

Essential Medicines *for* Reproductive Health:

Guiding Principles
for Their Inclusion
on National
Medicines Lists



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Section 1

Introduction

“Trying to run sexual and reproductive health programmes without contraceptives ... and other reproductive health commodities is like trying to eradicate smallpox without vaccines. It simply cannot be done.”

Steven Sinding, Director-General
International Planned Parenthood Federation, 2003¹

After immunisation for common childhood illnesses, appropriate use of essential medicines is one of the most cost-effective components of modern health care.² In 1977, the World Health Organization (WHO) launched its first list of essential medicines. The model list was designed to prioritise the most important medicines for public health and was the centrepiece of a strategy to enhance their availability, especially in less-developed countries.³ Essential medicines lists (EMLs) give priority status to medicines that address a country’s most pressing public health problems—they are a vital tool for improving and maintaining health. For almost three decades, WHO has continued to devote substantial effort to an essential medicines programme that seeks to improve access to the most needed medicines.

Poor reproductive health constitutes a significant portion of the disease burden in developing countries, yet essential reproductive health medicines often are not available to the majority of the population in these countries. For example, it is estimated that some 201 million couples at risk of unintended pregnancy who would like to space or limit their births are not using modern contraception to do so.⁴ Lack of access to medicines needed to maintain good sexual and reproductive health services threatens the well-being of individuals, families, and communities.

Ensuring the availability of and access to essential reproductive health medicines—contraceptives, medicines for prevention and treatment of sexually transmitted infections (STIs) and HIV/AIDS, and medicines to ensure healthy pregnancy and delivery—requires strong government commitment and a range of activities to guarantee financing, logistics systems, procurement, and effective service delivery. WHO, the United Nations Population Fund (UNFPA), and other agencies have established a common nonproprietary list of essential reproductive health medicines (Appendix 1). To augment this effort, this introductory guide, *Essential Medicines for Reproductive Health: Guiding Principles for Their Inclusion on National Medicines Lists*, provides an overview of the process for including reproductive health medicines on national essential medicines lists at the country level based on the essential medicines concept. This guide presents the rationale for including specific reproductive health medicines on national EMLs.

Problem statement

Even where national essential medicines lists are available at the country level, reproductive health medicines often are not listed. In 2002, WHO reviewed 55 national medicine policies and 112 (of a total 192) WHO member countries' national EMLs to determine the degree to which they included reproductive health medicines. The study compared the medicines found on these EMLs to the draft *Interagency List of Essential Medicines for Reproductive Health*. The review showed that the majority of national medicine policies contained virtually no mention of reproductive health.⁵

The study also found that reproductive health medicines are not represented comprehensively on national EMLs—even when a solid evidence base for their effectiveness exists. Magnesium sulphate, for example, is a cost-effective medicine demonstrated to be effective in preventing pre-eclampsia and treating eclampsia, leading causes of maternal death and illness that affect

approximately 3.2 percent of all pregnancies and lead to over 63,000 maternal deaths worldwide each year.⁶ Yet magnesium sulphate was included on the EMLs of only 45 (40 percent) of the countries included in the study. On average, only three of nine family planning methods surveyed* could be found on any one EML. Condoms, an important method in preventing pregnancy and the primary method for preventing transmission of STIs, including HIV, were listed on only 35 percent of the EMLs. Of 22 reproductive tract/STI medicines and 27 HIV/AIDS medicines assessed, only 12 (55 percent) and 5 (18 percent), respectively, were found on any one EML.⁵ Table 1 compares the number of medicines included on the list used in the review with the average number of medicines found on national lists.

Table 1. Comparison of national essential medicines lists for reproductive health medicines to the Interagency list.+

Type of medicine	No. of medicines on Interagency list	Average no. of medicines listed on national lists
Safe motherhood/maternal health antihypertensives, oxytocics, antimalarials, etc.	111	75 (68 percent)
Family planning hormonal contraceptives, condoms	9	3 (33 percent)
Sexually transmitted and reproductive tract infections (RTIs) antibiotics, antifungals	22	12 (55 percent)
HIV/AIDS antiretroviral drugs, medicines for opportunistic infections	27	5 (18 percent)

+The UNFPA-led Interagency Group included WHO and the Joint United Nations Programme on HIV/AIDS.

Source: WHO.⁵

*Low-dose combined pills, progestin-only pills, spermicides, contraceptive foams/gels, medroxy-progesterone acetate (depot injection), copper intrauterine device, condoms, and diaphragms.

These notable omissions indicate that how an EML is developed and applied is vital to its usefulness.

What is the objective of the guide and who will use it?

The objective of this guide is to provide background on the EML process and information on the importance of including reproductive health medicines on EMLs. It also provides tips for incorporating key reproductive health medicines into EMLs at the national level. It is intended to be used by reproductive health programme managers, national-level essential medicines committees, and those responsible for selecting, procuring, and ensuring the quality of reproductive health medicines.

What is in this guide?

Many people in the reproductive health community, both globally and at the country level, are unfamiliar with EMLs and the role they play in improving access to medicines. The guide is intended to help advocates, policymakers, and decision-makers at all levels—local and national governments, bilateral and multilateral donors, and nongovernmental organizations (NGOs)—stimulate use of the EML for country-level decision-making on reproductive health medicines. This guide does not aim to be a comprehensive manual on reproductive health or essential medicines and, therefore, includes resource lists at the end of each section to direct readers to additional resources that provide more in-depth technical analysis of reproductive health or essential medicines issues.

Some groups may find some sections more relevant than others and may choose to read only those parts that are pertinent to their particular line of work. Although the issues are intricately related, each topical section can stand alone. The document contains case studies to help illustrate key points. Whilst the case studies are not specific to reproductive health, they provide examples that could be adapted to reproductive health.

The guide is organised into three main sections:

- **Reproductive health: a public health priority** highlights the consequences of poor reproductive health and the importance of devoting resources to its betterment. This section is particularly relevant to EML managers and pharmaceutical services staff.
- **EMLs: application of a global concept** provides a brief overview of the concept of EMLs and their significance. This section is particularly relevant to reproductive health programme managers, advocates, and policymakers.
- **Adding reproductive health medicines to EMLs** outlines the steps necessary for including reproductive health medicines on country-level EMLs. This section is particularly relevant to reproductive health programme managers, advocates, and policymakers.

The guide also contains four appendices. Appendix 1 is the *Interagency List of Essential Medicines for Reproductive Health*. Appendix 2 is a checklist of activities to ensure that reproductive health medicines are included on national essential medicines lists, whilst Appendix 3 includes the necessary information for adding a medicine to, changing, or deleting a medicine from the *WHO Model List of Essential Medicines*. Appendix 4 contains policy briefs for 16 essential reproductive health medicines. These briefings provide clinical evidence and other information needed by national-level essential medicines committees considering inclusion of a new reproductive health medicine on their own national essential medicines lists.

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Section 2

Reproductive health: a public health priority

Section objective

Provide an overview supporting the importance of addressing reproductive health needs. This section is particularly relevant to EML managers and pharmaceutical services staff.

Key points

- ▶ Sexual and reproductive health is essential to human well-being.
- ▶ Reproductive health problems account for a significant part of the burden of disease amongst adolescents and adults in developing countries.
- ▶ Reproductive health problems can be significantly reduced if essential reproductive health medicines are available, affordable, of good quality, and properly used.

What is the global perspective on reproductive health?

The 1994 International Conference on Population and Development (ICPD) adopted a Programme of Action that established sexual and reproductive health as essential to human well-being. The Programme of Action defines reproductive health as a state of “physical, mental, and social well-being in all matters related to the reproductive system and to its functions and processes.”⁷ The ICPD made reproductive and sexual rights a priority at both the national and international levels, and the Programme of Action intended to make universally available high-quality reproductive health services.

Reproductive health is not simply the absence of disease. It covers a range of conditions that include healthy sexual development, reproductive and fertility regulation, prevention of STIs and HIV/AIDS, and safe motherhood. Reproductive health also means that people are able to have a satisfying and safe sex life and that they have the capability and freedom to make informed choices about reproduction.⁸ The ICPD Programme of Action states that it is the right of men and women to be “informed and to have access to safe, effective, affordable, and acceptable methods of family planning of their choice, as well as other methods of their choice for regulation of fertility, which are not against the law,” and that they have “the right of access to health care services that will enable women to go safely through pregnancy and childbirth.”⁷ The five- and ten-year reviews of the ICPD reinforced that consensus.

In 2002, the United Nations agreed to the Millennium Development Goals (MDGs)—a broad set of targets that established international development priorities. Improving sexual and reproductive health is fundamental to achieving most, if not all, of the goals.⁴ According to the United Nations Millennium Development Project, “universal access to sexual and reproductive health services, information, and education should be guaranteed as an intrinsic part of strategies to reduce child deaths and improve maternal health.” The Millennium Development Project holds that access to reproductive health information and services would have “far reaching effects for virtually every other MDG, including the Goals for HIV/AIDS, gender, education, environment, hunger, and income poverty.”⁹

Similarly, in response to a request to develop a strategy for accelerating progress toward the attainment of the MDGs and other international goals related to improving reproductive health, WHO adopted its first strategy on reproductive health in 2004. The strategy targets five priority aspects of reproductive and

sexual health: 1) improving antenatal, delivery, postpartum, and newborn care; 2) providing high-quality services for family planning, including infertility services; 3) eliminating unsafe abortion; 4) combating STIs (including HIV), RTIs, cervical cancer, and other gynaecological morbidities; and 5) promoting sexual health.¹⁰

What is the burden of poor reproductive health?

Reproductive health problems, such as early and unwanted childbearing, HIV infection, STIs, and pregnancy-related illness and death, account for a significant part of the burden of disease amongst adolescents and adults in developing countries.⁸ WHO estimates that poor reproductive health accounts for up to 18 percent of the global burden of disease and 32 percent of the total burden of disease for women of reproductive age.⁴ Poor reproductive health is responsible for more than one-third of all disability-adjusted life years (DALYs) lost by women during their reproductive years.¹¹ Table 2 illustrates the burden of reproductive ill health in terms of percent of DALYs lost.

Table 2. The burden of poor reproductive health.

Health problem	Percent of disability-adjusted life years (DALYs) lost, 2001	
	Total population (men and women)	Women aged 15–44 years
Sexual and reproductive health conditions	17.8	31.8
Respiratory conditions	10.7	4.1
Cardiovascular conditions	9.8	4.3
Neuropsychiatric conditions	13.0	25.4
Injuries	12.2	12.4
Other communicable conditions	19.6	8.8
Other noncommunicable conditions	16.8	13.2
Total	100.0	100.0

Source: The Alan Guttmacher Institute.⁴

Three groups of conditions contribute significantly to poor reproductive health: maternal mortality and morbidity, HIV/AIDS, and other STIs. Globally, maternal mortality and morbidity rates are unacceptably high. Every year, 20 million women suffer severe maternal morbidity as a result of pregnancy, and more than 500,000 women die from pregnancy-related causes that, if managed appropriately, need not have been fatal.^{4,12} Nearly all of these deaths occur in developing countries amongst poor women. Maternal mortality is highest by far in Africa, where the lifetime risk of maternal death is 1 in 16, compared with 1 in 2,800 in developed countries.¹³ For each woman who dies, an estimated 100 women survive childbearing but suffer from serious disease, disability, or physical damage caused by pregnancy-related complications.¹⁴ With skilled and responsive care at and after birth, nearly all fatal outcomes and disabling sequelae can be averted.¹⁵

Malnutrition, anaemia, young maternal age, closely spaced births, and a high number of previous pregnancies also increase the risks for both mother and infant. Newborn deaths contribute to approximately 40 percent of all deaths of children younger than five years globally and to more than half of infant mortality.¹³ Nearly three-quarters of all neonatal deaths could be prevented if women were adequately nourished and received appropriate care during pregnancy, childbirth, and the postnatal period.¹³

A mother's death has a devastating effect on her family and a serious impact on the health of her surviving children. In many developing countries, the risk of death for children under age five is doubled or tripled after their mothers die.¹⁴ WHO estimates that up to 100,000 maternal deaths could be avoided each year if women who did not want children used effective contraception.⁶ Nevertheless, in many developing countries, the need for family planning and reproductive health medicines and services persists. At least 200 million women of reproductive age worldwide would like to prevent or space their births but are not using effective contraception.¹² It also has been estimated that expanding contraceptive services to meet the needs of couples who wish to avoid pregnancy but currently are not using contraception could prevent as many as 850,000 deaths per year amongst children under age five.¹⁵ When maternal illnesses also are taken into account, preventing unwanted pregnancies could avert the loss of 4.5 million DALYs each year.

Furthermore, every year there are an estimated 120 million unwanted pregnancies, resulting in 46 million abortions, 20 percent of which are unsafe and lead to severe morbidity and mortality for women.¹² For example, unsafe

abortion accounts for 13 percent of maternal deaths.¹³ When performed by trained health care providers with proper equipment, correct technique, and sanitary standards, abortion carries little or no risk. The case fatality rate is no more than 1 per 100,000 procedures, which is less than the risk of a pregnancy carried to term in the best of circumstances.⁶

The AIDS pandemic compounds the situation of high fertility rates and poor child and maternal health in many of the poorest countries. At least 40 million people were living with HIV in 2004. In addition, the incidence of other STIs is increasing. Untreated STIs increase the risk of acquiring HIV by six to ten times and are the underlying cause of one-half of the 60 to 80 million cases of infertility found worldwide.¹² The spread of HIV has a tremendous impact on both national economies and household income. Households affected by HIV infection and AIDS are more likely to be poor than those not affected. The care and treatment of individuals with HIV, as well as the lost income when complications of AIDS make it impossible for the infected individual to work, can shrink household income by 66 to 80 percent.¹⁶

What is the role of essential medicines?

In many developing countries, reproductive health services are of poor quality, partly because supplies of essential reproductive health medicines are inadequate and unreliable. In WHO's review of 112 member countries' EMLs, there was little mention of reproductive health medicines. Contraceptive methods in particular are generally not regarded as essential medicines; when budget cuts are made, these commodities are the first to fall off the list. This practice undermines the importance of these commodities. The problem is compounded by the fact that contraceptives are seen as preventative rather than "therapeutic." In addition, user preference is an important factor in the selection of reproductive health medicines, making it more difficult to advocate for their inclusion using standard approaches such as prevalence of disease, impact on general health, and cost of treatment.

