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THE WORLD MEDICINES SITUATION 2011

SELECTION OF ESSENTIAL MEDICINES

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The World Medicines Situation 2011

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SUMMARY

- Essential medicines are those that satisfy the priority health-care needs of the population. Essential medicines lists (EMLs) support the systematic delivery of medicines in the health-care system.
- The selection process of the WHO Model List of Essential Medicines has evolved since 1977 from expert evaluation to evidence-based selection that includes: systematic review of evidence of efficacy and safety; consideration of public health needs, availability and costs; and a transparent process.
- The Model List and its supporting documents serve as a valuable resource for advocacy, selection, purchasing and supply at the country level.
- In 2007, at least 134 countries had a national EML and the majority had been updated in the previous five years.
- The Model List has been expanded to include the WHO Model List of Essential Medicines List for Children (EMLc), to address the priority health-care needs of children.
- In the future, countries will face challenges in selecting high-cost medicines for oncology, orphan diseases and other conditions.

1.1 BACKGROUND

Since 2002, essential medicines have been defined as "*those that satisfy the priority health-care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. 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 adequate information, and at a price the individual and the community can afford. 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.*"(1) This definition has evolved from the first definition in 1977, which was adopted in the Alma-Ata Declaration of 1978 (2). The key change has been in the process of selection from an expert-based approach to one that is evidence-based.

Essential Medicines Lists have been one of the cornerstones of ensuring consistent medicine supply and management

An essential medicines list (EML) is a limited number of carefully selected medicines. For many decades, such lists have been published as formularies and institutional lists of medicines that are made available to health facilities and health workers. These may not be called EMLs but they serve the same function. EMLs have been one of the cornerstones of public health delivery and the basis for efforts to ensure consistent medicine supply and management. The EML is an important strategy in improving access to and use of medicines, especially for the vulnerable segment of a population. Furthermore, an EML can be used as an advocacy tool to help countries spend their limited resources on the medicines that are most needed and offer the best value for money.

The development of the WHO Model List. Since 1977, WHO has produced a Model List of Essential Medicines which is revised every two years by the WHO Expert Committee on the Selection and Use of Essential Medicines. The aim of the Committee is to provide countries with a model list and a model process for drawing up their national list. Expert Committee members have particular expertise in clinical pharmacology, pharmacy, public health and evidence-based medicine.

The evolution of the WHO Model List and its relevance to countries has been reviewed at different points in time by Howard and Laing in 1991, and by Laing et al. in 2003 (3,4). From 1999 onwards, the selection process for medicines in the Model List evolved from expert evaluation to an evidence-based approach (5–8). Annex 1 summarizes the changes in the selection process.

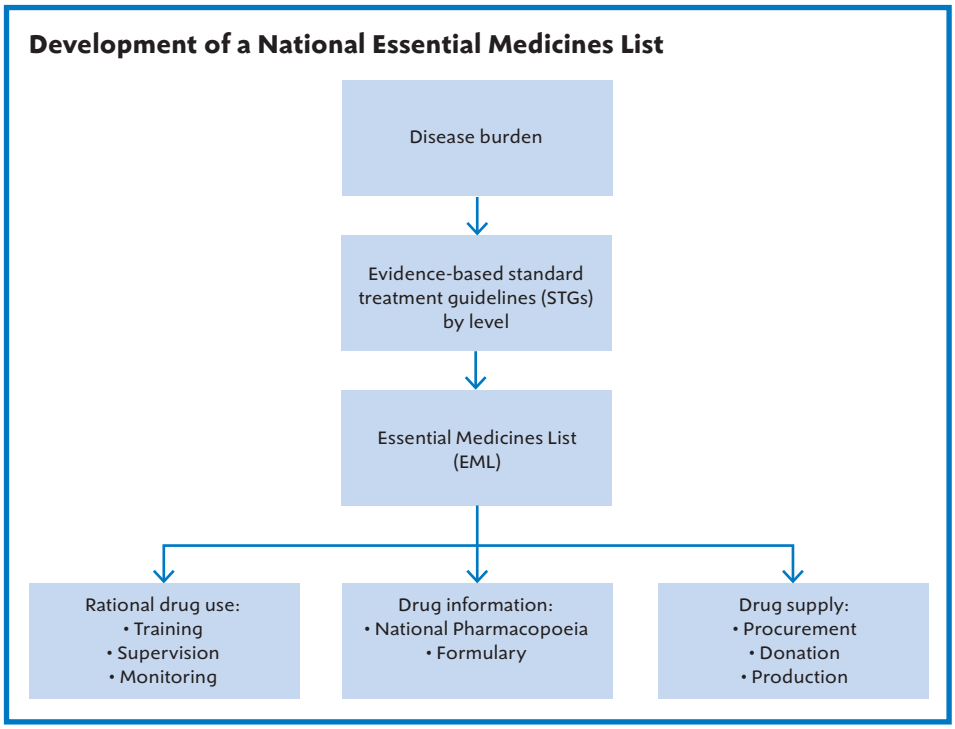
The Model List consists of a core list and a complementary list. The core list includes the medicines needed for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority diseases and conditions. The complementary list presents essential medicines for priority diseases which are effective and safe, but for which specialized health-care facilities or experience may be needed.

