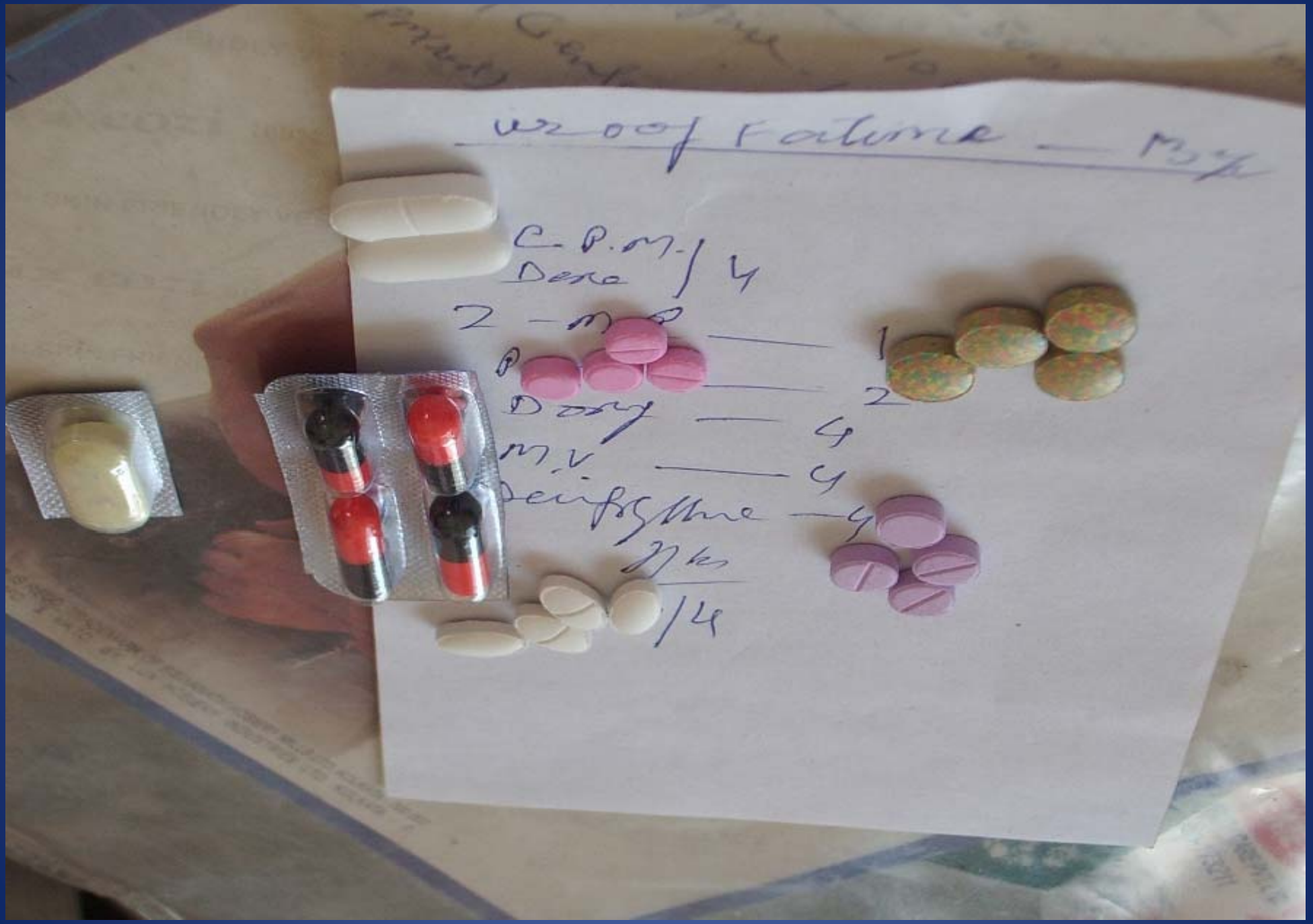
World Health Statistics 2007

http://www.who.int/child_adolescent_health/data/child/en/index.html

supply chain

stock outs

Uhjin Kim,
Nauru 2008


C.P.M. 1/4
Dexa
Doxy
M.V.

Factors influencing medicines use

- EML including medicine exists
- Dosage form exists / available
- Medicine is registered
- Medicine is licensed for indication
- Medicine is procured
- Medicine available at reasonable cost
- Guidelines include EML medicines
- Implementation strategy exists
- Cultural / social issues related to use of medicines considered
- Incentives / counter incentives considered

Research recommendations of EMLc committee

- Pharmacokinetics studies in neonates, for example oral amoxicillin
- Effects of malnutrition on pharmacokinetics
- Medicines for resuscitation in neonates, and determining proper dosage
- Timing of drug administration in relation to food intake when relevant.

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Standards for Conduct of Clinical Trials in Children

- Reporting standards (RCTs and CRTs)
- Regulatory standards for new drugs and formulations
- Review of Ethical Guidelines: Identify gaps and inconsistencies in ethical guidelines for research in children

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Data Sources

- Survey of Current Guidance for Child Health Clinical Trials. The StaR Child Health Project: Standards for Research with Children. September, 2009.
- Best Practices For Research Involving Children And Adolescents: Genetic, Pharmaceutical, Longitudinal Studies And Palliative Care Research. Centre De Recherche En Droit Public (Crdp), Université De Montréal, September 10th 2009.
- International Compilation Of Human Research Protections, 2009 Edition, Compiled By The Office For Human Research Protections, Us Department Of Health And Human Services. Final Version.
- 14 guidelines: 2 international (WHO, CIOMS); 1 regional (EMEA), 1 consensus document (ICH), 12 from African countries, and 1 from India.

Inclusion of Children

- Some ethical guidelines do not mention children at all.
- A few guidelines state that children should be included in research studies or that research in children is beneficial.
  - "The inclusion of children in research promotes their safety and well-being."
  - "indispensible," "necessary"
- Age of children
  - Different age cutoffs: 12, 18, 21….
  - Neonates rarely mentioned except in context of sample collection

Common Features

- Recommend special safeguards for consent and assent.
  - Conditions under which consent is necessary, procedures for assent and dissent of the child, and waiver of consent.
- Research conducted in children must be justified and relevant to the health needs of children
- Pain management and facilities must be appropriate to children
- Ethical review committees should contain pediatric expertise

Risk Benefit Ratio

- Should less risk be tolerated in children, or should more benefit be demanded?
- Should large (above minimal) risks ever be tolerated?
  - If a child has a fatal condition, should they get an experimental treatment that is a known risk?
  - For example, should children be candidates for gene therapy studies, a known high a risk.
- Placebo controlled studies should be limited

Inclusion of Healthy Children

- Excluded if guideline stipulates that children should be included in research that has greater than minimal risk only if there is a direct benefit to the participant
  - direct benefit defined variously to include treatment only or treatment, diagnosis, prevention (ie, vaccine testing)