If essential reproductive health medicines are available, affordable, of good quality, and properly used, they can significantly reduce reproductive health problems. However, political commitment is a first and necessary step toward ensuring the availability of reproductive health medicines—when national policies do not prioritise reproductive health medicines, reproductive health problems are compounded. One way to reverse this trend is to mandate that reproductive health medicines be included on EMLs and that EMLs be used to

guide public expenditures and policies related to access. A comprehensive list of essential reproductive health medicines, such as that developed collaboratively by WHO and partners, is an important starting point.

Additional resources

Cairo Conference website. Available at: <http://www.iisd.ca/cairo.html>. Accessed January 1, 2006.

Global Health Council. *Banking on Reproductive Health: The World Bank's Support for Population, the Cairo Agenda and the Millennium Development Goals*. Washington, DC: Global Health Council; 2004. Available at: http://www.globalhealth.org/view_top.php3?id=488.

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Section 3

EMLs: application of a global concept

Section objective

Provide an overview of the rationale for and impact of the essential medicines programmed. This section is particularly relevant to reproductive health programme managers, advocates, and policymakers.

Key points

- ▶ The selection of essential medicines is one of the core components of a national drug policy.
- ▶ For a national EML to have an effect on access to medicines, a number of in-country components need to be in place, including a well-established consensus-building process on how to develop and use national EMLs.
- ▶ An EML can decrease barriers to medicine access by maintaining a focus on a limited list of proven medication choices.

What are essential medicines?

Defined by WHO as those medicines that satisfy the priority health care needs of the majority of a given population, essential medicines are selected with due consideration of public health relevance, evidence of their efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available at all times in adequate amounts, appropriate dosages, with quality assurance and adequate information, and at a price the individual and the community can afford.²

The essential medicines concept states that use of a *limited* number of carefully selected essential medicines with proven efficacy, safety, and quality leads to better health care, better management of medicines, and lower health care costs for the majority of the population with common diseases. The selection and use of a limited number of essential medicines leads to an improved supply of medicines, more rational prescribing, and lower costs.¹⁶

What is the WHO Model List of Essential Medicines?

The *WHO Model List of Essential Medicines* (hereafter referred to as the **WHO model list**) is a list of individual medicines that provide safe, effective treatments for the world's most common infectious and chronic diseases. The first WHO model list was published in 1977 and is reviewed and modified every two years by the Expert Committee on the Selection and Use of Essential Medicines (WHO Expert Committee). The selection process has evolved to focus on transparency and evidence-based decision-making. Originally, selection mainly involved decisions made by members of the WHO Expert Committee, often with little evidence.¹⁷ Until 1999, the addition of a medicine to the model list was generally the result of application from WHO programme staff and the pharmaceutical industry. However, in 2002, WHO adopted an evidence-based approach that included public health relevance, efficacy, safety, and to a secondary degree, cost-effectiveness. As a result, WHO publishes decisions for adding to or deleting medicines from the model list that are accompanied by clear explanations and evidence for these decisions.¹⁷

The WHO model list focuses on medicines that address conditions that pose the greatest public health threat. As a guide for national and institutional EMLs, the WHO model list also provides a “best buy” reference for countries that lack the internal expertise to determine the most cost-effective options. These reasons are inextricably linked to evidence-based clinical guidelines for treatment of those priority conditions, with special emphasis on public health impact and, to a secondary degree, cost-effectiveness.* The 14th model list prepared by the WHO

Expert Committee in March 2005 contains 312 individual medicines and is divided into a core list and a complementary list.[†] Medicines are specified by the international nonproprietary name (INN) or generic name, without reference to brand names or specific manufacturers.

What are the practical implications of essential medicines?

Essential medicines lists are intended to be flexible and adaptable in any country—in both the private and the public sectors; in referral hospitals, as well as primary health care units; and in both rural and urban areas—and are a vital element of a national drug policy. A national drug policy expresses and prioritises the medium- to long-term goals set by the government for the pharmaceutical sector and identifies the main strategies for attaining these goals. The general objectives of a national drug policy are to ensure:

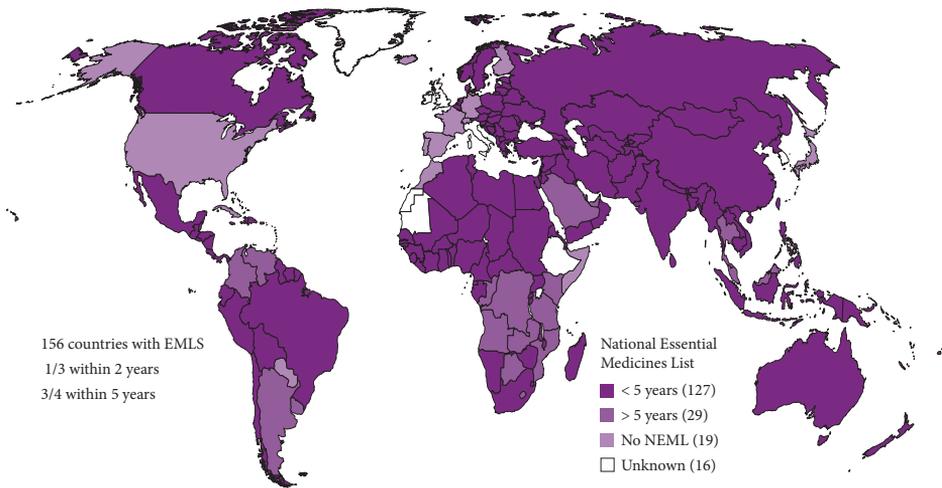
- Access: equitable availability and affordability of essential medicines.
- Quality: the quality, safety, and efficacy of all medicines.
- Rational use: the promotion of therapeutically sound and cost-effective use of medicines by health professionals and consumers.

The selection of essential medicines is one of the core components of a national drug policy, because it helps to set priorities for all aspects of the pharmaceutical sector. Countries face different challenges with regard to costs, drug effectiveness, morbidity patterns, and reasons for prescribing. Medicines on the WHO model list are intended for selective inclusion on country-level lists; the determination of which medicines are regarded as essential remains a national responsibility. National-level EMLs include medicines that governments or other institutions deem vital for the most common health conditions facing their populations. By the end of 1999, 156 countries had official EMLs, 127 of which had been updated in the previous five years (Figure 1). Medicines on an EML merit special efforts to ensure availability and correct use.

*Cost-effectiveness is used as a secondary criterion within a therapeutic class. This means that where there are multiple products within a therapeutic group, WHO identifies the most cost-effective option. However, countries are encouraged to choose within the group based on local considerations.

[†]“Core” medicines are defined as “efficacious, safe and cost-effective medicines for priority conditions selected on the basis of current and estimated future public-health relevance and potential for safe and cost-effective treatment.” “Complementary” medicines are defined as “medicines for priority diseases which are efficacious, safe and cost-effective, but not necessarily affordable, or for which specialized health care facilities or services may be needed.”¹⁸

Figure 1. Countries with a national EML, 1999.²



Countries that have an official selective list for training, supply, and reimbursement. Some countries have state/province lists instead of or in addition to national lists.

Who selects the medicines for a national EML?

An objective, transparent, evidence-based process for the selection of medicines for an EML is critical to its acceptance and use. In most countries, the ministry of health (MOH) appoints a committee to identify medicines for inclusion in the national EML. The committee typically includes representation from the MOH; the procurement department; regional and local government health facilities from different health fields, such as medicine, nursing, pharmacology, pharmacy, public health, and consumer affairs; and health workers from the community. It is highly recommended that EML committees have both professional and gender balance.

To maintain objectivity, manufacturers and advocacy groups are encouraged to submit data for consideration and may be invited to present their views in an open session, but they should not participate in the decision-making process. To help ensure a well-considered process, the committee also may organise formal and informal consultations with interested parties, such as representatives of professional bodies, pharmaceutical manufacturers, consumer organizations, and the government budget and finance group. Case study 1 describes the development of an essential medicines policy in South Africa.

South Africa: getting essential medicines to the people¹⁹

South Africa did not have a national essential medicines policy when the new government came into office in 1994. The public sector purchased more than 2,600 different pharmaceutical products, and there was a strong bias toward tertiary-level medicines. The Minister of Health appointed a National Essential Drugs List Committee in 1995. Members included pharmacists, general practitioners, medical specialists, pharmacologists, and public health experts. The committee's mandate was to develop standard treatment guidelines and essential medicines lists for all health care levels. Primary care was the first target; work on the tertiary level came later. The aim was to strengthen equity, cost-effectiveness, and the rational selection and use of medicines. Committee members drew up an initial list of the most prevalent conditions at the primary-care level and drafted initial treatment guidelines. These drafts were widely circulated for comment. The committee then prepared consensus standard treatment guidelines and derived a list of essential medicines from these guidelines. The criteria used to select South Africa's essential medicines list were substantially based on the WHO criteria for selection of essential medicines.

Fifty thousand copies of the first edition of the Standard Treatment Guidelines and Essential Drugs List for Primary Health Care (the "green book") were printed and distributed in April 1996. A Primary Health Care Review Expert Committee then evaluated the comments received on the first edition. An impact study by the South African Drug Action Programme assessed the usefulness of the publication at primary health care centres:

- Eighty-six percent of facilities had a copy of the book.
- Sixty-five percent of prescribers had a personal copy.
- Eighty-five percent of key medicines were available (the review team identified a basket of 30 "key" medicines to measure the availability of essential medicines).
- Ninety percent of the diagnoses recorded in the survey were included in the standard treatment guidelines.
- Seventy percent of the medicines prescribed were on the primary care essential medicines list (some nonessential medicine list items were still available in the system and needed to be phased out).
- Primary health care workers asked for further training in diagnosis and referral.

How are essential medicines selected for a national EML?

EMLs must be developed in a systematic way in conjunction with clinical standard treatment guidelines (STGs) for common health conditions or problems. STGs may be defined as “systematically developed statements to help practitioners or prescribers make decisions about appropriate treatments for specific clinical conditions.”¹⁸ Based on global evidence of effectiveness, STGs help standardize treatments throughout a health system and provide reasons and evidence for specific prescription practices. Widespread adoption and application of standardized treatments, in conjunction with morbidity and patient attendance data, provide a basis for quantification of medicine requirements. Standard treatment guidelines serve as ready reference texts for consultation during the course of daily clinical work and as resource materials for basic and in-service prescriber training.²⁰ They are valuable for auditing and supervisory purposes as well.

At a minimum, STGs should include information about clinical features, diagnostic criteria, nondrug and drug treatments, and referral criteria. STGs include a recommended first-choice treatment, which may be limited to one or more medicines or to various forms of nonmedicine treatments.¹⁸ Which treatment is recommended depends on many factors, such as the pattern of prevalent diseases; treatment facilities; the training and experience of available personnel; financial resources; and genetic, demographic, and environmental factors. For example, certain drug-resistant strains of an STI-causing organism may be prevalent in one country and not in another, thereby necessitating different treatment regimens.

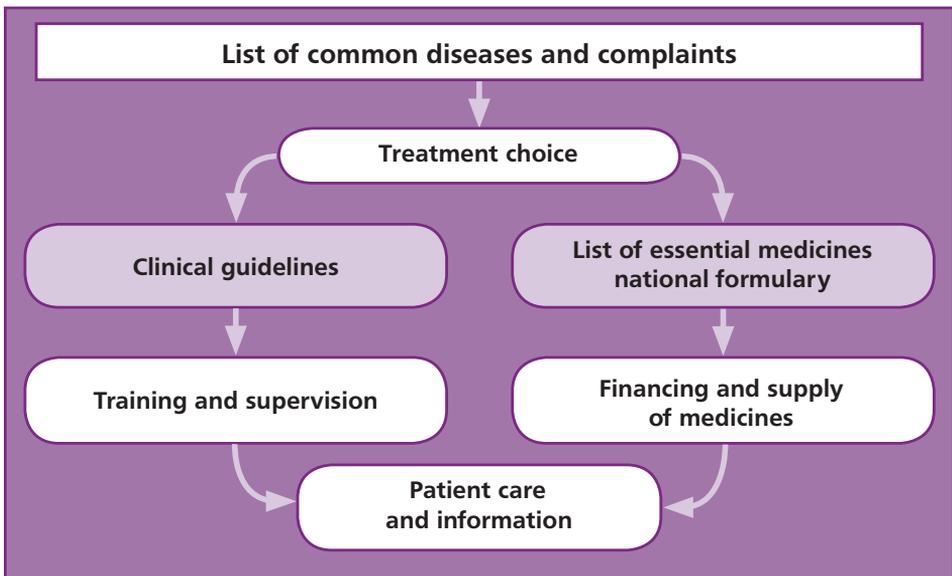
STGs lead to the identification of essential medicines, and the EML is developed based on the choice of treatment for the select health conditions. Selection of essential medicines should be driven by the following criteria used by the WHO Expert Committee:

- Only medicines for which sound and adequate evidence of efficacy and safety in a variety of settings is available should be selected.
- Relative cost-effectiveness is a major consideration for choosing medicines within the same therapeutic category. In comparisons between medicines, the total cost of the treatment—not just the unit cost of the medicine—must be considered and be compared with its efficacy. As mentioned in Section 2, contraceptive methods are not considered therapeutic; therefore, treatment

cost analysis for these commodities should be handled differently than therapeutic medicines.

- In some cases, the choice may also be influenced by other factors, such as pharmacokinetic properties, or by local considerations, such as the availability of facilities for manufacture or storage.
- Each medicine selected must be available in a form in which adequate quality, including bioavailability, can be ensured; its stability under the anticipated conditions of storage and use must be determined.

Figure 2. The systematic formulation of EMLs.²



An approved EML forms the basis for a national formulary, which contains summary information on the medicines. The formulary serves as a reference tool for health care workers. It typically contains the generic name of the medicine, the indications for use, dosage schedules, contraindications, side effects, and important information that should be given to the patient.¹⁸

How are national EMLs used?

National EMLs, together with STGs, should serve as the basis of formal education and in-service training of health professionals and of public education about medicine use. They should also be the basis for public-sector procurement and distribution and for medicine donations. EMLs and information about the benefits of medicine selection can also be used to influence practice in the private sector through education—for example, through basic training for medical students and continuing medical education through universities and professional associations.