One of the ways in which the Model List provides flexibility for countries creating their own EML is the use of the square box symbol. The square box indicates that a listed medicine should be seen as a representative example from a group of clinically equivalent medicines (within a pharmacological class). The medicine listed on the Model List is intended to be the product for which there is the most clinical evidence within the group, but national lists countries could select for other medicines from the class depending on local availability and/or costs.

The use of standard treatment guidelines (STGs) in developing a national EML. Figure 1.1 shows how the medicines for an EML should ideally be selected. The first step is to identify the most common health problems in a country. Evidence-based standard treatment

FIGURE **1.1**

The process of selecting the essential medicines and developing the national EML should always be consistent and coincide with the development of STGs.



guidelines (STGs) should be systematically developed to assist prescribers in deciding on appropriate treatments for specific clinical problems. STGs will indicate the first treatment of choice. STGs also usually include diagnostic criteria for starting treatment or for choosing an alternative therapy. Medicines that are recommended in the national STGs should also then be listed in the country EML. This process ensures that the EML is consistent with the STGs. In practice, however, both in WHO and at country level it can be difficult to ensure that the development of guidelines and definition of EMLs coincide. The flow chart above demonstrates the ideal approach that can be worked towards.

The Model List and its supporting documentation serve as a valuable resource for advocacy, purchasing and supply at the country level. A locally adapted EML based on STGs can help countries spend their limited resources on the medicines that are the most needed and affordable. WHO surveys in 2007 showed that 86% of countries have been developing and updating their national EML (*9*).

1.2 CURRENT SITUATION

1.2.1 The WHO Model List

The process for developing and updating the WHO Model List has evolved over time, with emphasis now on the evidence that supports the assessment of comparative effectiveness, safety and cost (Annex 1).

From expert decision to evidence-based selection. Over the first 20 years of the WHO Model List, the selection of medicines was determined by the experience of the members of the Expert Committee. There was no systematic search and reporting of evidence to support the selection. In the current selection process, applications for additions, deletions or changes to medicines can be submitted by various groups, including WHO departments, pharmaceutical companies and patient advocacy groups (*10*). In addition, the application procedure has been revised to require: documentation supporting the public health relevance; refer-

ence to the Standard Treatment Guidelines; a summary of comparative efficacy and safety in different clinical settings; and information about the regulatory status. Summaries of the evidence of efficacy may include tables evaluating the methodological strengths and weaknesses of the supporting studies. The existence of pharmacopoeial standards, such as the British Pharmacopoeia, International Pharmacopoeia and United States Pharmacopeia, is also documented. Since 2002, details about the international availability of medicines should also be provided in the application.

Evidence-based selection is supported by documentation on public health relevance, standard treatment guidelines, evidence of efficacy and safety, and regulatory status of the medicines.

From cost comparison to cost-effectiveness. The 1977 selection criteria put the emphasis on the need to select low-priced medicines. Today the main criterion for deciding if a medicine is essential is *effectiveness*. Therefore, the high cost of an effective medicine is not a reason for excluding it. The WHO application procedure requires that information on "*comparative cost and cost-effectiveness*" are presented "*as a range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained*". The cost of a treatment course can be considered. For example, a shorter course using a more expensive medicine may be cost-effective. Cost can also be a factor when selecting medicines within a therapeutic class to identify the best value for money, recognizing that other products are equal in efficacy.

Transparency of information and evaluation has also improved. Before 2001 the recommendations and underlying evidence for the selection of essential medicines were only briefly summarized in the reports of the Expert Committee, which were sometimes published a year or more after the meeting. In an effort to ensure greater transparency in the selection process, the Expert Committee suggested that the process of receiving the applications, the reviewing of the information and the recommendation from these reviews be carefully documented and posted on a web site. Members of the Expert Committee now provide written reviews of the application materials, and the applications, reviews and all supporting documentation are made publicly available. Timelines are also published to define when applications should be submitted and reviewed. All materials are placed on the WHO web site, including comments on submissions. These revisions were approved by the WHO Executive Board in December 2001. Meanwhile, efforts are made to prevent undue influence being placed on Expert Committee members. For example, reviews are published without author attribution, and apart from an initial open to the public session, all decisions are made in closed sessions. A draft of the revised list and the meeting report are posted on the WHO web site soon after the meeting ends.

Transparency in selecting medicines is ensured by making documentation publicly available and through efforts to prevent undue influence on Expert Committee members who are required to disclose their ties and interests.

Conflict of interest is an issue that WHO addresses seriously. Conflict of interest means that the expert or his/her partner ("partner" includes a spouse or other person with whom the expert has a similar close personal relationship), or the administrative unit with which the expert has an employment relationship, has a financial or other interest that could unduly influence the expert's position with respect to the subject matter being considered (*11*).