- Could be included if
  - the risks are negligible
  - risks comparable to a risk to which the child would be exposed in ordinary life or routine medical care
  - the least vulnerable children (e.g. older children) are considered first
  - the research has the prospect of major scientific or medical significance
  - generalizable knowledge about the child's disorder or condition that is of vital importance is gained

Inclusion of Healthy Children

- Pharmacokinetic (PK) studies could be precluded by the criterion requiring direct benefit
  - Few guidelines specifically states that PK studies should be conducted in children

Timing of Studies in Children

- Studies in children should always be carried out after the phase III clinical trials in adults.
  - Studies in children were considered permissible without initial testing in adults only if the drug had a therapeutic value in a primary disease of the children.
- Phase 4 studies of safety in children were generally considered permissible as long as they were not being conducted for marketing purposes

Payments to Participants

- Majority of guidelines that do mention payments allow reimbursement and compensation
  - reimbursement payment - compensates the parents and the child for their expenses incurred by their participation, such as transportation, meals and lodging
  - compensation payment - compensates the parents and the child for their time and inconvenience
- A few prohibit incentive payments – encouragements to participate
- Lack of clarity about payments to parents and /or children
  - Some that only children, and not parents, can be paid.
  - No consistency about whether appreciation payments should be disclosed to children.

Ongoing activities

- Review existing evidence
- Develop appropriate standards and capacity for the conduct of clinical trials in children in resource poor settings
- Encourage development of appropriate dosage forms of medicines for children;
- Promote access to essential medicines for children
- Scale up established interventions that result in better use of medicines in children.

Questions

- Should guidelines contain a positive statement that research in children is necessary and beneficial to children?
- Can an acceptable risk benefit ratio for children be defined, including a clear distinction of how this might differ from an acceptable ratio in adults?
- Can studies of diagnostic tests or preventive interventions be considered to directly benefit participating children?

Questions

- Should the timing of clinical trials in children, relative to studies conducted in adults, be reconsidered?
- What is the best way to conduct ethical PK studies in children, particularly healthy children?
- What is the best way to conduct ethical tests for safety in children, particularly healthy children?
- Can more specific guidance regarding payments to children and parents or guardians be developed?

Bill & Melinda Gates Foundation project

- Promote research and development of essential medicines for children, by reviewing existing evidence for priority treatments for some diseases in children, developing appropriate standards and capacity for the conduct of clinical trials in children in resource poor settings
- Filling knowledge gaps for priority medicines for children and encouraging development of appropriate dosage forms of medicines for children;
- Promote access to essential medicines for children in priority countries by promoting their inclusion in national essential medicines lists, treatment guidelines and procurement schemes; working with drug regulatory authorities to expedite regulatory assessment of essential medicines for children; and developing measures to monitor and manage their prices;
- Promote improved use of medicines for children by scaling up established interventions that result in better use of medicines in children in two priority countries.

Specific targets

- Upstream
  - Global position on dosage forms
  - Global standards for research & regulation
  - New FDCs – malaria, HIV, TB
  - Progress on missing medicines – eg antibiotics, analgesics
- Implementation
  - Advocacy across professional groups
  - EML, guidelines, policy interest in Africa, India
  - Data on pricing and supply chains in Africa and India
  - Work on use of medicines in Africa

Liquids

- Short shelf lives
- Often require refrigeration
- Bulky and heavy
  (issue for storage and transport)