Many national EMLs have what is called a “leveled medicines list,” which defines the range of medicines for procurement and distribution at each level of care (primary, secondary, and tertiary and referral health centres). The number of medicines typically increases to match the level of care.¹⁸ Using the national EML as a starting point, different care institutions (such as district hospitals, primary health centres, and dispensaries) within a health system can develop their own lists of STGs and medicines.

No public-sector or health insurance system can afford to supply or reimburse all medicines that are available on the market. EMLs are used to guide the procurement and supply of medicines in the public sector, systems that reimburse medicine costs, medicine donations, and local pharmaceutical manufacturers. International organizations, such as the United Nations Children’s Fund, UNFPA, the United Nations High Commission for Refugees, NGOs, and international nonprofit supply agencies have adopted the essential medicines concept for their supply systems. In developing countries, health insurance is less widespread, but coverage is growing, and systems are generally based on reimbursement for essential medicines. In view of the rapidly rising costs of medicines in most countries, health insurance systems need an evidence-based medicine selection process to contain costs.

For a national EML to have an effect on access to medicines, a number of in-country components need to be in place, including a well-established consensus-building process on how to develop and use national EMLs. The relationship between the presence of products on a national EML and the availability of those products is significantly influenced by a host of factors: the legal framework, pricing structure, systems for selecting and approving products, procedures for procurement and distribution, and measures for quality control.

How does an EML help increase access to medicines?

Major barriers to medicine access include the unavailability of products—either because supply and procurement systems are unreliable, the products are not offered in a particular region, or the products are not offered commercially—and cost. An EML can help overcome these barriers by maintaining a focus on a limited list of proven medication choices (Table 3).

Table 3. Advantages of a limited list of essential medicines.¹⁸

Supply
<ul style="list-style-type: none"> • Easier procurement, storage, and distribution. • Lower stocks. • Better quality assurance. • Easier dispensing.
Cost
<ul style="list-style-type: none"> • Lower prices. • More competition. • Lower overhead costs with limited range of products in stock.
Prescribing
<ul style="list-style-type: none"> • Training more focused and therefore easier. • More experience with fewer medicines. • No irrational treatment alternatives available. • Focused drug information. • Better recognition of adverse drug reactions.
Patient use
<ul style="list-style-type: none"> • Focused education efforts. • Reduced confusion and increased adherence to treatment. • Improved medicine availability.

As shown in case study 2, a state-level approach to rational medicine use by local governments in India has improved access to essential medicines through better medicine selection. Similarly, the inclusion of reproductive health medicines on a national EML could increase the probability that those medicines become widely available within a country.

Case study 2

The Delhi model: improved access to medicines through better selection²¹

The Government of India, working with WHO and the Delhi Society for Promotion of Rational Use of Drugs, an NGO, launched the Rational Use of Drugs Programme in 1994, when the medicine supply was erratic and uncoordinated. Although 30 to 35 percent of the hospitals' budgets were spent on medicines, shortages were chronic.

As an initial step, a high-level EML committee drew up a common list of 250 essential medicines for hospitals and a second list of 100 medicines specifically for dispensaries. Treatment guidelines at primary health centres were issued to help doctors. The guidelines included treatment for the conditions most commonly encountered by physicians: 15 diseases affecting adults and 5 affecting children. A common pool for procuring medicines was introduced, supervised by a special purchase committee.

Soon all hospitals run by the Delhi government began to use the same medicines. The new measures and bulk buying resulted in a sharp fall in the procurement prices of essential medicines. A savings of 30 percent in the annual medicines bill for the government was estimated. These savings were mobilised for procuring more medicines, which led to a more than 80 percent improvement in the availability of medicines at health facilities. Furthermore, positive changes in prescribing behaviour—in which more than 80 percent of prescriptions were for drugs on the EML and patients were receiving 70 to 85 percent of the medicines prescribed—resulted from new training programmes for prescribers.

The Delhi model illustrates that changing managerial systems with minimal additional expenditures can lead to better use and availability of medicines.

For public-sector supply programmes, there are advantages to concentrating procurement and logistics efforts on a limited number of medicines, including reduction in the number of different products that must be stocked, distributed, and monitored. Essential medicines usually are available from multiple suppliers, and increased competition reduces prices.¹⁸ The Pakistan Network for Rational Drug Use has successfully campaigned for the abolition of sales tax on essential medicines in Pakistan, leading to increased affordability.¹⁷ As shown in case study 3 on the next page, similar policies have been observed in Burkina Faso.

In addition, by limiting the number of different medicines used to treat a particular clinical problem, larger quantities of the selected medicine will be needed, which brings potential opportunities to achieve economies of scale in procurement. Quality assurance efforts also can be more effectively focused on a smaller group of medicines.

The selection of a list of essential medicines facilitates efforts to provide medicine information and education, both of which further rational prescribing and use.¹⁸ Since the publication of the first WHO EML, Acción Internacional Para la Salud (AIS) in Bolivia has translated and distributed the list throughout Bolivia, using a network of 15 volunteer groups. AIS also uses the EML as a basis for consumer education and campaigning to ensure that essential medicines remain in production and are available and affordable.¹⁷

As seen in the examples and case studies, proper use of STGs and EMLs can improve the availability and proper use of medicines within health care systems, and measures that lead to a regular availability of essential medicines will result in real health gains and increased public confidence in health services. The EML process is a cornerstone of good pharmaceutical management and rational medicine use. Applied to the field of reproductive health, it can increase the accessibility of lifesaving reproductive health medicines.

Increased access to injection devices in Burkina Faso^{22,23}

In 1995, the Ministry of Health of Burkina Faso reformed the national drug policy to improve access to essential medicines and medical consumables, including disposable injection devices, in all public health care facilities with a pharmaceutical depot. Two studies indicated that injection safety improved dramatically between 1995 and 2000, but the impact on the use of injectable medicines was unknown. In April 2001, Pharmaciens Sans Frontières, a pharmaceutical NGO, and WHO conducted a study to determine to what extent the new national drug policy was related to the increased access to disposable injection devices.

This retrospective review assessed the situation between 1995 and 2000. In 2001, the investigators visited 52 public primary health care facilities and their public pharmaceutical depots adjacent to the facilities. Data were collected on injection device availability and the percentage of prescriptions including at least one injection. Amongst all facilities visited, the number of facilities selling injection devices through their depots rose from 13 (26 percent) to 50 (96 percent) between 1995 and 2000. Of 50 depots visited, 96 percent had disposable 5-mL syringes available in 2001. Patients were buying injection devices at the facility depots for injections given by a health care worker. Although injection devices were available in more facilities, the proportion of prescriptions including at least one injection remained stable at 26 to 24 percent between 1995 and 2000.

The national list of essential medicines provided a framework that improved the availability of essential medicines and injection devices in Burkina Faso. To maintain affordable prices, retail prices of essential medicines and consumables included on the national list were fixed by the Ministry of Health and reviewed on an annual basis. In addition, the government removed importation taxes for essential medicines and essential consumables included on the national list of essential medicines. With the retail price of disposable syringes remaining fixed from 1997 to 2001, increased access to disposable injection devices and inclusion on the national list are likely the key factors contributing to the increased use of safe, disposable injection devices.

Additional resources

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4

Section 4

Adding reproductive health medicines to EMLs

Section objective

Identify the processes to guide action to ensure that reproductive health medicines are included on national EMLs. The following outlines tips for updating EMLs with reproductive health medicines for countries that have an existing EML. Appendix 2 provides a checklist for implementing these steps. This section is particularly relevant to reproductive health programme managers, advocates, and policymakers.

Key points

- ▶ Widespread support of reproductive health opinion leaders, relevant government bodies, and professional organizations working in reproductive health is vital to the process of adding reproductive health medicines to the national EML.
- ▶ It is essential that the process for selecting the reproductive health medicines is consultative and transparent, the selection criteria are explicit, and the selection of the reproductive medicines is linked to evidence-based standard clinical guidelines.
- ▶ National authorities can use the reproductive health medicines listed on the revised EML to guide resource allocation, import duties, medicines benefits within reimbursement schemes, donations, manufacturing subsidies, and mark-ups for the private sector.

Contact the essential medicines committee and inquire about the EML revision process

A country with an established essential medicines programme should have a multidisciplinary essential medicines committee. This committee is likely to be housed within the medicines or pharmaceutical department of the health ministry, which also can provide a copy of the EML. The national EML often includes a list of committee members and their affiliations and is a good starting point for identifying appropriate contacts who can provide information on the next update, the process, and requirements for the addition of new medicines.

The composition of the committee, as discussed previously, should be gender balanced and broadly representative, and at the same time should ensure relevant expertise. In consideration of the need to include reproductive medicines on national EMLs, the committee also should have a representative familiar with reproductive health issues, STGs, and medicines. To begin the process of adding reproductive health medicines to the EML, it is important to determine when the country's committee is meeting next and what the process is for requesting additions to the EML.

Identify reproductive health experts who will provide input to the national EML process

The addition of essential reproductive health medicines to national EMLs requires planning and coordination. Efforts should be guided by the ministry of health and other partner groups, including the medicines control council or equivalent national bodies. Widespread support of reproductive health opinion leaders, relevant government bodies, and professional organizations working in reproductive health is vital. Clinicians with reproductive health expertise should be included in these efforts. NGOs working in reproductive health also have a role to play in advocating support for the inclusion of reproductive health medicines on the EML—for instance, by producing materials that can be used for the evidence-based review process.

When identifying individuals with reproductive health expertise, it is important to include individuals with HIV/AIDS expertise. In many countries, HIV/AIDS and reproductive health programmes are driven independently of one

another (in some places, maternal and child health programmes are even run independently of newborn health programmes). Including representatives from these various groups is an important part of national priority-setting with respect to reproductive and sexual health. In fact, it may be helpful to identify three working groups for each of the following reproductive health areas: maternal/neonatal health, contraception, and STI/RTI and HIV/AIDS treatment.

Identify which medicines need to be added to the EML

It is essential that the process for selecting the reproductive health medicines is consultative and transparent, the selection criteria are explicit, and the selection of the reproductive medicines is linked to evidence-based STGs. As mentioned in Section 3, the STGs help determine a medicine's inclusion on national EMLs and the national formulary. A list of the most widespread reproductive health needs will guide the formation of STGs. Such guidelines may already exist in country for the majority of the reproductive health conditions included on the WHO model list. In the case of contraceptive methods, the issue of STGs is less relevant, as counsellors generally present two to three choices of contraceptives based on a client's individual history (for instance, different formulations for hormonal contraceptives may be more appropriate for different clients). Given that a country cannot afford to include all reproductive health medicines, the *Interagency List of Essential Medicines for Reproductive Health* (Appendix 1) as well as the *WHO Model List of Essential Medicines* can help a country decide which to include on and which to leave off of their national lists. The *WHO Medical Eligibility Criteria for Contraceptive Use* and the WHO Reproductive Health Library are also important resources.

Based on the STGs and local data, the reproductive health working group, with input from the EML committee, should identify the most common reproductive health issues, conditions, and diseases, and the appropriate treatment of each in the country. These should be ranked on the basis of prevalence, severity, impact on the general health of the population, and the cost of treating the conditions. An important principle that must be recognized is that not all evidence is equally strong. For example, the result of a systematic review of clinical trials of an antiretroviral treatment carries more weight than the result of an observational study without controls and much more weight than the personal experiences of individual experts. The strength of the evidence defines the strength of the recommendation.

Based on this information, the group should define a list of reproductive health medicines to be added to the national EML. The clinical guidelines and the EML should be divided into levels of care. The majority of reproductive health medicines are intended to be used at the primary health care level. Policy and programmatic guidelines must also be revised to support access to services and appropriate prescribing practices.

Next, the group should collect and organise the data, evidence, and information requested for each new submission to the EML committee. Appendix 4 proposes policy briefs for some of the priority reproductive health medicines to support their submission. A revision form is one mechanism that is often used in country for updating EMLs. The revision form usually requires information about the pharmacological action of the medicine, its proposed indication, and evidence from the literature to support inclusion on the EML. Appendix 3 lists the information called for in the application of inclusion, change, or deletion of a medicine on the WHO model list. In-country revision forms will likely require similar information. Proposals should be submitted by the deadline set up by the committee.

Implement the new EML

When the EML is updated and printed, it should be launched and made widely available. It may be useful to issue an informational leaflet that summarizes the changes or to make the changes known through a newsletter or drug bulletin. The revised list of essential medicines and clinical guidelines should be available in all health care facilities and to all health care providers in both printed and electronic versions. The intended use, legitimacy, and authority of the EML should be clear to all. In addition, the involvement of government officials, such as the minister of health or the president, and intensive press coverage could be an important part of launching the revised EML.

For the implementation of the revised EML to be successful, the specific legal or administrative authority of the EML for training, procurement, reimbursement, and public information must be clear. As discussed in Section 3, national authorities can use the reproductive health medicines listed on the revised EML to guide resource allocation, import duties, medicines benefits within reimbursement schemes, donations, manufacturing subsidies, and markups for the private sector. The EML also may guide product selection, procurement, distribution, quality assurance, and other national health activities.

Advocates at the policy level and the press can promote the use of the EML. NGOs have a role to play in this process as well. There are several examples of NGOs influencing use of the EML, including the following:

- In Malaysia, the National Poison Centre educates the public about essential medicines by regularly publishing articles in the Malaysian newspaper *New Strait Times*.¹⁹
- In Latvia, the independent drug bulletin *Cito!* led campaigns to stop the sales of inessential medicines, such as obsolete antidiarrhoeals and painkillers, using the essential medicines concept.¹⁷
- In 1982, the Dutch parliament adopted a decision that development aid could be used only to purchase essential medicines. This action was stimulated by WEMOS (the Dutch Working Group on Health and Development Issues).¹⁷

WHO recommends that national STGs, the EML, and the formulary be reviewed at least every other year and that their use and impact be monitored.