WHO requires complete and accurate disclosures of financial ties and other competing interests. This is done by obliging all experts and advisers to complete a specific, detailed and structured declaration of interest form that allows the organization to obtain as much information as possible about the nature and extent of the competing interests. If WHO judges the conflict of interest to be significant, the expert or advisor may be recused from all or part of the committee meeting.

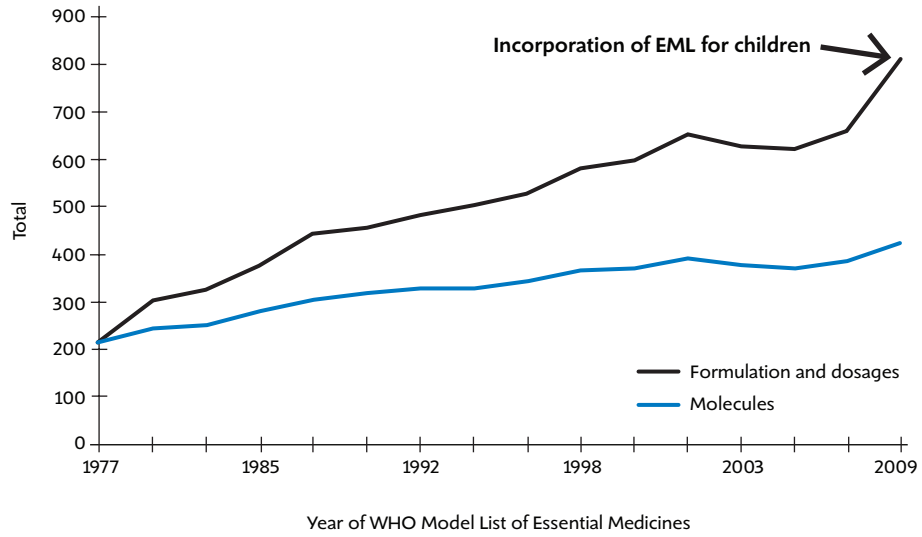
Fixed-dose combination (FDC) medicines, according to the current selection criteria, may be selected only when the combination products have proven to have advantage in therapeutic effect, safety and adherence and in decreasing the emergence of drug resistance. For example, FDCs are encouraged for the treatment of malaria, tuberculosis and HIV-related disease.

1.2.2 Expansion of the WHO Model List and the inclusion of children`s medicines

Since the development of the WHO Model List in 1977, the list has been revised every two years and the number of selected medicines has grown (Figure 1.2).

FIGURE **1.2**

WHO Model List of Essential Medicines. Total medicines in the core list and the complementary list over time (including duplicates)



The first WHO Model List contained 216 molecules including duplicates[1] and 204 molecules excluding duplicate listings. The most recent version (2011) of the WHO Model List contains 445 medicines and 358 molecules excluding duplicates (*12*).

The most significant addition to the WHO Model List has been the Essential Medicines List for Children (EMLc). In May 2007, the World Health Assembly adopted resolution WHA 60.20 Better Medicines for Children, setting goals and calling for action by Member States and WHO to address the global need for children's medicines (*13*). Medicines used by adults are not suitable for children and need special adjustments in the dosage, formulation and delivery. However, the lack of clinical trials in children hinders the evidence-based selection of essential medicines for children (*14*).

In developing countries millions of child deaths due to priority diseases and conditions could be prevented by ensuring the availability of appropriate essential medicines.

Almost eight million children under five years old die each year, mainly in developing countries, due to priority diseases and conditions such as malaria, pneumonia, tuberculosis, HIV-related diseases, and diarrhoea. Many of these deaths could be prevented by ensuring the availability of essential medicines appropriate for children's needs (*15,16*).

[1] Duplicates are defined as molecules that are listed for different indications and are therefore listed multiple times in different sections of the WHO Model List.

Children may suffer disproportionately or from different diseases than adults. Children differ from adults when it comes to ingestion, absorption, metabolism and excretion of a medicine. Even between age groups in children there is a significant difference in the above parameters depending on the age, weight and physical condition of the child. Furthermore, the formulation of some medicines can be problematic. For example, tablets are not easy for children to swallow and there may be choking. Although medicines in liquid formulations may solve this problem, they have the disadvantage of lower stability, a shorter shelf-life and, in some cases, require refrigeration. In addition, their volume makes transport and storage difficult and their price is sometimes prohibitive (*17,18*).

In 2006, WHO and UNICEF held a joint meeting to consult with experts about ways to address the lack of essential medicines for children (*14*). One of the meeting's key recommendations was to update the WHO Model List with the addition of essential medicines specifically for children. A subcommittee of the Expert Committee on the Selection and Use of Essential Medicines was established to oversee a comprehensive update of the Model List. The first meeting in July 2007 established the first EMLc which was approved by the Expert Committee in October 2007 (*19,20*). At the second meeting, in September 2008, the subcommittee prepared the draft of the second version of the EMLc and there was a separate meeting on dosage forms of medicines for children (*21,22*). In March 2009 this second list was approved by the Expert Committee.