Solid formulations

Powders for suspension

- Mixed correctly with sterile fluids
- Affected by humidity

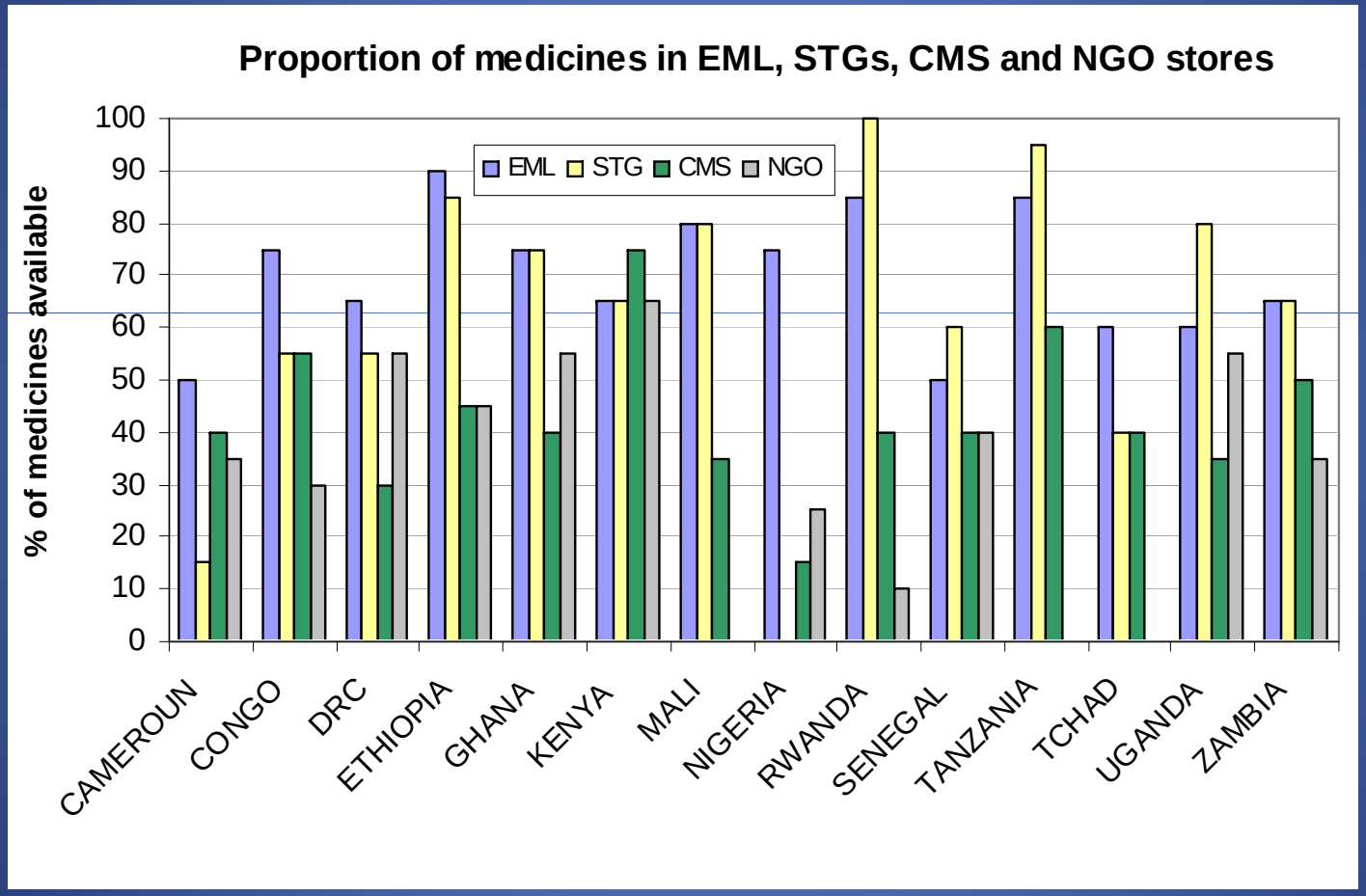
Chewable tablet

- Tolerated by children two years and older
- Limited dose variation

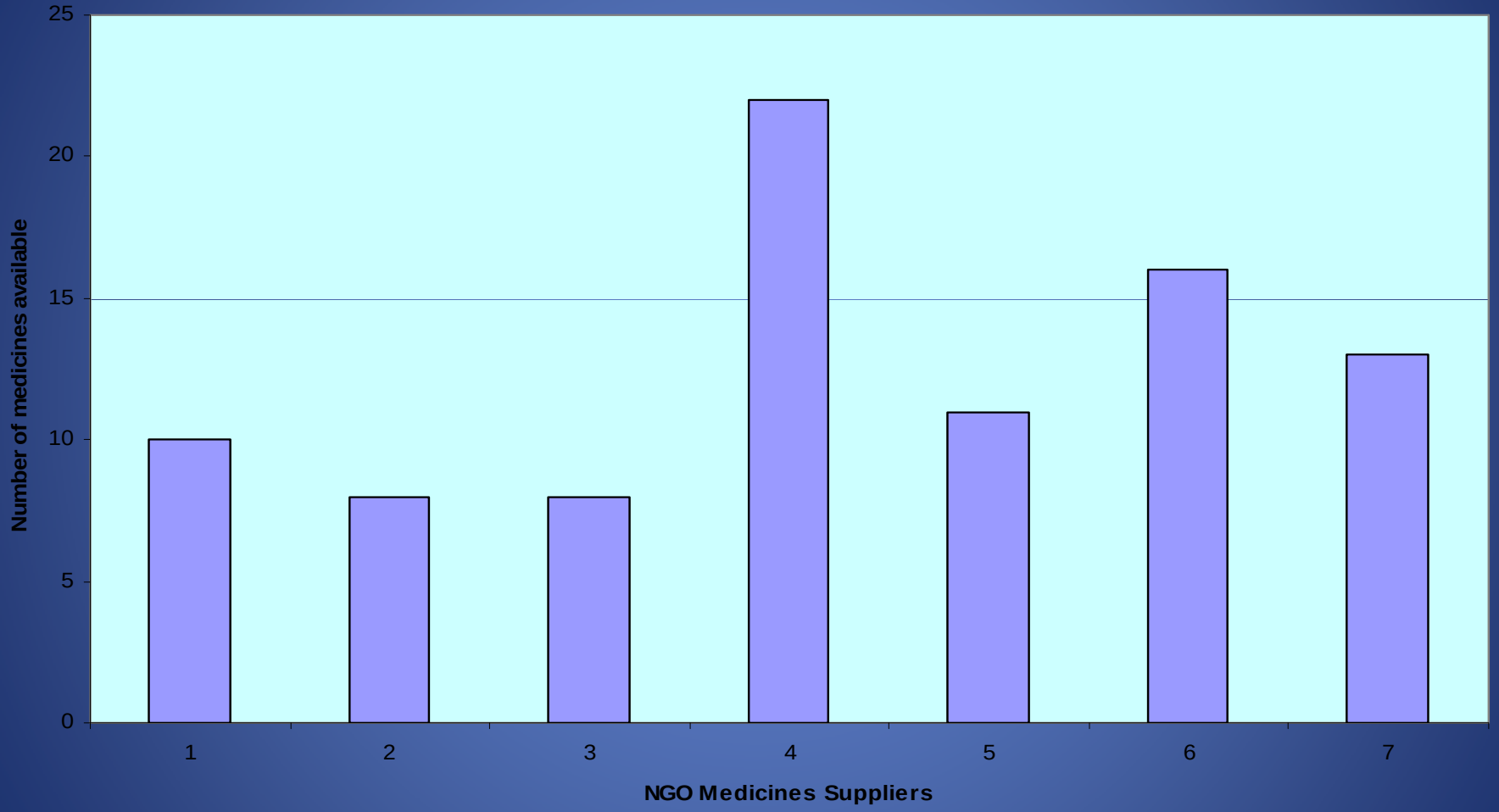
Survey of 29 countries: Problems identified for other acute and chronic illnesses in childhood

- 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

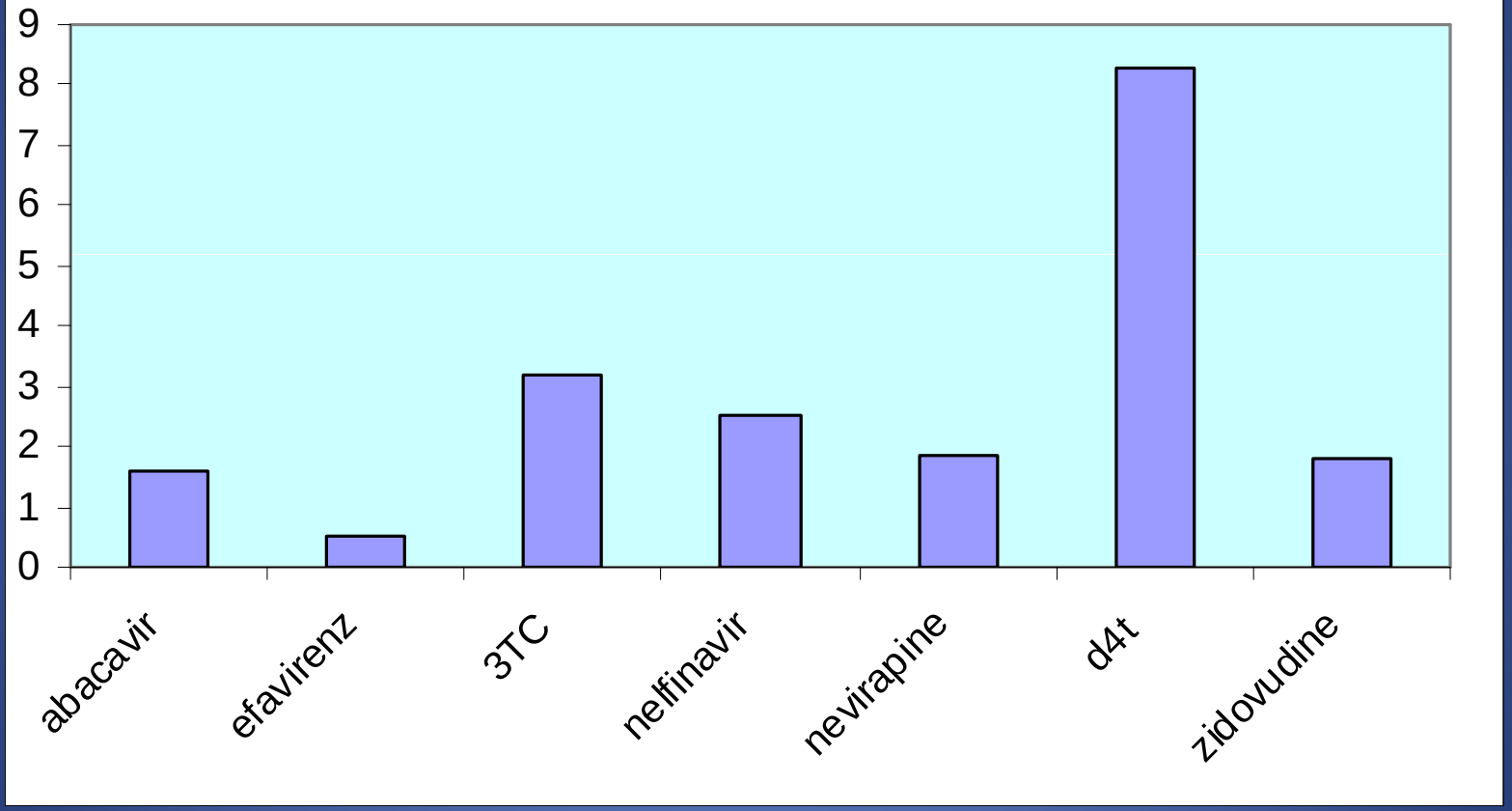
Are essential medicines for children available?