Conclusion

The potential health impact of availability and access to essential reproductive health medicines is remarkable. Simple iron folate preparations can reduce maternal and child mortality from pregnancy-related anaemia, family planning can reduce the rate of unintended pregnancies, and STI treatment can reduce transmission of HIV. As the United Nations Millennium Project notes, “expanding access to sexual and reproductive health services, including family planning and contraceptive information and services, and closing funding gaps for supplies and logistics are achievable priorities.”⁹

The addition of appropriate reproductive health medicines to EMLs can result in enhanced equity in access to and cost containment of essential reproductive health medicines, and improve quality of care. Procuring fewer items in larger quantities results in more price competition and economies of scale with regard to quality assurance, procurement, storage, and distribution. Such economies can lead to improved medicine availability at lower costs, benefiting those who are most in need. Reproductive health experts must understand the national EML process and invest time and effort to bring about changes to national EMLs.

Including reproductive health medicines on national EMLs is only the first step in the process of improving access to reproductive health medicines for the populations that need them. Country-wide efforts, including strengthening health systems and action at the policy level, to overcome barriers to making these medicines and products available are also critical. Ensuring access to high-quality reproductive health information, products, and services requires commitment and action across a range of sectors.



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Appendices

Appendix 1:

Interagency list of essential medicines for reproductive health

Appendix 2:

Checklist of activities to ensure that reproductive health medicines are included on national essential medicines lists

Appendix 3:

Information to be included with an application for inclusion, change, or deletion of a medicine on the *WHO Model List Of Essential Medicines*

Appendix 4:

Policy briefs for 16 essential reproductive health medicines

Appendix 1

Interagency list of essential medicines for reproductive health

This revised *Interagency List of Essential Medicines for Reproductive Health* presents the current international consensus on rational selection of essential reproductive health medicines. The list is intended to support decisions regarding the production, quality assurance, national procurement, and reimbursement schemes of these medicines.

The basic objective has been to ensure that all reproductive health medicines on the interagency list are also part of the World Health Organization's *WHO Model List of Essential Medicines* (WHO model list). In other words, the interagency list will be a subset of the model list.

The *Interagency List of Essential Medicines for Reproductive Health* is presented by therapeutic class as in the WHO model list but includes only the numbered sections of the model list in which reproductive health medicines are mentioned.

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 variety of settings.

When the strength of a drug is specified in terms of a selected salt or ester, this is mentioned in parentheses; when strength refers to the active moiety, the name of the salt or ester in parentheses is preceded by the word "as."

The square box symbol (□) is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness

and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Therapeutic equivalence is indicated only on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price. Medicines are listed in alphabetical order, within sections.

1. Anaesthetics

1.1 General anaesthetics and oxygen	
<input type="checkbox"/> halothane	inhalation
ketamine	injection, 50 mg (as hydrochloride)/ml in 10-ml vial
nitrous oxide	inhalation
oxygen	inhalation (medicinal gas)
<input type="checkbox"/> thiopental	powder for injection, 0.5 g, 1.0 g (sodium salt) in ampoule
1.2 Local anaesthetics	
<input type="checkbox"/> lidocaine	injection, 1 percent, 2 percent (hydrochloride) in vial; injection for spinal anaesthesia, 5 percent (hydrochloride) in 2-ml ampoule to be mixed with 7.5 percent glucose solution topical forms, 2-4 percent (hydrochloride)
lidocaine + epinephrine (adrenaline)	injection, 1 percent, 2 percent (hydrochloride) + epinephrine 1:200 000 in vial; dental cartridge, 2 percent (hydrochloride) + epinephrine 1:80 000
Complementary list	
ephedrine	injection, 30 mg (hydrochloride)/ml in 1-ml ampoule (for use in spinal anaesthesia during delivery, to prevent hypotension)

1.3 Preoperative medication and sedation for short-term procedures

atropine	injection, 1 mg (sulfate) in 1-ml ampoule
<input type="checkbox"/> diazepam	injection, 5 mg/ml in 2-ml ampoule; tablet, 5 mg
morphine	injection, 10 mg (sulfate or hydrochloride) in 1-ml ampoule
promethazine	elixir or syrup, 5 mg (hydrochloride)/5 ml

2. Analgesics, antipyretics, nonsteroidal anti-inflammatory medicines (nsaims), medicines used to treat gout, and disease-modifying agents in rheumatoid disorders (dmards)

2.1 Nonopioids and nonsteroidal anti-inflammatory medicines (NSAIMs)

acetylsalicylic acid	tablet, 100-500 mg; suppository, 50-150 mg
paracetamol*	tablet, 100-500 mg; suppository, 100 mg; syrup, 125 mg/5 ml * not recommended for anti-inflammatory use due to lack of proven benefit to that effect

2.2 Opioid analgesics

morphine	injection, 10 mg in 1-ml ampoule (sulfate or hydrochloride); oral solution, 10 mg (hydrochloride or sulfate)/5 ml; tablet, 10 mg (sulfate)
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3. Antiallergics and medicines used in anaphylaxis

<input type="checkbox"/> chlorphenamine	tablet, 4 mg (hydrogen maleate); injection, 10 mg (hydrogen maleate) in 1-ml ampoule
dexamethasone	injection, 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule
epinephrine (adrenaline)	injection, 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule
hydrocortisone	powder for injection, 100 mg (as sodium succinate) in vial
<input type="checkbox"/> prednisolone*	tablet, 5 mg, 25 mg * there is no evidence for complete clinical similarity between prednisolone and dexamethasone at high doses

4. Antidotes and other substances used in poisonings

Section 4 will be reviewed at the next meeting of the Expert Committee on the Selection and Use of Essential Medicines (Expert Committee).

4.2 Specific

atropine	injection, 1 mg (sulfate) in 1-ml ampoule
calcium gluconate	injection, 100 mg/ml in 10-ml ampoule
naloxone	injection, 400 mcg (hydrochloride) in 1-ml ampoule

5. Anticonvulsants/antiepileptics

<input type="checkbox"/> diazepam	injection, 5 mg/ml in 2-ml ampoule (intravenous or rectal)
magnesium sulfate*	injection, 500 mg/ml in 2-ml ampoule, 500 mg/ml in 10-ml ampoule * for use in eclampsia and severe preeclampsia and not for other convulsant disorders
phenobarbital	tablet, 15-100 mg; elixir, 15 mg/5ml
phenytoin	capsule or tablet, 25 mg, 50 mg, 100 mg (sodium salt); injection, 50 mg/ml in 5-ml vial (sodium salt)

6. Anti-infective medicines

6.1 Anthelmintics

6.1.1 Intestinal anthelmintics

<input type="checkbox"/> mebendazole	chewable tablet, 100 mg, 500 mg
pyrantel	chewable tablet, 250 mg (as embonate); oral suspension, 50 mg (as embonate)/ml

6.2 Antibacterials

6.2.1 Beta-lactam medicines

Applications for cefalexin and cefazolin are anticipated for the next meeting of the Expert Committee.

amoxicillin	capsule or tablet, 250 mg, 500 mg (anhydrous); powder for oral suspension, 125 mg (anhydrous)/5 ml
ampicillin	powder for injection, 500 mg, 1 g (as sodium salt) in vial
benzathine benzylpenicillin	powder for injection, 1.44 g benzylpenicillin (= 2.4 million IU) in 5-ml vial
benzylpenicillin	powder for injection, 600 mg (= 1 million IU), 3 g (= 5 million IU) (sodium or potassium salt) in vial
cefixime*	capsule, 400 mg * only listed for single-dose treatment of uncomplicated anogenital gonorrhoea
<input type="checkbox"/> cloxacillin	capsule, 500 mg, 1 g (as sodium salt); powder for oral solution, 125 mg (as sodium salt)/5 ml; powder for injection, 500 mg (as sodium salt) in vial
procaine benzylpenicillin	powder for injection, 1 g (= 1 million IU), 3 g (= 3 million IU) in vial

Complementary list

ceftriaxone	powder for injection, 250 mg, 1 g (as sodium salt) in vial
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6.2.2 Other antibacterials

azithromycin*	capsule, 250 mg, 500 mg; suspension, 200 mg/5 ml * only listed for single-dose treatment of genital C. trachomatis and of trachoma
chloramphenicol	capsule, 250 mg; oral suspension, 150 mg (as palmitate)/5 ml; powder for injection, 1 g (sodium succinate) in vial; oily suspension for injection, 0.5 g (as sodium succinate)/ml in 2-ml ampoule
<input type="checkbox"/> ciprofloxacin*	tablet, 250 mg (as hydrochloride) * final selection depends on indication for use
doxycycline*	capsule or tablet, 100 mg (hydrochloride) * final selection depends on indication for use
<input type="checkbox"/> erythromycin	capsule or tablet, 250 mg (as stearate or ethyl succinate); powder for oral suspension, 125 mg (as stearate or ethyl succinate); powder for injection, 500 mg (as lactobionate) in vial

<input type="checkbox"/> gentamicin*	injection, 10 mg, 40 mg (as sulfate)/ml in 2-ml vial * final selection depends on indication for use
nitrofurantoin	tablet, 100 mg
<input type="checkbox"/> metronidazole	tablet, 200-500 mg; injection, 500 mg in 100-ml vial; suppository, 500 mg, 1 g; oral suspension, 200 mg (as benzoate)/5 ml
spectinomycin	powder for injection, 2 g (as hydrochloride) in vial
sulfamethoxazole + trimethoprim	tablet, 100 mg + 20 mg, 400 mg + 80 mg; oral suspension, 200 mg + 40 mg/5 ml; injection, 80 mg + 16 mg/ml in 5-ml and 10-ml ampoules

Complementary list

clindamycin	capsule, 150 mg; injection, 150 mg (as phosphate)/ml
sulfadiazine	tablet, 500 mg; injection, 250 mg (sodium salt) in 4-ml ampoule

6.2.3 Antituberculosis medicines

ethambutol	tablet, 100-400 mg (hydrochloride)
isoniazid	tablet, 100-300 mg
isoniazid + ethambutol	tablet, 150 mg + 400mg
pyrazinamide	tablet, 400 mg
rifampicin	capsule or tablet, 150 mg, 300 mg
rifampicin + isoniazid	tablet, 60 mg + 30 mg, 150 mg + 75 mg, 300 mg + 150 mg, 60 mg + 60 mg (for intermittent use three times weekly), 150 mg + 150 mg (for intermittent use three times weekly)
rifampicin + isoniazid + pyrazinamide	tablet, 60 mg + 30 mg + 150 mg, 150 mg + 75 mg + 400 mg, 150 mg + 150 mg + 500 mg (for intermittent use three times weekly)
rifampicin + isoniazid + pyrazinamide + ethambutol	tablet, 150 mg + 75 mg + 400 mg + 275 mg

6.3 Antifungal medicines

clotrimazole	vaginal tablet, 100 mg, 500 mg; vaginal cream, 1 percent, 10 percent
<input type="checkbox"/> fluconazole	capsule, 50 mg; injection, 2 mg/ml in vial; oral suspension, 50 mg/5 ml
nystatin	tablet, 100 000 IU, 500 000 IU; lozenge, 100 000 IU; pessary, 100 000 IU

6.4 Antiviral medicines

6.4.1 Antiherpes medicines

<input type="checkbox"/> aciclovir	tablet, 200 mg; powder for injection, 250 mg (as sodium salt) in vial
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6.4.2 Antiretrovirals

Adequate resources and specialist oversight are prerequisites for the introduction of this class of drugs. Antiretroviral drugs do not cure HIV infection—they only temporarily suppress viral replication and improve symptoms. They have various adverse effects, and patients receiving these drugs require careful monitoring by adequately trained health professionals. For these reasons, continued rigorous promotion of measures to prevent new infections is essential, and the need for this has not been diminished in any way by the addition of antiretroviral drugs to the WHO model list. Sufficient resources and trained health professionals are prerequisites for the introduction of this class of drugs. Effective therapy requires commencement of three or four drugs simultaneously, and alternative regimens are necessary to meet specific requirements at start-up, to substitute for first-line regimens in the case of toxicity, or to replace failing regimens. In order to simplify treatment, facilitate storage and distribution, and improve patients' adherence to treatment plans, the Expert Committee recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations. These include modified dosage forms, nonrefrigerated formulations, and paediatric formulations with assured pharmaceutical quality and interchangeability with the single products as approved by the relevant drug regulatory authority.

6.4.2.1 Nucleoside reverse transcriptase inhibitors

abacavir (ABC)	tablet, 300 mg (as sulfate); oral solution, 100 mg (as sulfate)/5 ml
didanosine (ddI)	buffered chewable, dispersible tablet, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg; buffered powder for oral solution, 100 mg, 167 mg, 250 mg packets; unbuffered enteric coated capsule, 125 mg, 200 mg, 250 mg, 400 mg
lamivudine (3TC)	tablet, 150 mg; oral solution, 50 mg/5 ml

stavudine (d4T)	capsule, 15 mg, 20 mg, 30 mg, 40 mg; powder for oral solution, 5 mg/5 ml
zidovudine (ZDV or AZT)	tablet, 300 mg; capsule, 100 mg, 250 mg; oral solution or syrup, 50 mg/5 ml; solution for IV infusion injection, 10 mg/ml in 20-ml vial

6.4.2.2 Non nucleoside reverse transcriptase inhibitors

efavirenz (EFV or EFZ)	capsule, 50 mg, 100 mg, 200 mg; oral solution, 150 mg/5 ml
nevirapine (NVP)	tablet, 200 mg; oral suspension, 50 mg/5 ml

6.4.2.3 Protease inhibitors

Selection of two or three protease inhibitors from the WHO model list will need to be determined by each country after consideration of local treatment guidelines and experience, as well as the comparative costs of available products. Ritonavir is recommended for use in combination with indinavir, lopinavir, and saquinavir as a booster, and not as a drug in its own right.

indinavir (IDV)	capsule, 200 mg, 333 mg, 400 mg (as sulfate)
ritonavir	capsule, 100 mg; oral solution, 400 mg/5 ml
lopinavir + ritonavir (LPV/r)	capsule, 133.3 mg + 33.3 mg; oral solution, 400 mg + 100 mg/5 ml
nelfinavir (NFV)	tablet, 250 mg (as mesilate); oral powder, 50 mg/g
saquinavir (SQV)	capsule, 200 mg

6.5.3 Antimalarial medicines¹

6.5.3.1 For curative treatment

Medicines for the treatment of *P. falciparum* malaria cases should be used in combination.