The EMLc was integrated into the WHO Model List for adults, although a separate list is also maintained. New symbols were introduced to indicate the following : [c] medicines with a restricted indication for use in children; *[c]* when specialist care was needed in treatment of children with the medicine; and [a] any age-restriction. Two new sections were added: medicines for the treatment of ear, nose and throat conditions in children and specific medicines for neonatal care.

1.2.3 National lists of essential medicines

In 2007, a WHO survey of 156 countries showed that 86% of responding countries have a national EML, including all low-income countries and most middle-income countries (Table 1.1) (*9*). The number of medicines included in the national EML varies, with a global median of 397.

The lists are commonly used in public sector procurement across all countries and in high-income countries for public insurance reimbursement. However, only a small fraction of countries use the EML in reimbursement for private insurance. Most of the 130 responding countries (89%) report having a committee for the selection of medicines for the national EML.

It is important that the EML is regularly updated to ensure that it is relevant to the health needs of the population, adapted to changes in therapeutic modalities, concordant with local treatment guidelines, and aligned with the logistics and budget of the health system. The survey showed that 69% of responding countries had updated their list within the previous five years. Eighty one percent of low-income countries had revised the EML within the past five years.

The concept of essential medicines provides the parameters as to which medicines should be included in the country list. These should be the medicines to treat the major diseases and conditions that affect the population and those that the health system can afford. The number of medicines on a country list can be very different from the number of medicines approved to be sold in the market. Figure 1.3 shows the median number of medicines in the

TABLE **1.1**

Details of national essential medicines lists by country income level

	Country income level[a]							
	Low (48)		Middle (73)		High (35)		Global (156)	
	yes/resp. countries	% yes	yes/resp. countries	% yes	yes/resp. countries	% yes	yes/resp. countries	% yes
Existence of national EML	48/48	100%	63/73	86%	23/34	68%	134/155	86%
Update of EML within last 5 years[b]	39/48	81%	54/73	74%	14/34	41%	107/155	69%
Use of EML in different sectors								
Public sector procurement	44/46	96%	59/65	91%	22/22[c]	100%	125/133	94%
Public insurance reimbursement[c]	14/40	35%	20/50[c]	40%	13/18[c]	72%	47/108[c]	44%
Private insurance reimbursement[c]	4/35	11%	6/49[c]	12%	2/8[c]	25%	12/92[c]	13%
Committee for EML medicines selection	38/44	86%	59/67	88%	19/19[c]	100%	116/130	89%
	Median [25th, 75th percentile]		Median [25th, 75th percentile]		Median [25th, 75th percentile]		Median [25th, 75th percentile]	
Number of medicines in EML	355		441		1706		397	
	[272,	384]	[350,	601]	[1143,	3272]	[334,	580]
	n=34		*n=52*		*n=8*[c]		*n=94*[c]	

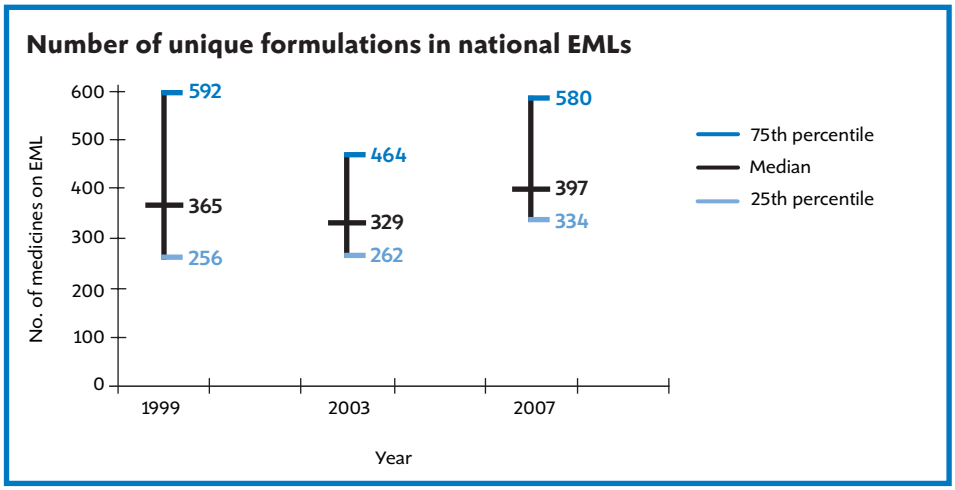
[a] World Bank list

[b] Since many countries with a national EML did not provide dates and very few provided dates beyond the previous 5 years, it was assumed that those countries not providing dates had not updated their EML in the last 5 years

[c] More than 30% of countries did not provide an answer to this question

national EMLs of countries surveyed in 1999, 2003 and 2007. It shows that the majority of countries now have at least 300 unique formulations in their list. Over the years, variation between countries in the total number of medicines on the EML has decreased.