Availability of 22 medicines for children from International NGO Medicine Suppliers



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



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

Terms of reference for sub committee

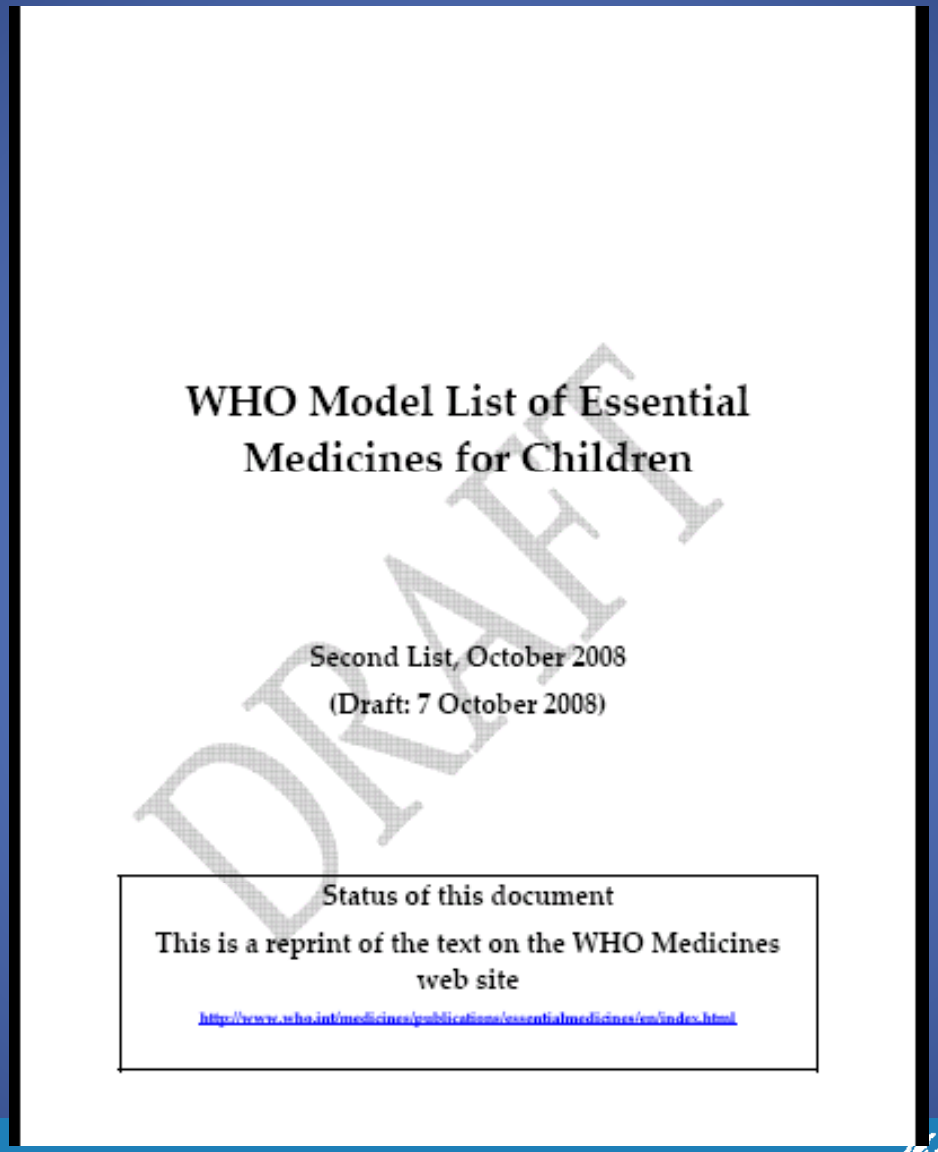
(1)To prepare a list of medicines for children, based on their clinical needs and the burden of disease, that the WHO Expert Committee on the Selection and Use of Essential Medicines can use to revise and regularly update the WHO Model List of Essential Medicines to include missing essential medicines for children:

(2) To determine suitability criteria for dosage forms of medicines for children, with particular attention to conditions prevailing in the developing countries:

(3) To review the feasibility of manufacturing appropriate formulations for those priority medicines for which no dosage form for children currently exists, specifically considering requirements for use in resource-limited settings and availability of data on efficacy and safety in the appropriate age groups:

(4) To identify the clinical-research gaps regarding safety and efficacy of essential medicines for children in order to improve suboptimal prescribing and dosing, and to facilitate regulatory approval of paediatric formulations:

(5) To report to the Expert Committee on the Selection and Use of Essential Medicines in 2009.