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
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

6.5.3.2 For prophylaxis

chloroquine	tablet, 150 mg (as phosphate or sulfate); syrup, 50 mg (as phosphate or sulfate)/5 ml
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)

6.5.4 Antipneumocystosis and antitoxoplasmosis medicines

pyrimethamine	tablet, 25 mg
sulfamethoxazole + trimethoprim	injection, 80 mg + 16 mg/ml in 5-ml ampoule, 80 mg + 16 mg/ml in 10-ml ampoule

Complementary list

pentamidine	tablet, 200 mg, 300 mg
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6.5.5 Antitrypanosomal medicines

6.5.5.1 African trypanosomiasis

Complementary list

pentamidine	tablet, 200 mg, 300 mg
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10. Medicines affecting the blood

10.1 Antianaemia medicines

ferrous salt	tablet, equivalent to 60 mg iron; oral solution, equivalent to 25 mg iron (as sulfate)/ml
ferrous salt + folic acid	tablet, equivalent to 60 mg iron + 400 mcg folic acid (nutritional supplement for use during pregnancy)
folic acid	tablet, 1 mg, 5 mg

10.2 Medicines affecting coagulation

heparin sodium	injection, 1000 IU/ml, 5000 IU/ml, 20 000 IU/ml in 1-ml ampoule
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phytomenadione	injection, 10 mg/ml in 5-ml ampoule; tablet, 10 mg
protamine sulfate	injection, 10 mg/ml in 5-ml ampoule

11. Blood products and plasma substitutes

11.1 Plasma substitutes

<input type="checkbox"/> dextran 70*	injectable solution, 6 percent * polygeline, injectable solution, 3.5 percent is considered as equivalent
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12. Cardiovascular medicines

12.1 Antianginal medicines

glyceryl trinitrate	tablet (sublingual), 500 mcg
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12.2 Antiarrhythmic medicines

This subsection will be reviewed at the next meeting of the Expert Committee, when it is anticipated that applications for amiodarone and sotalol will be received.

digoxin	tablet, 62.5 mcg, 250 mcg; oral solution, 50 mcg/ml; injection, 250 mcg/ml in 2-ml ampoule
epinephrine (adrenaline)	injection, 1 mg (as hydrochloride)/ml in ampoule
lidocaine	injection, 20 mg (hydrochloride)/ml in 5-ml ampoule

12.3 Antihypertensive medicines

hydralazine*	tablet, 25 mg, 50 mg (hydrochloride); powder for injection, 20 mg (hydrochloride) in ampoule * hydralazine is listed for use in the acute management of severe pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of more evidence of efficacy and safety of other medicines
methyldopa*	tablet, 250 mg * methyldopa is listed for use in the management of pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of more evidence of efficacy and safety of other medicines

12.4 Medicines used in heart failure

This subsection will be reviewed at the next meeting of the Expert Committee.

digoxin	tablet, 62.5 mcg, 250 mcg; oral solution, 50 mcg/ml; injection, 250 mcg/ml in 2-ml ampoule
<input type="checkbox"/> furosemide	tablet, 40 mg; injection, 10 mg/ml in 2-ml ampoule

13. Dermatological medicines (topical)

13.1 Antifungal medicines

<input type="checkbox"/> miconazole	ointment or cream, 2 percent (nitrate)
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13.2 Anti-infective medicines

methylrosanilinium chloride (gentian violet)	aqueous solution, 0.5 percent; tincture, 0.5 percent
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15. Disinfectants and antiseptics

15.1 Antiseptics

<input type="checkbox"/> chlorhexidine	solution, 5 percent (digluconate) for dilution
<input type="checkbox"/> ethanol	solution, 70 percent (denatured)
<input type="checkbox"/> polyvidone iodine	solution, 10 percent

15.2 Disinfectants

<input type="checkbox"/> chlorine base compound	powder (0.1 percent available chlorine) for solution/calcium hypochlorite
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16. Diuretics

<input type="checkbox"/> furosemide	tablet, 40 mg; injection, 10 mg/ml in 2-ml ampoule
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17. Gastrointestinal medicines

17.5 Medicines used in diarrhoea

17.5.1 Oral rehydration

oral rehydration salts* (for glucose-electrolyte solution)	glucose:	75 mEq
	sodium:	75 mEq or mmol/l
	chloride:	65 mEq or mmol/l
	potassium:	20 mEq or mmol/l
	citrate:	10 mmol/l
	osmolarity:	245 mOsm/l
	glucose:	13.5 g/l
	sodium chloride:	2.6 g/l
	potassium chloride:	1.5 g/l
	trisodium citrate dihydrate+:	2.9 g/l
<p>+ trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/l. However, as the stability of this latter formulation is very poor under tropical conditions, it is only recommended when manufactured for immediate use</p> <p>* in cases of cholera, a higher concentration of sodium may be required</p>		

17.5.2 Medicines for diarrhoea in children

zinc sulfate*	<p>tablet or syrup in 10 mg per unit dosage forms</p> <p>* in cases of acute diarrhoea, zinc sulfate should be used as an adjunct to oral rehydration salts</p>
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18. Hormones, other endocrine medicines, and contraceptives

18.3 Contraceptives

This subsection will be reviewed at the next meeting of the Expert Committee.

18.3.1 Oral hormonal contraceptives

<input type="checkbox"/> ethinylestradiol + <input type="checkbox"/> levonorgestrel	tablet, 30 mcg + 150 mcg
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<input type="checkbox"/> ethinylestradiol + <input type="checkbox"/> norethisterone	tablet, 35 mcg + 1.0 mg
levonorgestrel	tablet, 30 mcg, 750 mcg (pack of two), 1.5 mg

18.3.2 Injectable hormonal contraceptives

medroxyprogesterone acetate	depot injection, 150 mg/ml in 1-ml vial
norethisterone enanthate	oily solution, 200 mg/ml in 1-ml ampoule

18.3.3 Intrauterine devices

copper-containing device

18.3.4 Barrier methods

condoms

diaphragms

18.5 Insulins and other antidiabetic agents

insulin injection (soluble)	injection, 40 IU/ml in 10ml vial, 100 IU/ml in 10-ml vial
intermediate-acting insulin	injection, 40 IU/ml in 10-ml vial, 100 IU/ml in 10-ml vial (as compound insulin zinc suspension or isophane insulin)

19. Immunologicals

19.2 Sera and immunoglobulins

All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (Revised 1992). WHO Expert Committee on Biological Standardization, 43rd report (WHO Technical Report Series, No. 840, 1994, Annex 2).

anti-D immunoglobulin (human)	injection, 250 mcg in single-dose vial
antitetanus immunoglobulin (human)	injection, 500 IU in vial

19.3 Vaccines

All vaccines should comply with the WHO Requirements for Biological Substances.

19.3.1 For universal immunization

BCG vaccine

diphtheria vaccine

hepatitis B vaccine

poliomyelitis vaccine

tetanus vaccine

20. Muscle relaxants (peripherally-acting) and cholinesterase inhibitors

suxamethonium	injection, 50 mg (chloride)/ml in 2-ml ampoule; powder for injection (chloride), in vial
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21. Ophthalmological preparations

This section will be reviewed at the next meeting of the Expert Committee.

21.1 Anti-infective agents

<input type="checkbox"/> tetracycline	eye ointment, 1 percent (hydrochloride)
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22. Oxytocics and antioxytocics

22.1 Oxytocics

<input type="checkbox"/> ergometrine	injection, 200 mcg (hydrogen maleate) in 1-ml ampoule
oxytocin	injection, 10 IU in 1-ml ampoule

Complementary list

misoprostol	vaginal tablet, 25 mcg
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mifepristone* - misoprostol*	tablet, 200 mg - tablet, 200 mcg * requires close medical supervision
Where permitted under national law and where culturally acceptable.	

22.2 Antioxytocs

nifedipine	immediate-release capsule, 10 mg
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26. Solutions correcting water, electrolyte, and acid-base disturbances

26.1 Oral

oral rehydration salts (for glucose-electrolyte solution)	see subsection 17.5.1
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26.2 Parenteral

glucose	injectable solution, 5 percent, 10 percent isotonic, 50 percent hypertonic
glucose with sodium chloride	injectable solution, 4 percent glucose, 0.18 percent sodium chloride (equivalent to Na ⁺ 30 mmol/l, Cl ⁻ 30 mmol/l)
sodium chloride	injectable solution, 0.9 percent isotonic (equivalent to Na ⁺ 154 mmol/l, Cl ⁻ 154 mmol/l)
sodium lactate, compound solution	injectable solution

26.3 Miscellaneous

water for injection	2-ml, 5-ml, 10-ml ampoules
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27. Vitamins and minerals

retinol	sugar-coated tablet, 10 000 IU (as palmitate) (5.5 mg); capsule, 200 000 IU (as palmitate) (110 mg); oral oily solution, 100 000 IU (as palmitate)/ml in multidose dispenser; water-miscible injection, 100 000 IU (as palmitate) (55 mg) in 2-ml ampoule
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This information is also available as a separate document.

World Health Organization, International Planned Parenthood Federation, John Snow, Inc., PATH, Population Services International, United Nations Population Fund, World Bank. *The Interagency List of Essential Medicines for Reproductive Health*. Geneva: WHO; 2006. Available at: <http://www.who.int/medicines/publications/essentialmedicines/WHO-PSM-PAR-2006.1.pdf> and <http://www.who.int/reproductive-health/new/index.html>. Accessed April 3, 2006.

Appendix 2:

Checklist of activities to ensure that reproductive health medicines are included on national essential medicines lists

1. Contact the essential medicines committee and inquire about the list revision process.
 - Identify the national essential medicines committee and contact persons who can provide information on the list revision process.
 - Obtain the national list of essential medicines and standard treatment guidelines (STGs).
 - Determine the application process and requirements for the addition of new medicines to the national essential medicines list (EML).
 - Verify timing of the next EML revision.

2. Identify reproductive health experts who will provide input into the national EML process.
 - Contact reproductive health stakeholders and develop a reproductive health working group (RHWG) to add reproductive health medicines to the EML.
 - Identify three working groups, one for each of the following reproductive health areas: maternal/neonatal health, contraception, and sexually transmitted infections (STI)/reproductive tract infections (RTI) and HIV/AIDS treatment.
 - Inform the EML committee about the reproductive health review by the RHWG. Propose to nominate members of the EML committee to integrate into the RHWG and participate in the review.

- Prepare a plan of action for the review process with the RHWG, including meeting planning and collection of information. Be cognizant of the deadline for submitting proposals to the EML committee before the next revision.
3. Identify which medicines need to be added to the EML.
- Explain the EML review process to the RHWG.
 - Review reproductive health medicines included on the EML and compare with the *Interagency List of Essential Medicines for Reproductive Health*.
 - Define the gaps/discrepancies according to STGs, local data, and context, and define a list of reproductive health medicines to be added to the national EML. Indicate levels of care recommended for each of the medicines submitted.
 - Collect and organise data, evidence, and information requested for each new submission to the EML committee.
 - Use the revision form proposed by the EML committee to submit your changes, additions, or deletions. Include all information requested for the review.
 - Submit proposals for revision to the EML committee by the deadline set up by the committee.
4. Implement the new EML.

By the ministry of health (MOH)

- Launch the updated EML and make it widely available.
- Make the revised list of essential medicines and clinical guidelines available in all health care facilities and to all health care providers in printed and electronic versions, if appropriate.
- Verify with procurement services in both public and private sectors and with regulatory authorities that medicines added to the EML are available in the country.

By the reproductive health working group

- Propose issuing an informational leaflet, newsletter, or drug bulletin that summarizes the changes in the area of reproductive health in collaboration with the EML committee and the MOH.
- Inform the general public by publishing articles in newspapers (press releases).
- Advocate for the review of the STGs (if needed) according to the updated national EML.
- If essential medicines are exempt from taxes in the country, verify that the new medicines added are also tax exempt. If not, advocate for tax exemption for all medicines and commodities on the EML.
- Assess and monitor availability and use of the reproductive health essential medicines at all levels of care in the country in collaboration with the MOH and the EML committee.

Appendix 3

Information to be included with an application for inclusion, change, or deletion of a medicine on the WHO Model List of Essential Medicines

1. Summary statement of the proposal for inclusion, change, or deletion.
2. Name of the focal point within the World Health Organization (WHO) who is submitting or supporting the application.
3. Name of the organization(s) that was consulted and/or is supporting the application.
4. International nonproprietary name (INN) or generic name of the medicine.
5. Formulation proposed for inclusion; including adult and paediatric (if appropriate).
6. International availability - sources, if possible manufacturers.
7. Whether listing is requested as an individual medicine or as an example of a therapeutic group.
8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population).
9. Treatment details (dosage regimen and duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills).
10. Summary of 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 (appraisal of quality, outcome measures, summary of results).
 - Summary of available estimates of comparative effectiveness.

11. Summary of comparative evidence on 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.
12. Summary of available data on comparative cost* and cost-effectiveness within the pharmacological class or therapeutic group:
 - Range of costs of the proposed medicine.
 - 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).
13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well).
14. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia).
15. Proposed (new/adapted) text for the WHO Model Formulary.

* Information on cost and cost-effectiveness should preferably refer to average generic world market prices as listed in the *International Drug Price Indicator Guide*, an essential medicines pricing service provided by WHO and maintained by Management Sciences for Health. If this information is not available, other international sources, such as the WHO, United Nations Children's Fund, and Médecins sans Frontières price information service, can be used. All cost analyses should specify the source of the price information.

Appendix 4

Policy briefs for 16 essential reproductive health medicines

In collaboration with partners, we have developed this set of briefing papers on key medicines included on the *Interagency List of Essential Medicines for Reproductive Health*.

The purpose of these briefs is to provide a short rationale and the evidence base for including key reproductive health medicines in national policies, on national essential medicines lists, and in programmatic guidelines, procurement programmes, and budgets.

The audiences for these briefs are not only medical officers and pharmacists. They are also the career civil servant, the programme manager, finance officer, and other decision-makers who have to either advocate for and/or provide the evidence to promote the use of these essential medicines.

The briefs are technically accurate but remain drafts because we are seeking your feedback. We would like to know:

- a) If you have found these briefs useful for the purpose described above and in what way.
- b) What did you find most useful about these briefs?
- c) What did you find least useful?
- d) What additional information, if any, would be useful in initiating the process of including reproductive health medicines on national essential medicines lists?