FIGURE **1.3**



Number of countries responding (1999=106; 2003=86; 2007=94)

1.2.4 Impact of the Model Essential Medicines List: a study of 12 countries

A comparative analysis was undertaken of recent national EMLs from 12 countries and the WHO Model List 2005.[1] The aim of this analysis was to describe in which way national EMLs differ from the WHO Model List, both quantitatively (e.g. number of molecules and number of dosage forms and formulations) and qualitatively (e.g. differences in the selection of specific molecules) (Annex 2).

In the comparative analysis, 7 of the 12 selected national EMLs contained a greater number of medicines than the 312 that were included in the WHO Model List of 2005. The ratio of dosage forms ranged from 1.2 to 2.1 compared to 1.7 in the WHO Model List (Table 1.2).

TABLE **1.2** **Comparison of national EMLs with WHO Model List 2005**

	Total number of medicines on national EML (excluding duplicates)	Total number dosage forms on national EML	Ratio dosage forms to medicines
Tanzania (2007)	319	504	1.6
Congo (2006)	264	435	1.7
South Africa (2006)	413	707	1.7
Brazil (2006)	359	597	1.7
Djibouti (2007)	218	281	1.3
Egypt (2006)	385	579	1.5
Yemen (2007)	309	397	1.3
Latvia (2007)	313	661	2.1
Moldova (2006)	447	821	1.8
Bhutan (2007)	299	366	1.2
Sri Lanka (2006)	335	415	1.2
Philippines (2007)	248	523	2.1
WHO Model List (2005)	**312**	**620**	**1.7**

Countries were purposively chosen based on the following criteria: the list must be from the year 2006 or 2007 and the WHO Regions (AFRO, AMRO, EMRO, EURO, WPRO and SEARO) must be represented, each with a minimum of two countries. All the lists are compared with the 14th WHO Model EML (2005).

The difference in number of medicines is due to considerations such as the national disease burden, local availability and pricing and differing cultural norms and selection processes, specifically addition and deletion.

As expected there were differences between the medicines selected for the national EMLs and those on the WHO Model EML. Medicines which appear on the Model List may not be included in national EMLs and vice versa (Annexes 2 and 3). There are several reasons for these differences, including the in-built flexibility of the square box listed medicines on the Model List, and considerations such as the national disease burden, local availability and pricing, and differing cultural norms. In addition, the process of selection can vary by country.

One specific reason for the difference could be that some medicines have been deleted from the WHO Model List due to lack of efficacy, but have not yet been removed from national EMLs. For example, cromoglicic acid appeared on five of the selected national EMLs. This product was added to the WHO Model List in 1979 but removed in 2005 due to lack of

[1] van den Ham R. Selection of Essential Medicines. Background paper. Utrecht, 2009. http://www.pharmaceuticalpolicy.nl/Publications/Reports/Selection%20of%20Essential%20Medicines%20-%20Background%20paper%20Final%202.0.pdf

evidence of efficacy. In March 2009, the Expert Committee considered an application for its reinstatement, but this was rejected because its superior efficacy and safety compared to placebo were not sufficiently demonstrated in the studies reviewed .

Another reason for discrepancies between the WHO Model List and country EMLs is that country lists may contain medicines that are widely used and/or included in local STGs, but for which there has been no application to the Model List. Omeprazole is an example of a medicine that was widely used in countries before it appeared on the WHO Model List. In 2005, omeprazole appeared on nine of the selected country EMLs but was not included in the WHO Model List until 2009 (*15*). This is a limitation in the current process of the WHO Model List, which depends on the initiation of applications by individuals or groups. As a result, some medicines may not be included in the WHO Model List unless an application is submitted. The WHO Department of Essential Medicines and Pharmaceutical Policies is now taking a more proactive approach through regular systematic review of the different sections of the list. Countries should also regularly review both their STGs and national EMLs.

The local burden of disease can also account for differences between the Model List and national EMLs. Meanwhile, in some countries the selection of specific products for the national EML may depend on the national cultural and legal acceptability. A recent example of this is the combination of mifepristone and misoprostol for medical abortion which was listed in the 2005 WHO Model List with the additional qualification *"Where permitted under national law and where culturally acceptable"*.

1.4 FUTURE CHALLENGES AND ISSUES

1.4.1 Essential Medicines for Children

The creation of the EMLc represents a critical first step towards achieving UN Millennium Development Goals Four (MDG4: Reduce child mortality) and Six (MDG6: Combat HIV/AIDS, malaria and other diseases). However, much remains to be done to ensure that children have access to essential medicines. For example, at its initial meeting in 2007 the Sub-Committee on Essential Medicines for Children noted the need for: determining suitable criteria for dosage forms for children; reviewing the feasibility of manufacturing appropriate formulations for priority medicines; and identifying the clinical research gaps regarding the safety and efficacy of essential medicines for children (*23*).

Important factors in promoting access to essential medicines for children include defining appropriate dosage forms and formulations, the feasibility of manufacture, and identifying clinical research gaps on safety and efficacy.