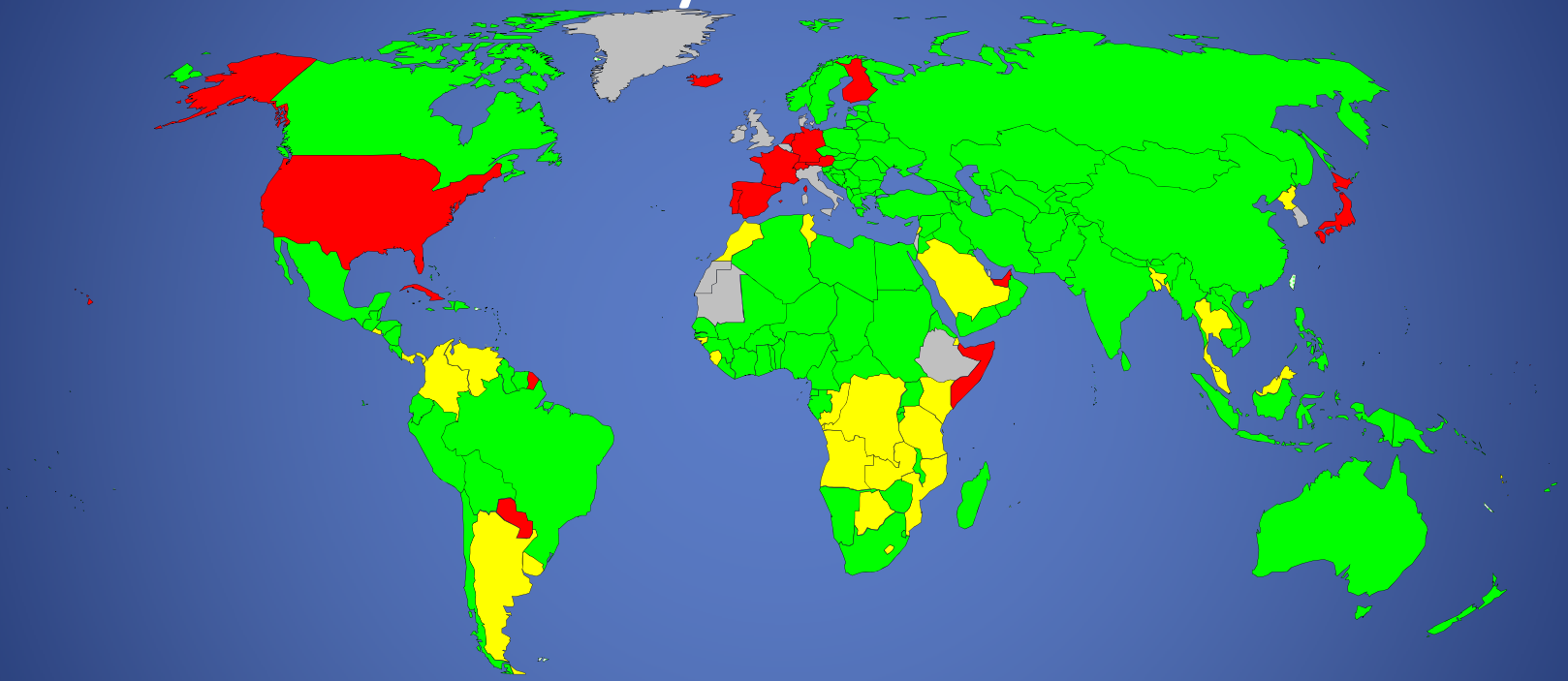


World Health Organization

The WHO Model List of Essential Medicines is a model product, model process and public health tool

- Independent Membership of the Committee, careful consideration of conflict of interest
- Transparent process, standard application, web review
- Link to evidence-based clinical guidelines
- Systematic review of comparative efficacy, safety, cost-effectiveness and public health relevance
- Rapid dissemination, electronic access
- Regular review

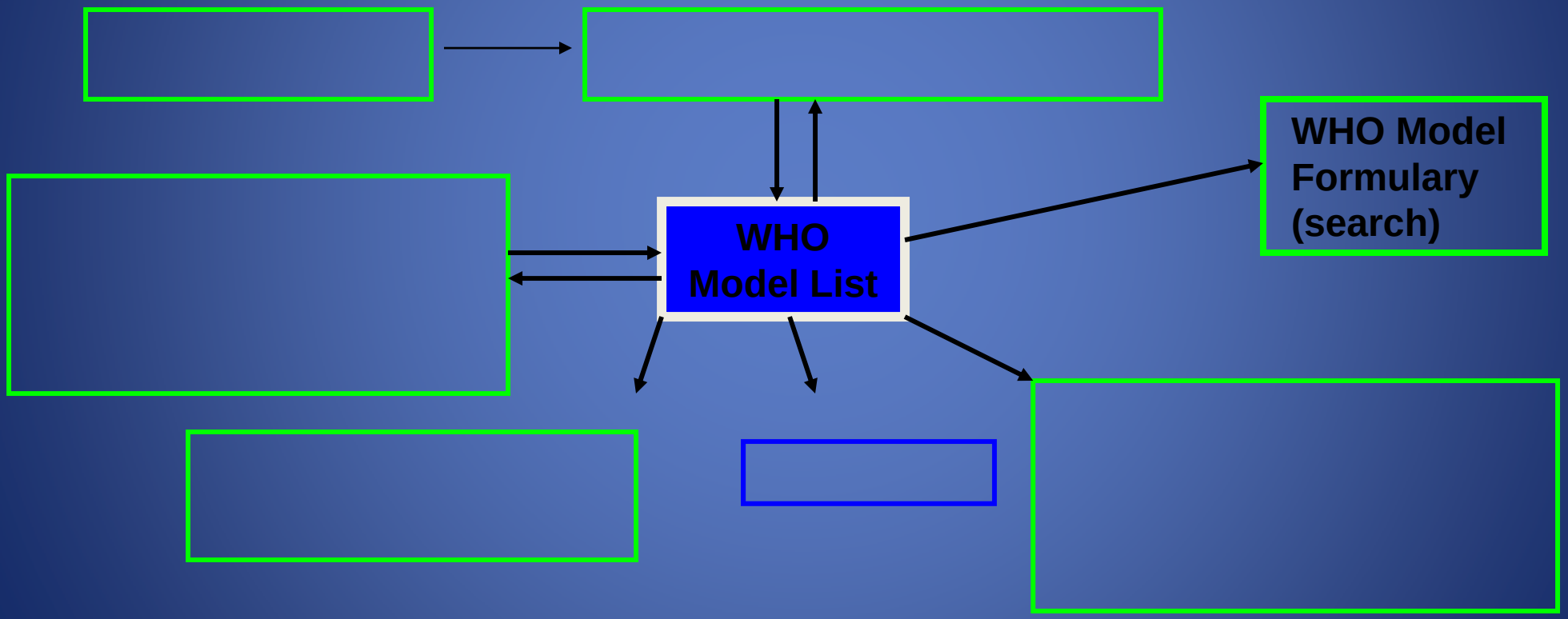
The essential drugs concept is nearly universal



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.