Your feedback is important to us, as we want to develop materials that will help these essential medicines become part of policies and practice settings.

Please email your response to the Department of Medicines Policy and Standards, World Health Organization (WHO) in Geneva, Switzerland, at stimpsonp@who.int.

Thank you for your assistance.

Azithromycin: treatment of genital chlamydia

Background

Sexually transmitted infections (STIs) remain a public health problem of major significance in most parts of the world. Effective management of STIs is one of the cornerstones of STI control, as it prevents the development of complications and sequelae and decreases the spread of the infections in the community. Medicines selected for treating STIs should meet the following criteria: high efficacy (at least 95%), low cost, acceptable toxicity and tolerance, organism resistance unlikely to develop or likely to be delayed, single dose, oral administration, not contraindicated for pregnant or lactating women.

Chlamydia trachomatis causes nongonococcal urethritis in men. It may also cause epididymitis and chronic prostatitis. In women, infection is associated with cervicitis, salpingitis, endometritis, and long-term sequelae of tubal infertility and ectopic pregnancy. Infants born to mothers with cervical infection can develop purulent conjunctivitis (chlamydial ophthalmia) or pneumonia.

Evidence summary

Azithromycin, a macrolide antibiotic, has antimicrobial activity against a wide variety of microbes. Azithromycin is more effective than erythromycin against some gram-negative organisms, such as *Chlamydia trachomatis*. Its effectiveness against *Chlamydia trachomatis* genital infection with a single dose has been demonstrated.¹ Studies show that azithromycin is safe for use in both adolescents and in pregnancy, conditions for which tetracyclines, the main alternatives, are contraindicated.² The safety of using azithromycin in these groups in the population, combined with the advantages offered by a single-dose curative regimen, support the selection of azithromycin for the treatment of this particular infection.^{2,3} Furthermore, single-dose oral azithromycin is as effective as topical antibiotic ointments in treating trachoma.

Indications and dosage

- Azithromycin, capsule, 250 mg, 500 mg; oral suspension, 200 mg/5 ml

Treatment of uncomplicated genital chlamydial infection; trachoma.

Uncomplicated genital chlamydial infection:

By mouth, adult over 45 kg, 1 g as a single dose; under 45 kg, 20 mg/kg as a single dose.

Trachoma:

By mouth, one single dose of 20 mg/kg, to a maximum of 1 g.

Remarks

In view of its efficacy, safety, and ease of use relative to the principal alternatives, azithromycin was added to the 13th WHO Model List of Essential Medicines (2003) for the single-dose treatment of genital *Chlamydia trachomatis* infection and of trachoma only. The use of azithromycin does not require special medical facilities or specialist medical care.

Azithromycin is not recommended for the treatment of *Neisseria gonorrhoeae* because macrolide resistance emerges rapidly when it is used for this infection. When gonococcal infection is suspected in chlamydial infection patients, azithromycin should be combined with an effective antibiotic for gonorrhoea.

International drug price indicator 2005 (Supplier price in US\$)⁴

Azithromycin, capsule, 250 mg, median price/capsule: 0.242

Azithromycin, oral suspension, 200 mg/5 ml, median price/ml: 0.050

References

1. World Health Organization (WHO). *WHO Model Formulary, Edition 2004*. Geneva: WHO; 2004. Available at: <http://mednet3.who.int/EMLib/wmf.aspx>.
2. WHO. *Guidelines for the Management of Sexually Transmitted Infections*. Geneva: WHO; 2003. Available at: www.who.int/reproductive-health/publications/rhr_01_10_mngt_stis/index.html.
3. WHO. *The Selection and Use of Essential Medicines. Report of the WHO Expert Committee, 2003 (including the 13th Model List of Essential Medicines)*. Geneva: WHO; 2004. WHO Technical Report Series, No. 920. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_920.pdf.
4. Management Sciences for Health and WHO. *International Drug Price Indicator Guide*. Cambridge, MA: Management Sciences for Health; 2005. Available at: http://erc.msh.org/dmpguide/pdf/DrugPriceGuide_2005_En.pdf.

Additional resources

1. Antibacterial drugs. Macrolides. In: *British National Formulary (BNF)*. 50th ed. London: British Medical Association (BMA) and Royal Pharmaceutical Society of Great Britain (RPSGB); 2005:289–290.
2. WHO. Medicine uses: azithromycin page. WHO Essential Medicines Library (EMLib) website. Available at: <http://mednet3.who.int/EMLib/DiseaseTreatments/MedicineDetails.aspx?MedIDName=423@azithromycin>. Accessed February 6, 2006.

Cefixime: treatment of gonorrhoea

Background

Gonococcal infections occur worldwide and are the most common cause of urethral discharge in men; they are predominantly asymptomatic in adult women and adolescent girls. These infections are responsible for complications such as pelvic inflammatory disease, with long-term consequences such as infertility, ectopic pregnancy, and chronic pelvic pain. In pregnancy, they may also be vertically transmitted to the newborn, causing neonatal conjunctivitis, which can cause blindness if not treated early.

Cefixime is an orally administered, broad-spectrum, third-generation cephalosporin with a longer duration of action than the other oral cephalosporins.¹ It is active against gram-positive and gram-negative aerobic bacteria. Besides its use in treating urinary tract infection and respiratory tract infection, cefixime has been shown to be effective in the treatment of gonorrhoea. It has the advantage over other third-generation cephalosporins in that it can be administered orally. Cefixime has been included as one of the first-line drugs in many guidelines for the treatment of uncomplicated gonococcal anogenital infection.²

Evidence summary

Oral administration of cefixime in doses of 400 mg or 800 mg as single-dose regimen has been compared with 250 mg of ceftriaxone intramuscularly as single dose in open label randomized clinical trials in patients with uncomplicated gonorrhoea. The overall cure rate was 96% and 98% with 400 mg and 800 mg of cefixime respectively, whereas the cure rate with ceftriaxone was reported at between 98% and 100%.^{3,4} The difference was not clinically significant.

Cefixime is well tolerated; the most common adverse drug reactions are related to the gastrointestinal system. These include diarrhoea, flatulence, nausea and epigastric pain. All of these are of mild to moderate intensity. A recent study suggests that it is safe for use during pregnancy.²

Indications and dosage

- Cefixime, capsule, 400 mg

Treatment of uncomplicated gonococcal anogenital infection, as a single dose.

Remarks

Cefixime 400 mg as a single dose was added to the 14th WHO Model List of Essential Medicines (2005) as one of the first-line medicines for the treatment of uncomplicated gonococcal anogenital infection.

Due to its efficacy, safety, and ease of administration, it is recommended that cefixime be included on national lists of essential medicines for the treatment of uncomplicated anogenital gonorrhoea. The use of cefixime does not require special medical facilities or specialist medical care.

International drug price indicator 2005 (Supplier price in US\$)⁵

Cefixime, capsule, 400 mg, median price/capsule: 0.853

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Clotrimazole: treatment of vulvovaginal candidiasis

Background

Two international data reviews established the high prevalence of vulvovaginal candidiasis worldwide. An estimated 75% of women will have at least one episode of candidiasis during their lifetime, and recurrence is common. By the time women reach their mid-20s, half of them will have had one episode of vulvovaginal candidiasis, and up to 25% of these women will suffer recurrent vulvovaginal candidiasis.¹ WHO recommends treating vulvovaginal candidiasis with topical imidazole antifungals, including clotrimazole.²

Evidence summary

There is good clinical evidence to support the efficacy and safety of topical and intravaginal clotrimazole in the treatment of vulvovaginal candidiasis. A systematic review based on five trials indicated that imidazoles were more effective than nystatin in treating vaginal candidiasis in pregnancy.³ Reported adverse events have been rare and not serious. Topical administration of clotrimazole is recommended in the WHO guidelines for the management of sexually transmitted infections.²

Indications and dosage

- Clotrimazole, vaginal tablet, 100 mg, 500 mg; vaginal cream, 1%, 10%

Treatment of acute or recurrent vulvovaginal candidiasis.

For acute vaginitis:

Vaginal cream, 1%, apply topically over the affected area 2 to 3 times daily for 7 days.

Vaginal cream, 10%, insert 5 grams intravaginally at bedtime as a single dose.

Vaginal tablet, 100 mg, use 1 intravaginal tablet at bedtime for 7 nights.

Vaginal tablet, 500 mg, use a single application of 1 tablet at bedtime.

For recurrent vulvovaginitis:

Vaginal tablet, 100 mg, use 2 intravaginal tablets twice weekly at bedtime.

Vaginal tablet, 500 mg, use 1 intravaginal tablet weekly for up to 6 months.

In pregnancy:

Vaginal tablet, 100 mg, use 1 tablet intravaginally at bedtime for 7 nights.

Remarks

In view of its efficacy, safety, and ease of use relative to the principal alternatives, clotrimazole was added to the 14th WHO Model List of Essential Medicines (2005) for the treatment of vulvovaginal candidiasis.

Clotrimazole is widely available without prescription in most countries. The use of clotrimazole does not require special medical facilities or specialist medical care.

International drug price indicator 2005 (Supplier price in US\$)⁴

Clotrimazole, cream, 1%, median price/gram: 0.0204

Clotrimazole, vaginal tablet, 100 mg, median price/tablet: 0.0605

Clotrimazole, vaginal tablet, 500 mg, median price/tablet: 0.6626

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Condoms: barrier contraceptive devices

Background

There is compelling evidence that the male latex condom, when used consistently and correctly, protects against unwanted pregnancy and the transmission of HIV, the virus that causes AIDS. Condoms also protect against several other STIs, although the level of protection has not been quantified for each specific STI.¹

Evidence summary

There are two systematic reviews of condom use and effectiveness, published in 2000 and 2002. The 2000 review concluded that male condoms, when used correctly and consistently, are effective for preventing unwanted pregnancy, HIV infection in women and men, and gonorrhoea in men.² The 2002 review concluded that condoms, when used consistently, substantially reduced HIV infection but did not totally eliminate the risk of infection. Using condoms consistently reduces sexual transmission of HIV infection.³

The female condom was developed in the 1990s and provides a barrier method for women to use, particularly in situations where they are unable to insist on male condom use by their partners. The product was marketed worldwide and introduced into national STI and HIV prevention and family planning programmes in the late 1990s. The female condom has been shown to be effective in pregnancy prevention and acceptable to users.^{4,5}

Indications and dosage

- Condoms

Barrier method of contraception and prevention of STIs, including HIV.

Remarks

It must be noted that oil-based products, including baby oil, massage oil, lipstick, petroleum jelly, and sun-tan oil, can damage latex condoms and render them less effective as barrier methods of contraception and protection against the transmission of STIs.

It is highly recommended that the female condom be included in all pregnancy and STI/HIV prevention programmes. There is now the possibility of cheaper products coming on the market, including a synthetic latex female condom. WHO, the United Nations Population Fund (UNFPA), and the joint United Nations Programme on HIV/AIDS work in collaboration with the International Standards Organization to establish the manufacturing standards and guidelines on quality assurance measures and procurement procedures to ensure that a quality product is manufactured, procured, and distributed.⁶

Condoms as barrier contraceptive devices have been on the *WHO Model List of Essential Medicines* since 1988.

International drug price indicator 2005 (Supplier price in US\$)⁷

Condom, male, median price/condom: 0.0288

Condom, female, median price/condom: 0.8569

References

1. World Health Organization (WHO) Department of Reproductive Health and Research. Male condoms page. WHO Department of Reproductive Health and Research website. Available at: www.who.int/reproductive-health/stis/male_condom.html. Accessed February 8, 2006.
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Ethinylestradiol + levonorgestrel: oral hormonal contraceptives

Background

Hormonal contraception is one of the most effective methods of reversible fertility control. Oral hormonal contraceptives containing an oestrogen and a progestogen, “combined oral contraceptives,” are the most effective preparation for general use and are the most widely used hormonal contraceptives. They produce a contraceptive effect mainly by suppressing the hypothalamic-pituitary system, resulting in prevention of ovulation, and by thickening the cervical mucus, which prevents fertilization of the ovum.

Evidence summary

There are several systematic reviews of the effects of oral contraceptives.^{1,2} The use of oral contraceptive combinations containing the progestogens levonorgestrel or norethisterone are associated with a slightly lower risk of venous thromboembolism compared with oral contraceptives containing the progestogens desogestrel or gestodene.

The ethinylestradiol + levonorgestrel tablet, 30 mcg + 150 mcg, is an example of a low-dose combined oral contraceptive with less than 35 mcg of ethinylestradiol.

Potential noncontraceptive benefits of combined oral contraceptives include decreases in menstrual blood loss, menstrual cramps, ovulation pain, symptoms of polycystic ovarian syndrome, and symptoms of endometriosis. Long-term use is associated with reduced risk of endometrial and ovarian cancer and symptomatic pelvic inflammatory disease. They also may help protect against ovarian cysts and low blood iron stores.

Indications and dosage

- Ethinylestradiol + levonorgestrel, tablet, 30 mcg + 150 mcg

Contraception, 1 tablet daily for 21 days; subsequent courses repeated after 7-day pill-free interval.

Remarks

The WHO guidelines, *Medical Eligibility Criteria for Contraceptive Use*, were developed to help health workers screen women appropriately for use of low-dose combined oral contraceptives. The *Medical Eligibility Criteria for Contraceptive Use* is one of WHO's two evidence-based guidelines on contraceptive use.³

If a pill is not taken on time, it should be taken as soon as possible, and the next one taken at the usual time. If administration is delayed by more than 12 hours, the woman should resume taking the pill at the usual time as soon as possible. Furthermore, because contraceptive efficacy is reduced, an additional method of contraception, such as the condom, is required for 7 days.⁴

The ethinylestradiol + levonorgestrel tablet, 30 mcg + 150 mcg, has been on the *WHO Model List of Essential Medicines* as a core medicine since 1979. Ethinylestradiol with levonorgestrel is representative of combined oral contraceptive preparations. Various combinations can serve as alternatives. The use of the ethinylestradiol + levonorgestrel tablet does not require special medical facilities or specialist medical care.

International drug price indicator guide 2005 (Supplier price in US\$)⁵

Ethinylestradiol + levonorgestrel, tablet, 30 mcg + 150 mcg, median price/cycle: 0.3502

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5. Management Sciences for Health and WHO. *International Drug Price Indicator Guide*. Cambridge, MA: Management Sciences for Health; 2005. Available at: http://erc.msh.org/dmpguide/pdf/DrugPriceGuide_2005_En.pdf.