In May 2007, at the World Health Assembly a resolution (60.20) was passed on "Better Medicines for Children." This resolution laid out expectations for what countries and what WHO should do to improve the medicines situation for children.

In 2008, WHO and UNICEF launched "Better Medicines for Children", a five-year joint campaign aimed at improving access to essential medicines for children by addressing the following strategic objectives:

(1) promote research on essential medicines for children by reviewing evidence for priority treatments for some diseases in children, developing a Model Formulary for children's medicines, and developing standards and capacity for the conduct of clinical trials in children in resource-poor settings;

(2) encourage the development of appropriate dosage forms for children;

(3) promote the inclusion of essential medicines for children in national EMLs, STGs and procurement schemes;

(4) work with regulatory authorities to expedite regulatory assessment of essential medicines for children, and develop mechanisms to monitor and manage their prices; and (5) promote improved use of medicines for children by scaling up interventions known to be effective in increasing the appropriateness of medicine use.

1.4.2 Essential Medicines for Reproductive Health

Countries should include in their EMLs essential medicines for reproductive health such as contraceptives, medicines for the prevention and treatment of STIs and HIV-related infections, and medicines to ensure healthy pregnancy and delivery.

Problems in reproductive health, such as unwanted pregnancy, HIV infection, sexually transmitted infections (STIs) and pregnancy-related illness and death account for a substantial portion of the disease burden among adolescents and adults in developing countries. Ensuring access to contraceptives, medicines for the prevention and treatment of STIs and HIV-related infections, and medicines to ensure healthy pregnancy and delivery is important to improve reproductive and thus public health.

A 2003 analysis by WHO showed that the majority of the countries did not specifically mention reproductive health issues in their national health policy and did not include important new essential medicines for reproductive health in their national EMLs (*24*). For example, magnesium sulphate, which is effective in treating pre-eclampsia and eclampsia, was included in only 40% of the national EMLs reviewed. Furthermore, medicines lists used by other UN agencies involved in reproductive health had many discrepancies (*25*).

In response, at an Interagency Consultation convened by WHO, a number of nongovernmental organizations and UN agencies working in reproductive health, together with WHO, agreed to develop a harmonized list of essential medicines for reproductive health (*26*) and a list of essential commodities (non-medicine items) (*27*). Existing WHO STGs on reproductive health needed to be updated in order to ensure that these are consistent with the harmonized lists.

It was agreed to submit 16 medicines for possible addition to or deletion from the WHO Model List. In March 2005, the Expert Committee decided to include the following medicines: misoprostol and mifepristone; cefixime and clotrimazole; and nifedipine as a tocolytic (*28*). The Interagency List of Essential Medicines for Reproductive Health was subsequently endorsed by all partner organizations in reproductive health. In addition, a guide was developed to assist countries in the selection process (*29*). Meanwhile, there is a continuing tension between the aims of reproductive health advocates, who wish to broaden patient choice by providing a range of alternative similar products, and essential medicines programme managers, who wish to limit the range of products being provided to ensure availability and the most effective use of funds. The resulting tension can only be resolved at national level through the active involvement of both groups in the selection process.

1.4.3 Essential Medicines in Oncology

National cancer control programme should include essential medicines for prevention, optimal treatment, symptom control and supportive care.

Cancer is an illness that contributes increasingly to morbidity and mortality in developing countries. While the availability of essential medicines for cancer therapy is important for treating the many different forms of cancer, many of the cancer medicines available today are costly and may have limited benefits. Meanwhile, efforts to assess the effectiveness of these agents are complicated by the variation in therapeutic end-points and the use of surrogate markers for assessing the impact of treatments. As a result, selection of cytotoxic medicines for an essential medicines list is challenging, especially for countries with limited resources.

One of the difficulties is that the treatment of cancer is not determined by the selection of appropriate cytotoxic medicines alone. Treatment with an effective cytotoxic protocol is just one single component of a national cancer control programme. A national cancer control programme also consists of primary prevention, such as hepatitis B immunization for the prevention of hepatoma and tobacco control for the prevention of lung cancer. It should also include a programme for early diagnosis, screening, and optimal treatment and symptom control. And since cancer patients often develop complications, it is equally important to provide supportive care with analgesics, antibiotics and anti-emetics.

In 1999, a consultation article described a systematic approach for the selection of cytotoxic medicines (30). The most commonly occurring types of cancer were categorized according to their treatability, and medicines were placed into different categories according to their cost-benefit ratio. Medicines categorized as treating curable cancers, and cancers for which the cost-benefit ratio favoured treatment with cytotoxic medicines, were suggested for inclusion in an essential medicines list. This kind of systematic approach has not yet been implemented at a global level because of the wide differences that exist between countries in the provision of other services. However, a similar approach was adopted in Zimbabwe in 1990. At the time, the Zimbabwe Essential Drugs Action Programme was active and the approach used by the cancer specialists in the country was consistent with the national programme. The categorization of conditions and cytotoxic products could serve as a possible model process for other countries planning to develop national programmes (*31*).