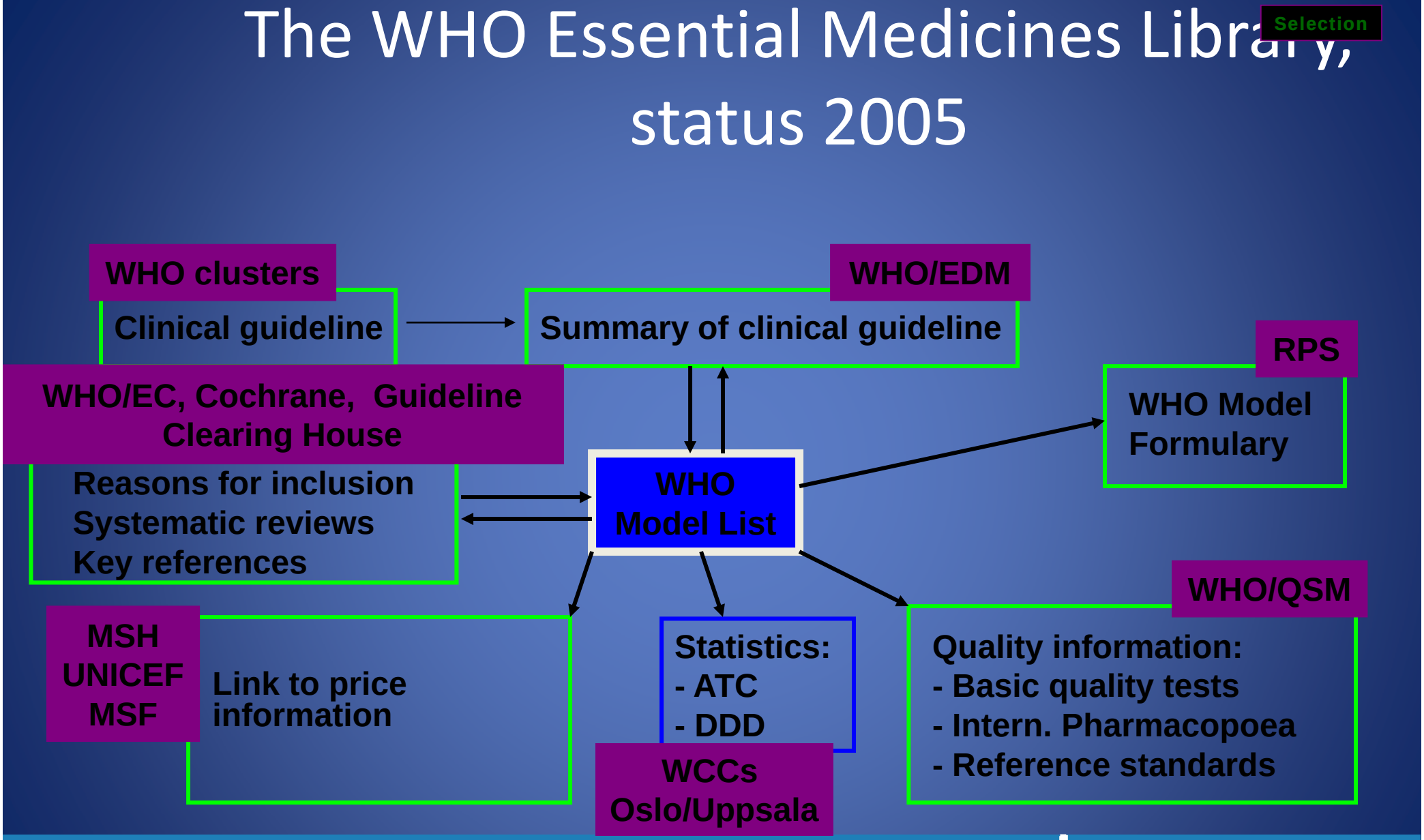
World Health Organization

The WHO Essential Medicines Library:



World Health Organization

The WHO Essential Medicines Library, status 2005



WHO Model List of Essential Medicines for Children

Explanatory Notes

16 August 2007

This Model List is intended for use for children up to 12 years of age.

The **core list** presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a

mefloquine*	**Tablet:** 250 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
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 hydrochloride/ml in 2-ml ampoule. **Tablet:** 300 mg (quinine sulfate) or 300 mg (quinine bisulfate). * 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.
6.5.3.2 For prophylaxis	
chloroquine*	**Oral liquid:** 50 mg (as phosphate or sulfate)/5 ml. **Tablet:** 150 mg (as phosphate or sulfate). * For use only in central American regions, for use for *P.vivax*.
doxycycline	**Capsule or tablet:** 100 mg (hydrochloride).
mefloquine	**Tablet:** 250 mg (as hydrochloride).
proguanil*	**Tablet:** 100 mg (hydrochloride). * For use only in combination with chloroquine.