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Ethinylestradiol + norethisterone: oral hormonal contraceptives

Background

Hormonal contraception is one of the most effective methods of reversible fertility control. Oral hormonal contraceptives containing an oestrogen and a progestogen, “combined oral contraceptives,” are the most effective preparation for general use and are the most widely used hormonal contraceptives. They produce a contraceptive effect mainly by suppressing the hypothalamic-pituitary system, resulting in prevention of ovulation, and by thickening the cervical mucous, which prevents fertilization of the ovum.

Evidence summary

There are several systematic reviews of the effects of oral hormonal contraceptives.^{1,2} The use of oral contraceptive combinations containing the progestogens levonorgestrel or norethisterone are associated with a slightly lower risk of venous thromboembolism compared with oral contraceptives containing the progestogens desogestrel or gestodene.

The ethinylestradiol + norethisterone tablet, 30 mcg + 1 mg, is an example of a low-dose combined oral contraceptive with less than 35 mcg of ethinylestradiol.

Potential noncontraceptive benefits of combined oral contraceptives include decreases in menstrual blood loss, menstrual cramps, ovulation pain, symptoms of polycystic ovarian syndrome, and symptoms of endometriosis. Long-term use is associated with reduced risk of endometrial and ovarian cancer and symptomatic pelvic inflammatory disease. They also may help protect against ovarian cysts and low blood iron stores.

Indications and dosage

- Ethinylestradiol + norethisterone, tablet, 30 mcg + 1 mg

Contraception, 1 tablet daily for 21 days; subsequent courses repeated after 7-day pill-free interval.

Remarks

The WHO guidelines, *Medical Eligibility Criteria for Contraceptive Use*, were developed to help health workers screen women appropriately for use of low-dose combined oral contraceptives. The *Medical Eligibility Criteria for Contraceptive Use* is one of WHO's two evidence-based guidelines on contraceptive use.³

If a pill is not taken on time, it should be taken as soon as possible, and the next one taken at the usual time. If administration is delayed by more than 12 hours, the woman should resume taking the pill at the usual time as soon as possible. Furthermore, because contraceptive efficacy is reduced, an additional method of contraception, such as the condom, is required for 7 days.⁴

The ethinylestradiol + norethisterone tablet, 30 mcg + 1 mg, has been on the *WHO Model List of Essential Medicines* as a core medicine since 1979. Ethinylestradiol with norethisterone is representative of combined oral contraceptive preparations. Various combinations can serve as alternatives. The use of the ethinylestradiol + norethisterone tablet does not require special medical facilities or specialist medical care.

International drug price indicator 2005 (Supplier price in US\$)

Not available.

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Copper-containing intrauterine contraceptive devices

Background

With nearly 160 million users, or 15% of the world's women of reproductive age, the intrauterine contraceptive device (IUD) is the second most popular contraceptive method worldwide, after sterilization (18% of the women). The IUD is one of the safest, best tolerated methods of contraception available.¹ Copper-containing IUDs consist of a plastic carrier wound with copper wire or fitted with copper bands; some also have a central core of silver to prevent fragmentation of the copper. Depending on the device, copper-containing IUDs are approved for use for 3 to 10 years. Fertility declines with age; and therefore, a copper intrauterine device fitted in a woman over 40 years of age may remain in the uterus until menopause.

Evidence summary

Intrauterine devices are a highly effective and rapidly reversible method of contraception (0.6-3.0% failure rate) but may produce undesirable local side effects.¹ The IUD is appropriate for women who expect to use it for continuous long-term contraception. It can be used by women of any age, whether or not they have had children. However, women with current pelvic inflammatory disease or those at very high individual risk of contracting STIs should not use an IUD. It can be used by women with HIV infection, including those with AIDS, provided they are clinically well on antiretroviral therapy. The IUD does not interfere with sexual intercourse or with any type of medication, and it is widely available throughout the world.¹

An IUD used as emergency contraception is also highly effective for preventing pregnancy. A copper-containing IUD can be inserted within 5 days of unprotected intercourse as an emergency contraceptive and can remain in place for ongoing contraception.²

Indications and dosage

- Copper-containing intrauterine device

Routine contraception and emergency contraception.

Remarks

For routine contraception, the device can be inserted during the first 12 days after the start of menstruation; and for emergency contraception, the device can be inserted at any time in the menstrual cycle within 5 days of unprotected intercourse.² There is an increased risk of infection for 20 days after insertion; this may be related to an existing lower genital tract infection or to nonsterile insertion. If sustained pelvic or lower abdominal pain occurs during the 20 days following insertion of the device, the woman should be treated as having acute pelvic inflammatory disease. The IUD can be kept in place during treatment.

Prophylactic antibiotics are generally not recommended for IUD insertion. However, in settings of both high prevalence of STIs and limited STI screening, such prophylaxis may be considered.¹

If the woman becomes pregnant, the device should be removed in the first trimester and the possibility of ectopic pregnancy considered; if the threads of the intrauterine device are already missing on presentation, the pregnancy is at risk of second trimester abortion, haemorrhage, preterm delivery, and infection.

The timing and technique of inserting an IUD are critical for its subsequent performance and require that it is done by a qualified health provider with proper training and experience.

International drug price indicator 2005 (Supplier price in US\$)³

Copper-containing intrauterine device, median price/device: 1.8264

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Levonorgestrel: oral hormonal contraceptive

Background

Hormonal contraception is one of the most effective methods of reversible fertility control. A progesterone-only contraceptive may offer a suitable alternative when oestrogens are contraindicated.

Evidence summary

Levonorgestrel is an example of an oral progesterone-only contraceptive that is effective and safe.¹ It may be an alternative when combined oral contraceptives containing oestrogen are contraindicated, but it has a higher failure rate than combined contraceptives. It is suitable for older women, for heavy smokers, and for those with hypertension, valvular heart disease, diabetes mellitus, and migraines. Menstrual irregularities are more common with progestogen-only contraceptives than with combined oral contraceptives but tend to resolve on long-term treatment.

Indications and dosage

- Levonorgestrel, tablet, 30 mcg

Progestogen-only contraception, 1 tablet daily at same time each day, starting on the first day of the menstrual cycle.

Remarks

If administration is delayed for 3 hours or more, it should be considered as a “missed pill.” The following advice is recommended by family planning organizations: If one pill is missed, the pill has to be taken as soon as possible and the next one taken at the usual time. If administration is delayed for more than 3 hours, the woman is not protected.¹

Levonorgestrel was included on the 14th WHO Model List of Essential Medicines (2005) on the core list.

International drug price indicator 2005 (Supplier price in US\$)²

Levonorgestrel, tablet, 30mcg, median price/cycle: 0.496

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Levonorgestrel: emergency contraception

Background

Emergency contraception (EC) refers to methods for contraceptive emergencies that women can use within the first five days after unprotected intercourse to prevent unwanted pregnancy. Any woman of reproductive age may need EC at some point to avoid an unwanted pregnancy; however, emergency contraceptive methods are not suitable for regular use.¹ EC is meant to be used in situations such as: when no contraception has been used, when there is a contraceptive failure or incorrect use; or in the case of sexual assault, when the woman was not protected by an effective contraceptive method.

Evidence summary

Emergency contraceptive pills work by interrupting a woman's reproductive cycle by delaying or inhibiting ovulation or blocking fertilization. Levonorgestrel emergency contraceptive pills have shown to prevent ovulation, and they do not have detectable effects on the endometrium or progesterone levels when given after ovulation. They are not effective once the process of implantation has begun and will not cause abortion.¹

Based on the reports from four studies including almost 5,000 women, the levonorgestrel regimen used within five days after unprotected intercourse reduces a woman's chance of pregnancy by 60% to 90%.¹ The levonorgestrel 1.5 mg tablet (two split doses or a single dose) offers high efficacy with an acceptable side effect profile.² Single dose simplifies the use of levonorgestrel for emergency contraception without an increase in side effects.² The regimen is more effective the sooner after intercourse it is taken.

Emergency contraceptive pills are for emergency use only and not appropriate for regular use as an ongoing contraceptive method because of the higher possibility of failure compared to modern contraceptives. There is no evidence of harmful effects to the foetus if pregnancy should occur. Possible side effects include nausea, vomiting, and light vaginal bleeding in the first week after treatment.

Indications and dosage

- Tablet, 750 mcg (2-tablet pack)
- Tablet, 1.5 mg (1-tablet pack)

For emergency contraception, adult (female), levonorgestrel, 1.5 mg as a single dose (taken within 120 hours [5 days] of unprotected intercourse); alternatively, levonorgestrel, 750 mcg (taken within 72 hours of unprotected intercourse), followed by a second dose of 750 mcg 12 hours later.³

Remarks

It should be explained to the woman that her next period may be early or late. She can start some methods, such as oral contraceptive pills, monthly injectables, or barrier methods immediately. If she wants to use a longer-acting method, she should use a back-up method until her period begins, and then return to start the method.

The use of levonorgestrel for EC does not require special medical facilities or specialist medical care. The levonorgestrel 1.5-mg tablet (pack of one) was added to the *13th WHO Model List of Essential Medicines* (2003) following the *13th WHO Expert Committee for the Selection and Use of Essential Medicines* recommendation, as the single dose simplifies the use of levonorgestrel for EC without an increase in side effects.⁴ Levonorgestrel, 750 mcg (pack of two), was already on the *12th WHO Model List of Essential Medicines* (2002).

International drug price indicator 2005 (Supplier price in US\$)⁵

Levonorgestrel, tablet, 750mcg, median price/tablet: 0.175

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Magnesium sulfate: prevention of seizures in eclampsia and preeclampsia

Background

In pregnancy, if hypertension occurs before 20 weeks gestation, it is classified as chronic hypertension. Hypertension occurring after 20 weeks gestation is called pregnancy-induced hypertension, and the presence of proteinuria changes the diagnosis to preeclampsia. Preeclampsia is estimated to complicate 2% to 8% of pregnancies and is a major cause of morbidity and mortality for both the woman and her child.¹

Eclampsia is a condition peculiar to pregnancy or a newly delivered woman, characterized by seizures that may be followed by more or less prolonged coma. The woman usually has hypertension and proteinuria. The seizures may occur in the antepartum, intrapartum, or postpartum periods. Preeclampsia can progress to eclampsia, but eclampsia can also occur in the absence of previous symptoms.

Evidence summary

Magnesium sulfate is used in women with preeclampsia who are at risk of developing eclampsia.² According to the published results of the Magnesium Sulfate for Prevention of Eclampsia (MAGPIE) trial, covering 10,141 women in 33 countries, treatment with magnesium sulfate halves the risk of eclampsia and probably reduces the risk of maternal death.¹ In 2003, a systematic review showed that magnesium sulfate is substantially more effective than diazepam for eclampsia.³ Magnesium sulfate is therefore the medicine of choice in eclampsia for the prevention of recurrent seizures.

Indications and dosage

- Magnesium sulfate, injection (solution for injection), 500 mg/ml, 2-ml ampoule, 10-ml ampoule

Prevention of recurrent seizures in eclampsia; prevention of seizures in preeclampsia.

Prevention of recurrent seizures in eclampsia:

Intravenous injection, adult and adolescent, initially 4 g over 5–15 minutes followed either by intravenous infusion, 1 g/hour for at least 24 hours after the last seizure; or by deep intramuscular injection, 5 g into each buttock then 5 g every 4 hours into alternate buttocks for at least 24 hours after the last seizure or delivery, whichever occurs later; recurrence of seizures may require additional intravenous injections of 2 g.

Prevention of seizures in preeclampsia:

Intravenous infusion, adult and adolescent, initially 4 g over 5–15 minutes followed either by intravenous infusion, 1 g/hour for 24 hours; or by deep intramuscular injection, 5 g into each buttock then 5 g every 4 hours into alternate buttocks for 24 hours; if seizure occurs, additional intravenous injections of 2 g.²

Remarks

For intravenous injection, the concentration of magnesium sulfate should not exceed 20% (dilute 1 part of magnesium sulfate injection 50% with at least 1.5 parts of water for injection); for intramuscular injection, mix magnesium sulfate injection 50% with 1 ml lidocaine injection 2%. The use of magnesium sulfate require monitoring of blood pressure, respiratory rate, and urinary output, as well as monitoring for clinical signs of overdosage (loss of patellar reflexes, weakness, nausea, double vision, and slurred speech—calcium gluconate injection is used for the management of magnesium toxicity).

Magnesium sulfate was added to the *WHO Model List of Essential Medicines* in 1997. In 2003, the WHO Expert Committee urged that magnesium sulfate be made more generally available in view of the compelling evidence demonstrating its benefit in the treatment of eclampsia and severe preeclampsia.¹

It was listed in the 14th *WHO Model List of Essential Medicines* (2005) in the core list under anticonvulsivants/antiepileptics for use in eclampsia and severe preeclampsia. It is not listed for other convulsant disorders.

International drug price indicator 2005 (Supplier price in US\$)⁴

Magnesium sulfate, injection, 500 mg/ml, median price/ml: 0.0611

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Medroxyprogesterone acetate: injectable hormonal contraceptive

Background

Hormonal contraception is one of the most effective methods of reversible fertility control. A progesterone-only contraceptive may be a suitable alternative when oestrogens are contraindicated. Medroxyprogesterone acetate is a long-acting progestogen given by intramuscular injection. There is no alternative three-month injectable contraceptive.¹ Medroxyprogesterone acetate is playing an important role in many national family planning and health programmes. For instance, UNFPA provided 12 million doses of injectables in 1992 and about 20 million in 1994.¹ It is used increasingly with the number of users estimated in 2004 to be approximately 10 million worldwide.¹

Evidence summary

Medroxyprogesterone acetate depot injection (DMPA) is the only three-month injectable contraceptive currently available and widely used in developing and developed countries, and the efficacy of this contraceptive has been reviewed and is well documented. It is as effective as the combined oral hormonal contraceptives.² Delayed return of fertility and irregular cycles may occur after discontinuation of treatment, but there is no evidence of permanent infertility.²

The risk of unintended pregnancy during the first year of usage was 3% among users and 0.3% among perfect users.¹ The accumulated evidence for its safety and efficacy was reviewed by an expert group on Medical Eligibility Criteria for Contraceptive Use.³

Indications and dosage

- Medroxyprogesterone acetate, depot injection, 150 mg/ml in 1-ml vial

Parenteral progestogen-only contraception.