1.4.4 Essential Medicines for Orphan Diseases

Orphan diseases are a complex and heterogeneous mosaic of an estimated 5000–8000 conditions. In the USA, they are defined as a disorder affecting less than 200 000 people, while in Europe a prevalence rate of less than 5 per 10 000 is used. Most of these disorders are of genetic origin and children account for 50%–75% of patients with rare diseases (*32*). Medicines for orphan diseases are a special challenge for the selection of essential medicines. In general, many of the medicine selection systems, such as the WHO Model List, focus primarily on essential medicines for the most common health problems in a region – thereby excluding medicines for treating rare orphan diseases.

For developing countries, inclusion of medicines for orphan diseases will remain problematic.

As a result of new research initiatives and government incentives created in the USA and Europe to help accelerate the development of medicines for rare diseases, new products are now available to treat orphan diseases. Developed countries have made special provisions to pay for these very expensive treatments for the few patients who need them. But for most developing countries, selection of medicines for orphan diseases will remain problematic – not only because of the costs but also because the necessary diagnostics and service facilities may not exist.

In 2006, an article by Stolk et al. in the *WHO Bulletin* proposed that a model list of essential medicines for orphan diseases should be created as a complement to the existing WHO Model EML and that it should be based on different selection criteria (*33*). In response, an editorial in the same issue by Reidenberg, Chairman of the Expert Committee at the time, argued that the existing criteria for inclusion in the Model List were based on the principle of distributive justice (i.e. the proper distribution of benefits and burdens) and that highly cost-effective medicines for rare diseases would be considered essential medicines under these criteria. Therefore there was no need to create a new separate list for orphan diseases, based on different criteria.

In 2007, the Expert Committee considered the topic of selection of medicines for orphan diseases. After review of the above publications (*33,34*), the Expert Committee decided to maintain their approach for the selection of all essential medicines, including medicines for orphan diseases.

At country level, decisions about the selection of medicines for orphan diseases will need to be taken within the context of the overall health system. The treatment of orphan diseases requires a complex arrangement of diagnostics, treatment monitoring and counselling services. Unless the full range of these services is available, selection of orphan disease medicines is likely to lead to the provision of ineffective, expensive care. However, a recent article from China by Wang JB et al. advocated for a national orphan diseases programme in China (*35*).

1.5 CONCLUSION

The WHO Model List provides an evidence-based list of medicines, including children's medicines, for priority diseases and conditions. The Model List and its supporting documentation provide a valuable resource for countries developing national EMLs.

To facilitate the development of national EMLs, WHO is developing guidance for countries (*36*). The new guidance document, which will be reviewed at the 2011 Expert Committee meeting, describes the steps that must be completed – from obtaining an overview of the most common health problems prevalent in the region to developing evidence-based standard treatment guidelines. The document provides guidance on forming essential medicines committees, systematically reviewing and evaluating the evidence, and ensuring transparency in the process.

The production of a national EML can help countries make the best use of limited resources to procure and make available the most appropriate treatments for the priority diseases and conditions. However, regular revision is essential to ensure that the selection remains current and credible.

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ABBREVIATIONS

EML	Essential Medicines List
EMLc	Essential Medicines List for Children
FDC	Fixed-dose combination
STGs	Standard Treatment Guidelines
STI	Sexually transmitted infection
WHO	World Health Organization

ANNEXES

Annex 1. Comparison of criteria for selection in 1977 and in 2009 (*10,11*)

Where are we coming from? (1977)	Where are we now? (2009)
– The selection of drugs should be based on the results of benefit and safety evaluations obtained in controlled clinical trials and/or epidemiological studies. When several drugs are available for the same indication, select the drug, pharmaceutical product and dosage form that provide the highest benefit/risk ratio. When two or more drugs are therapeutically equivalent, preference should be given to the drug that: is most thoroughly investigated, has the most favorable pharmacokinetic properties, has local reliable manufacturing facilities, has favourable stability, or storage facilities.	Comparative effectiveness in a variety of clinical settings: – identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data) – summary of available data such as appraisal of quality including clinical evidence, available estimates of comparative effectiveness. – summary of available estimates of comparative effectiveness.
The selection of drugs should be based on the results of benefit and safety evaluations obtained in controlled clinical trials and/or epidemiological studies.	Comparative evidence of safety: – estimate of total patient exposure to date – description of adverse effects/reactions – identification of variation in safety due to health systems and patient factors – summary of comparative safety against comparators.
Cost of the total treatment has to be taken in to account, together with the comparison between other drugs and non-pharmaceutical treatments.	Comparative cost and cost-effectiveness: – range of costs of the proposed medicines – comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)
Local health authorities should decide the level of expertise required to prescribe single drugs or a group of drugs in a therapeutic category.	Treatment details (reference to existing WHO and other clincical guidelines, need for special diagnostic or treatment facilities skills).
Regulations and facilities should be available to ensure that the quality of selected pharmaceutical products meets adequate quality control standards, including stability and, when necessary, bioavailability.	Regulatory status of the medicine (in country of origin, and preferably in other countries as well).
Fixed-ratio combinations are only acceptable if the following criteria are met: – justified by clinical documentation – therapeutic effect is greater than the sum of the effect of each – the cost of the combination product is less than the sum of the individual products – compliance is improved – sufficient drug ratios are provided to allow dosage adjustments satisfactory for the majority of the population	Most essential medicines should be formulated as single dose compounds. Fixed-dose combination products should be selected only when the combination has proven advantage in therapeutic effect, safety, and adherence or in decreasing the emergence of drug-resistance in malaria, tuberculosis and HIV/AIDS.
Not considered in 1977	Medicine is internationally available.
Not considered in 1977	Availability of pharmacopoeial standards (BP, IP, USP).
Not considered in 1977	Medicine has proven to be relevant for public health with information regarding to disease burden, assessment of current use and target population.