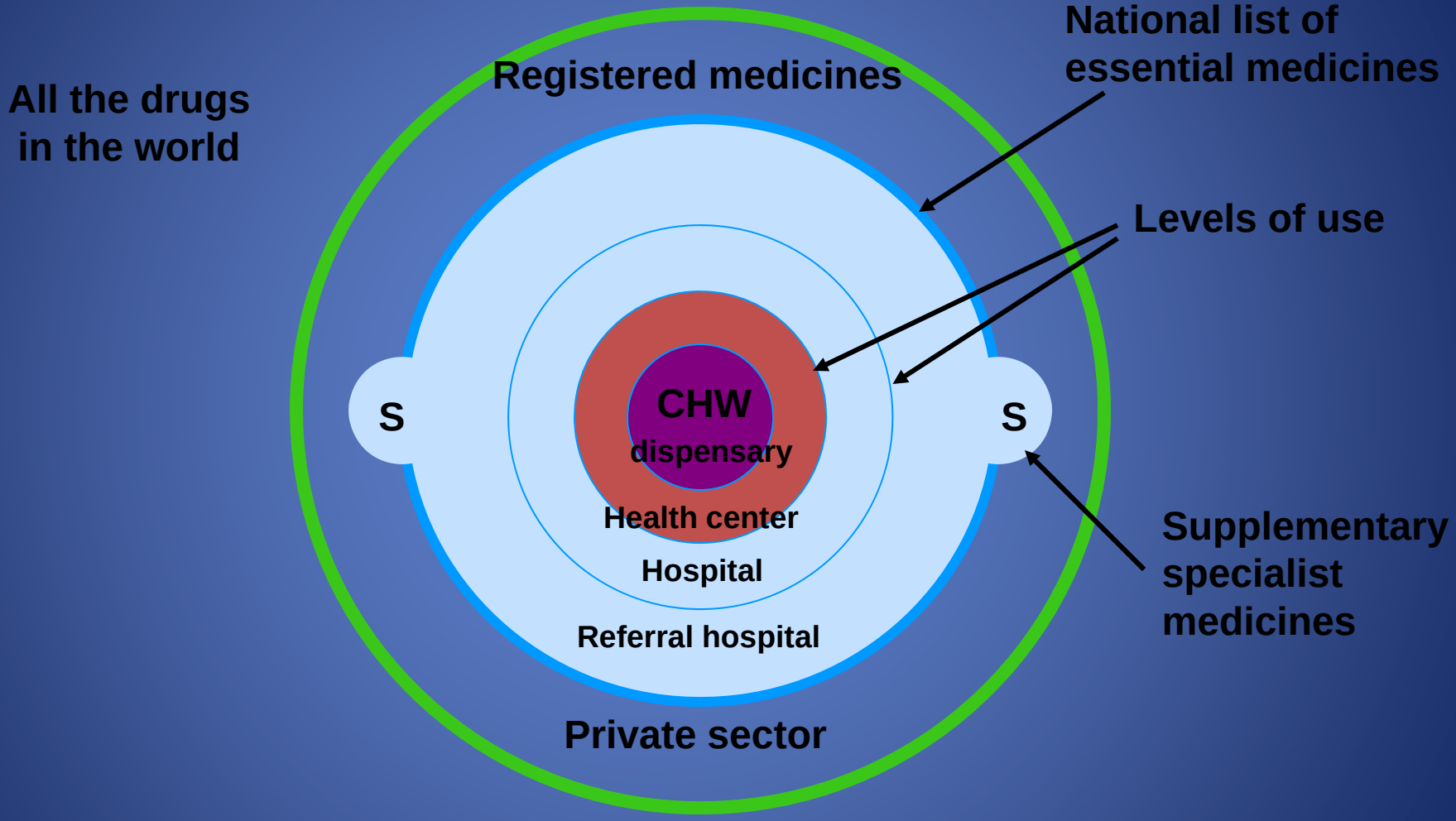
Process


Application lodged
Reviewed internally, published on web
External expert review and comment
[redacted]
[redacted]
Expert Committee review and recommendation

What could be done – medicines and vaccines?

- Vaccines
  - Measles, pneumococcus, Haemophilus influenza B, tetanus
  - Others?
- Flexible solid oral dosage forms of medicines
  - Oral rehydration salts + zinc
  - Public health pack of oral antibiotics – amoxicillin
  - Single use injectable antibiotics – ceftriaxone, gentamicin
- Newborn care
  - Prevention of sepsis (topical)
  - Treatment of sepsis - antibiotics
  - Caffeine citrate, surfactant?
- Antiretrovirals
  - Fixed dose combinations
  - Options for treatment – second line
- Antimalarials
  - Artemesinin combinations
  - Fixed dose combinations
- Tuberculosis
  - Fixed dose combinations
  - MDR treatment
- Neglected tropical diseases
  - leishmaniasis
  - Sleeping sickness
  - others

The Essential Medicines Target

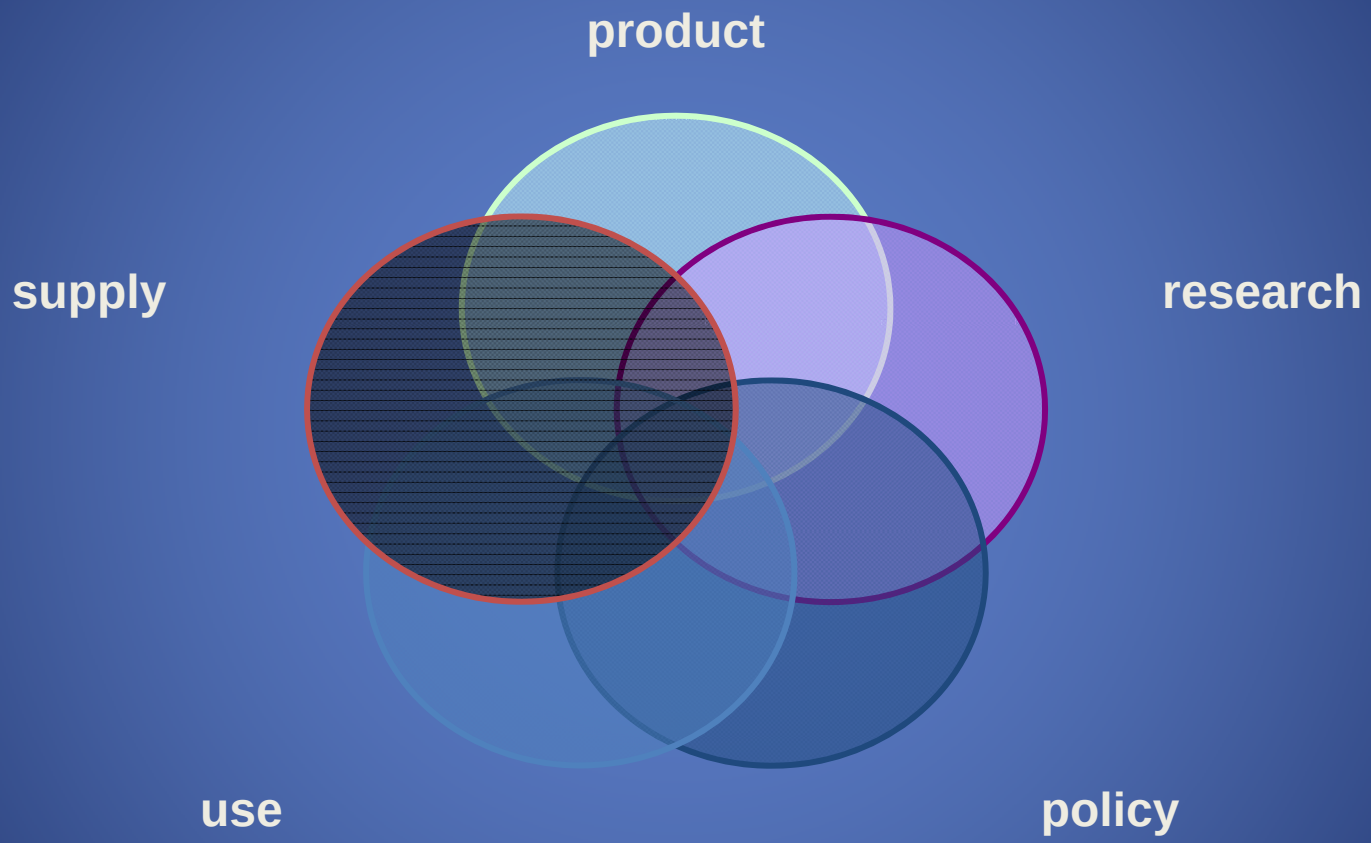


World Health Organization

History of the WHO Model List of Essential Drugs

- 1977 First Model list published, ± 200 active substances
- List is revised every two years by WHO Expert Committee
  - Efficacy, safety, public health need
- Latest revision 2009 – 350 active substances