Contraception (short term) by deep intramuscular injection, adult (female), 150 mg within first 5 days of cycle or within first 5 days after parturition (delay until 6 weeks after parturition if breastfeeding).

Contraception (long term) by deep intramuscular injection, adult (female), as for short term, repeated every 3 months.

Remarks

Women must receive full counselling before treatment concerning menstrual irregularities and the potential for a delay in return to full fertility.

The use of DMPA does not require special medical facilities or specialist medical care. Like any other injectable medicine, injection device security and safe injection practices should be observed, including the use of sterile, single-use syringes.

DMPA was moved from the complementary to the core list on the 14th WHO *Model List of Essential Medicines* (2005).

International drug price indicator 2005 (Supplier price in US\$)⁴

Medroxyprogesterone acetate, depot injection, 150 mg/ml in 1-ml vial, median price/ml: 1.0884

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Methyldopa: treatment of severe pregnancy-induced hypertension

Background

Hypertension in pregnancy is defined as a sustained diastolic blood pressure of 90 mmHg or more on two consecutive readings taken four hours or more apart.¹ Drug therapy for chronic hypertension during pregnancy remains controversial. Methyldopa, a centrally acting antihypertensive, is listed in the 14th WHO Model List of Essential Medicines (2005) for use in the management of pregnancy-induced hypertension only.

Evidence summary

There are at least two reviews of clinical trials of management of hypertension in pregnancy. In severe hypertension in pregnancy, there is currently no clear evidence favouring the use of one drug compared with another. Some drugs, such as the angiotensin-converting enzyme (ACE) inhibitors, are contraindicated in pregnancy since they may damage foetal and neonatal blood pressure control and renal function. Generally, until better evidence is available, the choice of antihypertensive should depend on the experience and familiarity of an individual clinician with a particular medicine and on what is known about adverse maternal and foetal side effects.²

Methyldopa is widely available at an affordable cost in many low-income countries.³ Therefore, the WHO Expert Committee recommended the retention of methyldopa on the WHO Model List of Essential Medicines for use in severe hypertension during pregnancy. Its use in the treatment of essential hypertension is not recommended in view of the availability of more evidence of efficacy and safety of other medicines.

Indications and dosage

- Methyldopa, tablet, 250 mg

Severe pregnancy-induced hypertension, by mouth, adult, initially 250 mg 2 to 3 times daily; if necessary, gradually increased at intervals of 2 or more days, maximum 3 g daily.

Remarks

Side effects are minimized if the daily dose is kept below 1 g. The 14th WHO Expert Committee (2005) recommended that the section 12.3 medicines for hypertension in pregnancy reviews be prepared and submitted for discussion at its next meeting in 2007.⁴ The use of methyldopa does not require special medical facilities or specialist medical care.

International drug price indicator 2005 (Supplier price in US\$)⁵

Methyldopa, tablet, 250 mg, median price/tablet: 0.0281

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Misoprostol: induction of labour at term

Background

Stimulating the uterus to begin labour is sometimes needed because of safety concerns for the mother or child. Methods of preparing the uterine cervix and inducing labour include: administration of oxytocin, prostaglandins, prostaglandin analogues, mifepristone, extra-amniotic saline solution infusion, or mechanical procedures. When the condition of the cervix is unfavourable in the third trimester, oxytocin has a high failure rate for labour induction. In those cases, prostaglandin preparations have proven beneficial, but most of them are expensive and unstable at room temperature. Misoprostol, a prostaglandin analogue, is used in the induction of labour.

Evidence summary

There is good evidence to show that misoprostol is effective in cervical ripening and labour induction.¹ In an initial dose of 25 mcg every 4 or 6 hours, vaginal misoprostol is more effective than oral and sublingual misoprostol. On the other hand, intravaginal misoprostol increases uterine hyperstimulation, sometimes with changes in fetal heart rate. There are anecdotal reports of uterine rupture following treatment with prostaglandin analogues in women with or without previous caesarean section, but this is a very rare outcome. Because it reduces the incidence of operative deliveries, vaginal administration of misoprostol may lead to cost savings. In prevention of postpartum haemorrhage, traditional uterotonics (oxytocin or ergot derivatives) outperform prostaglandin analogues. Misoprostol is easier to store and administer than other uterotonics, and no cold storage is needed.

Indications and dosage

- Misoprostol, vaginal tablet, 25 mcg

Induction of labour at term when there is a medical need.

Place misoprostol 25 mcg in the posterior fornix of the vagina. Repeat after 6 hours, if required. If there is no response after 2 doses of 25 mcg, increase to 50 mcg every 6 hours. Do not use more than 50 mcg at a time, and do not exceed 4 doses (200 mcg). Do not use oxytocin within 8 hours of using misoprostol.²

Remarks

The 14th WHO Expert Committee included misoprostol on the complementary list of the 14th *WHO Model List of Essential Medicines* (2005) for the induction of at-term labour. The Expert Committee recommended that misoprostol be administered as low-dose vaginal tablets and be used only in organised health services where monitoring equipment is available.

Compared with other prostaglandin analogues, misoprostol is cheaper than conventional uterotonics and can be stored at room temperature. Vaginal use of the 200-mcg oral tablet for the same purpose is dangerous and should be discouraged.

International drug price indicator 2005 (Supplier price in US\$)

Not available.

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Mifepristone with misoprostol: induction of medical abortion

Background

WHO defines unsafe abortion as a procedure for terminating an unintended pregnancy either by persons lacking the necessary skills or in an environment lacking the minimal medical standards, or both. According to WHO, 19 million women have unsafe abortion worldwide each year, and 18.5 million of these occur in developing countries.¹ Mortality due to unsafe abortion is estimated at about 68,000 women each year.² Complications from unsafe abortions include infection, uterine perforation, cervical laceration, incomplete evacuation, haemorrhage, miscarriage, future sterility, and death.³ The risk of death due to complications of unsafe abortion in developing countries is one hundred times higher compared to when the procedure is performed under safe conditions.¹ In settings where surgical termination of pregnancy is legal, it can still be unsafe when performed under inappropriate circumstances, such as in a nonsterile environment with a lack of proper equipment and emergency medicines or by untrained personnel.⁴ Medical methods offer a safe treatment alternative particularly in those settings, because their administration requires little training and a simpler infrastructure compared to surgical procedures.⁵

Evidence summary

A mifepristone/misoprostol combination is more effective than single agents for inducing abortion in the first trimester of pregnancy.⁶ A systematic review of 39 randomised controlled trials showed that sequential administration of a single-dose mifepristone oral 200-mg tablet followed by a vaginal single dose of misoprostol, 800 mcg in 36 to 48 hours, was effective and safe in inducing medical abortion until 9 weeks of pregnancy.⁴ Major complications appeared to be rare, the most common complication being blood transfusion (about 0.2%). It was reported that the side effects (nausea, vomiting, and diarrhoea) were mainly due to prostaglandins. Higher doses were associated with increased incidence of side effects.⁴

The risks of bleeding, abdominal pain, fever, and dizziness in the medical abortion population were slightly higher than those in the surgical abortion population. In addition, the duration of bleeding caused by medical abortion was longer than that caused by surgical abortion.⁵

The use of this medication in medical abortion should be undertaken under

close medical supervision. Its efficacy decreases if used after 9 weeks of gestation.

Indications and dosage

- Mifepristone with misoprostol, tablet 200-mg oral tablet+ 200 mcg vaginal tablet

Induction of medical abortion within 9 weeks of pregnancy.

Sequential regimen: a single dose of 200-mg mifepristone oral tablet followed by a vaginal single dose of misoprostol, 800 mcg (4 times 200 mcg), within 36–48 hours.

Remarks

In 2005, the 14th WHO Expert Committee included mifepristone with misoprostol on the complementary list of the *14th WHO Model List of Essential Medicines* (2005). The two items should not be listed individually to avoid the misuse of misoprostol.

The 14th WHO model list contains a note adjacent to the combination, stating “Where permitted under national law and where culturally acceptable.” The use of mifepristone with misoprostol requires specialist medical care. The desirable and safe setting for administration would be a well-organised service that could manage any adverse effects or complications.

Mifepristone/misoprostol regimen for medical abortion in the first 9 weeks of pregnancy has been registered in many countries, including several European countries and the United States.

International drug price indicator 2005 (Supplier price in US\$)

Not available.

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Nifedipine: a tocolytic medicine

Background

Preterm birth occurs in 5% to 22% of pregnancies and is a major cause of neonatal mortality worldwide. Preterm birth burdens health care systems and communities and is distressing to families. Preterm babies are at higher risk of dying or suffering complications and sequelae. Care of preterm premature babies usually demands a great amount of resources, including highly skilled personnel, technologically advanced equipment, and expensive treatments.¹ Management of preterm labour consists of tocolysis or allowing labour to progress.

Tocolytic medicines, such as nifedipine, postpone premature labour and are used to treat women with threatened preterm birth under the premise that stopping uterine activity will reduce preterm birth and will give more time for treatments aimed at maturing the baby's lungs.¹

Most tocolytics delay delivery. However, not all of them have been shown to reduce prematurity and its complications. Furthermore, beta₂ agonist tocolytics frequently cause adverse effects such as headache, hypotension, and tachycardia, affecting the mother or the baby sometimes seriously.

Evidence summary

Nifedipine is a dihydropyridine calcium channel blocker that is frequently used to treat high blood pressure and is also a tocolytic medicine. A systematic review of the scientific evidence has found that when women with threatened preterm labour before 34 weeks of gestation take nifedipine, their babies have fewer complications of prematurity. Furthermore, nifedipine has been found to have a lower risk of causing important adverse effects than other tocolytics.² There is strong evidence to support the use of nifedipine to inhibit preterm labour. Nifedipine was studied in 10 out of 12 randomised controlled trials in a systematic review.^{1,3} The results indicated that, compared with any other tocolytic agent (mainly betamimetics), nifedipine reduced the frequency of neonatal respiratory distress syndrome, necrotising enterocolitis, intraventricular haemorrhage, and neonatal jaundice. Nifedipine has been used throughout the world for many years.

Indications and dosage

- Nifedipine, immediate-release capsule, 10 mg

Acute tocolysis for women in uncomplicated premature labour between 20–33 weeks of gestation.

Acute tocolysis for women in premature labour, adult, initially sublingually, 10 mg repeated every 20 minutes to a maximum dose of 40 mg in the first hour. Once contractions cease, 20 mg every 4 hours for 48 hours, then maintenance, orally, 10 mg every 8 hours until 34 weeks of gestation.⁴

Nifedipine is effective and safe for this indication, and the sublingual route is pharmacologically equivalent to the conventional oral route because the medicine is absorbed low in the gastrointestinal tract.

Remarks

If less than 34 weeks of gestation, tocolysis should be accompanied by use of corticosteroids to improve fetal lung maturity.⁵

Nifedipine, as tocolytic, was added to the *14th WHO Model List of Essential Medicines* (2005).

The use of nifedipine does not require special medical facilities or specialist medical care.

International drug price indicator 2005 (Supplier price in US\$)⁶

Nifedipine, immediate-release capsule, 10 mg, median price/capsule: 0.0122

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Oxytocin: an injectable oxytocic

Background

Postpartum haemorrhage is the single most important cause of maternal death worldwide and one of the major causes of maternal death in developed and developing countries. It is estimated that it causes 125,000 deaths per year, affects 5% to 15% of women after giving birth, and increases morbidity in about 20 million women undergoing delivery. Oxytocic medicines, including ergometrine and oxytocin, are used to stimulate uterine contractions to control postpartum haemorrhages. Ergometrine and oxytocin differ in their actions on the uterus. In moderate doses, oxytocin produces slow, generalized contractions with full relaxation in between; ergometrine produces faster contractions superimposed on tonic contractions. High doses of both substances produce sustained tonic contractions. Induction of labour is sometimes needed because of safety concerns for the mother or child.¹ Oxytocin—but not ergometrine—is used for this purpose.

Evidence summary

According to several reviews of evidence for effectiveness and safety of oxytocics in the prevention of postpartum haemorrhage, oxytocin used alone has shown effectiveness in reducing postpartum haemorrhage. The combination of ergometrine with oxytocin is slightly superior for this outcome.^{2,3} However, maternal side effects are more frequent in women treated with the combination regimen than with oxytocin alone.³ Moreover, oxytocin is recommended for prevention of postpartum haemorrhage, since it is more thermostable than ergometrine.

Oxytocin is also recommended for use in induction or augmentation of labour.

Indications and dosage

- Oxytocin, injection, 10 IU in 1-ml ampoule

Induction of labour and prevention and treatment of postpartum haemorrhage.

Induction of labour, by intravenous infusion, adult and adolescent, initially 0.001–0.002 units/minute increased by 0.001–0.002 units/minute increments at intervals of 30 minutes until a maximum of 3–4 contractions occur every 10 minutes; maximum recommended rate is 0.02 units/minute; no more than 5 units should be administered in 24 hours.^{4,5}

Prevention of postpartum haemorrhage, by intramuscular injection, adult and adolescent, 10 units immediately after birth of baby.^{1,4}

Prevention of postpartum haemorrhage, by slow intravenous injection, adult and adolescent, 5 units immediately after birth of baby.⁴

Treatment of postpartum haemorrhage, by slow intravenous injection, adult and adolescent, 5–10 units or by intramuscular injection, 10 units, followed in severe cases by intravenous infusion; a total of 40 units should be infused at a rate of 0.02–0.04 units/minute, started after the placenta is delivered.⁴

Remarks

The dose shown above for induction of labour is suitable for use in a hospital where equipment to control the infusion rate is available.

As much as possible, oxytocin should be stored under refrigeration between 2° and 8° C. Unrefrigerated transport is permissible if it does not exceed one month at 30° C or 2 weeks at 40° C. In case refrigerated storage is not available, temporary storage outside the refrigerator at a maximum of 30° C is acceptable for a period not exceeding three months.⁶

International drug price indicator 2005 (Supplier price in US\$) ⁷

Oxytocin, injection, 10 IU in 1-ml ampoule, median price/ml: 0.1322

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