Comparison of national EMLs with WHO Model Essential Medicines List 2005

	Total number of medicines on national EML (excluding duplicates)	Total number of dosage forms on national EML	*Ratio of dosage forms to medicines*
Tanzania (2007)	319	504	*1.6*
Congo (2006)	264	435	*1.7*
South Africa (2006)	413	707	*1.7*
Brazil (2006)	359	597	*1.7*
Djibouti (2007)	218	281	*1.3*
Egypt (2006)	385	579	*1.5*
Yemen (2007)	309	397	*1.3*
Latvia (2007)	313	661	*2.1*
Moldova (2006)	447	821	*1.8*
Bhutan (2007)	299	366	*1.2*
Sri Lanka (2006)	335	415	*1.2*
Philippines (2007)	248	523	*2.1*
WHO Model List (2005)	**312**	**620**	***1.7***

Countries were purposively chosen based on the following criteria: the list must be from the year 2006 or 2007 and the WHO Regions (AFRO, AMRO, EMRO, EURO, WPRO, SEARO) must each be represented with a minimum of two countries. All the lists are compared with the 14th WHO Model EML (2005).

Annex 2. Medicines appearing on national EMLs but not on the WHO Model List 2005

Section of WHO Model EML	Medicines[a]	On WHO Model List 2009
Anaesthetics	propofol (5)	—
Analgesics	diclofenac (9), indomethacin (5), fentanyl (7), pethidine (7), tramadol (6)	—
Antiallergics	cetrizine (7), cromoglicic acid (5)	—
Anti-infectives	cefotaxime (6), cefalexin (6), cefazolin (5)	cefotaxmine, cefalexin, cefazoline
Antimigraine medicines	ergotaminetartrate (5)	—
Cytotoxic medicines	carboplatin (6)	carboplatin
Antiparkinsonism	trihexylphenidyl (8)	—
Medicines affecting the blood	enoxaparin (6)	—
Cardiovascular medicines	amiodarone (8), dobutamine (6), atorvastatine (6), simvastatine (5)	amiodarone, simvastatine
Dermatological medicines	zinc oxide ointment (6)	—
Gastrointestinal medicines	omeprazole (9), lactulose (7), glycerine/ glycerol (5)	omeprazole
Hormones, other endocrine medicines and contraceptives	gliclazide (5), carbimazole (7)	—
Immunologicals	DTP-vaccine (8)	
Ophthalmological preparations	acyclovir (7), chloramphenicol (7), diclofenac (5)	aciclovir
Psychotherapeutic medicines	risperidone (5), fluoxetine (6)	fluoxetine
Medicines acting on the respiratory tract	theophylline (9), aminophylline (7)	—
Solutions correcting water, electrolyte, and acid-base disturbances	sodium bicarbonate (8)	—
Vitamins and minerals	vitamin B complex (5)	—

[a] Medicines appear on 5 or more of the 14 national EMLs analysed and are not accommodated by a square box on the WHO Model List 2005. The third column indicates whether the medicine was added to the WHO Model List after 2005, during revisions in 2007 and 2009.

Annex 3. Medicines appearing on the WHO Model List 2005 but not on national EMLs

Section	Medicines[a]
Anti-infective medicines	pyrantel, suramin sodium, triclambendazole, oxamniquine, cefixime, imipenem + cilastatin, spectinomycin, trimethoprim, p-aminosalicylic acid, capreomycin, cycloserine, ethionamide, levofloxacin, flucytosine, potassium iodide, meglumine antimoniate, pentamidine, amodiaquine, mefloquine, artemether, artesunate, proguanil, eflornithine, benznidazole, nifurtimox[a]
Cytotoxic medicines	chlormethine, daunorubicine, levamisole
Dermatological medicines	sodium thiosulfate, selenium sulfide, neomycin sulfate + bacitracin, aluminium diacetate, dithranol, fluorouracil
Oxytocics and antioxytocics	mifepristone + misoprostol

[a] Medicines that do not appear in 10 or more national EMLs reviewed