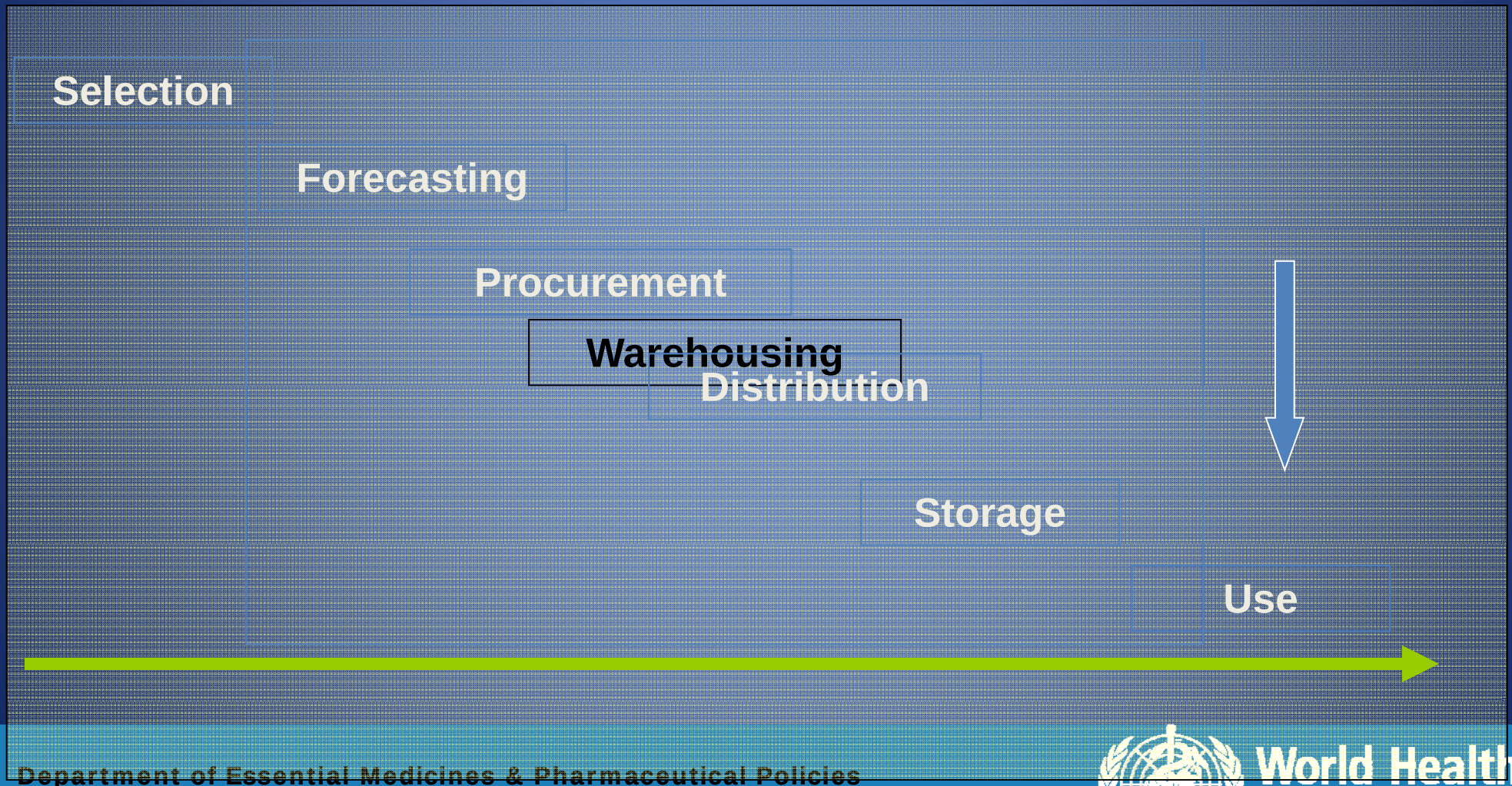
Medicines landscape



The story so far....

- August 2006: WHO- UNICEF consultation on essential medicines for children
- January 2007 – Executive Board Resolution – Better Medicines for Children
- March 2007 – Expert Committee recommendation for Sub-committee
- May 2007 – WHA resolution, EB resolution
- July 2007 – Sub Committee, first EML for children
- October 2007 – extraordinary Expert Committee meeting
- December 2007 – 'Make medicines child size' launch
- September 2008 – second Subcommittee
- October 2008 – Gates Foundation project
- March 2009 – Expert Committee, 2nd EMLc
- October 2009……

The supply chain



Developing better medicines for children

- Medicine
  - Optimal antibiotics for neonatal infection cf dose, form?
  - Topical products for skin diseases?
  - Medicines for treating mental health conditions in children?
  - Medicines for managing pain?
- Dose
  - In neonates (generally)?
  - Weight, height, age – and malnutrition?
  - For specific medicines – eg TB, some antibiotics, malaria?
- What are optimal dosage forms of medicines for children?
  - How best to enhance administration, adherence (and affordability) – packaging, labelling?
  - In different settings?
  - How much does age matter, and for what?
  - Does taste matter?
  - How simple is suitable? (standard platform, liquids)

Paediatric formulation issues

- Technical difficulties of manufacturing
- Storage and preparation
- Impact of various climates
- Taste of the medication
- Local factors and practice

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17th Expert Committee on Selection and Use of Essential Medicines

The 17th Expert Committee on the Selection and Use of Essential Medicines will be held from 23 to 27 March 2009.

Applications for inclusion, change or deletion of a medicine in the Model List of Essential Medicines have to be sent to the Secretary of the Committee whose address is below.

The Secretary of the 17th Expert Committee on the Selection and Use of Essential Medicines
Medicine Access and Rational Use (MAR)
Department of Essential Medicines and Pharmaceutical Policies (EMP)
World Health Organization
20 Avenue Appia
CH-1211 Geneva 27
Switzerland

Public comments, including letters of support on the applications may be submitted to: emlsecretariat@who.int.

All comments will be published on the web. The deadline for submission of comments is: **6th February 2009**

:: Application form [pdf 114kb]

:: All applications

:: All applications by sections

:: Medicines for children

AGENDA PAPERS

:: Draft Report of the Second Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines [pdf 1.61Mb]

:: Draft Second Essential Medicines List for Children [pdf 1.58Mb]

USEFUL DOCUMENTS

WHO Technical Report Series 950
Read more... [pdf 844kb]

First WHO Model List of Essential Medicines for Children

WHO Technical Report Series 946
Read more... [pdf 2.03Mb]

15th WHO Model List of Essential Medicines [pdf 378kb]

Better Medicines for Children

Policy	Essential Medicines List, regulatory guidance
Information & advocacy	Formulary, updated treatment guidelines, stakeholders involvement
Market & supply	Clinical trials, procurement, supply chain
Measurement/ data collection	Medicine availability, prices, use
Interventions	Behaviour change strategies to improve use