

SELECTION OF **ESSENTIAL** **MEDICINES** AT COUNTRY LEVEL

Using the WHO Model List
of Essential Medicines
to update a national
essential medicines list





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1. Introduction

Since 1977, WHO has been working with countries to design the package of essential medicines as an integral component of treatment within the continuum of care, developing and disseminating the Model List of Essential Medicines (Model List). WHO is committed to supporting Member States in sharing best practices in selecting essential medicines, and in developing processes for the selection of medicines for national essential medicines lists (national EMLs, or NEMs) consistent with the evidence-based methods used for updating the WHO Model List.

Achieving universal health coverage (UHC) requires access to safe, effective, quality and affordable essential medicines, vaccines and health products. The pillars of UHC are enshrined in the key leadership priorities for WHO, reaffirmed in the WHO 13th General Programme of Work 2019–2023 and captured in the Sustainable Development Goals (SDGs) (see Box 1). Equity in public health depends on access to essential, high-quality and affordable health-related technologies for all. However, ap-

proximately half the world's population lacks access to such essential health-related technologies, specifically essential medicines. Therefore, to achieve SDG target 3.8 of UHC for all by 2030, at least 1 billion more people will need to have access to essential health services in each five-year period between 2015 and 2030. Moving towards UHC requires that countries concentrate efforts on supporting a people-centred health system with primary care as its foundation, and essential medicines, community-based services, health promotion and disease prevention as key components. This document aims to support countries in developing their own NEMs and, through these lists and other medicine policy actions, to progress towards UHC and the goal of ensuring that all people and communities have access to highly effective medicines that are appropriate to their needs, affordable to individuals and health systems, and of assured quality.

The connection between the Model List and which medicines are available and affordable in countries might not be immedi-

BOX 1. WHO and affordable access to essential medicines: EMLs as an essential component of UHC

Sustainable Development Goal SDG 3: Ensure healthy lives and promote well-being for all at all ages*

3.8 Achieve universal health coverage, including financial risk protection, access to quality essential health care services, and **access to safe, effective, quality, and affordable essential medicines and vaccines for all.**

3.b Support the research and development of vaccines and medicines for communicable and non-communicable diseases that primarily affect developing countries, **provide access to affordable essential medicines and vaccines**, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health, which affirms the right of developing countries to use to the full the provisions in the Agreement on Trade-Related Aspects of Intellectual Property Rights regarding flexibilities to protect public health and, in particular, provide access to medicines for all.

WHO 13th General Programme of Work (2019–2023):

The foundation of WHO's work is SDG 3... WHO is an organization focused principally on promoting health rather than merely fighting disease, and especially on improving health among vulnerable populations and reducing inequities. Leaving no-one behind, the Organization aims to give women and men, girls and boys, in all social groups, the opportunity to live not just long but also healthy lives. WHO will explore measuring this foundation of its work using healthy life expectancy, which could serve as one overarching measure aligned with SDG 3, complemented by the triple billion goal, which leads to three more specific priorities, each with overlapping one-billion people goals.

WHO commitment on universal health coverage is ambitious, with 1 billion more people benefiting from UHC. GPW 13 is based on the SDGs and is relevant to all countries – low-, middle- and high-income.

WHO's work on UHC will be fully aligned with SDG target 3.8, which focuses on achieving UHC, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all.

With a commitment to achieving SDG 3, WHO will “lead a transformative agenda that supports countries in reaching all health-related SDG targets”.

*All SDGs and targets are intended to be achieved by 2030.

ate. But there are important real-world implications when a medicine is listed in the Model List, as it becomes a priority for access and reimbursement. A recommendation not to include a medicine on the Model List should also have implications at country level.

The target audience for this document are ministries of health responsible for NEMs or reimbursement lists, and policy or decision makers considering establishing systems for selecting medicines or updating medicines lists as part of efforts to ensure access to medicines and UHC.

BOX 2. **The essential medicines concept**

- ▼ Essential medicines are those that satisfy the priority health care needs of the population.
- ▼ Essential medicines are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and safety, and comparative cost-effectiveness.
- ▼ Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and community can afford.

The essential medicines concept is global and forward-looking. It incorporates the need to regularly update medicines selections to reflect new therapeutic options and changing therapeutic needs; the need to ensure drug quality; and the need for continued development of better medicines, medicines for emerging diseases and medicines to meet changing resistance patterns.

1.1. What are essential medicines? Links between the WHO Model List and NEMs

Essential medicines are those that satisfy the priority health care needs of a population. They are intended to be available in functioning health systems at all times, in appropriate dosage forms, of assured quality, and at prices individuals and the community can afford. Selection of a limited number of essential medicines, taking into consideration national disease burden and clinical need, can lead to improved access through streamlined procurement and distribution of quality-assured medicines, support more rational or appropriate prescribing and use, and lower costs both for health-care systems and for patients.

Every two years WHO publishes its Model List of Essential Medicines, intended as a guide for countries or regional authorities to adopt or adapt in accordance with local priorities and treatment guidelines, for the development of NEMs.

Useful resources

- ▼ The WHO Model Lists of Essential Medicines (current and previous) are available on the WHO EMP website at:
<http://www.who.int/medicines/publications/essentialmedicines/en/>

The uptake of the Model List has continued to increase over time, with countries using it to guide development and updates of their NEMs. Currently 131 NEMs are published online and are publicly available through the WHO Essential Medicines and Health Products Information Portal (WHO EMP Information Portal). The portal is an online repository of full-text publications on medicines and health products related to priorities of WHO, other United Nations (UN) partners, global nongovernmental organizations, development agencies and their partners, countries and academics.



Practice point

The WHO Essential Medicines Selection website provides access to all applications, reviews, comments and Expert Committee decisions relating to each update of the WHO Model List. Transparency in the process and reporting of updated NEMLs and reimbursement lists at country level is important to help ensure trust in the decisions made. Updated NEMLs and reimbursement lists should be available in the public domain, such as on ministry of health websites.

Useful resources

- ▼ The WHO EMP Information Portal includes an online repository that stores over 130 NEMLs that can be accessed by countries for review and benchmarking purposes when updating their own lists.
- ▼ Countries are encouraged to submit copies of their updated NEMLs for inclusion in the repository via email to: emlsecretariat@who.int
- ▼ Access the repository at: <http://apps.who.int/medicinedocs/static/PublicSubcollections/National-Essential-Medicines-Lists-NEMLs-Repository/index.html>

1.2. Uses of EMLs

The chief intended use of the WHO Model List is to provide a blueprint on which countries can base their own national lists. It is a key tool for achieving universal health coverage because it supports governments, health facilities and procurers in identifying which medicines are the best options in

terms of benefits for individuals and communities. In cases where governments or health systems do not directly procure medicines, the Model List provides an evidence-informed starting point for prioritizing reimbursement in countries. These priority medicines lists may operate at national, regional or health systems level, such as within a particular insurance system. At hospital level procurement or reimbursement lists can be developed by drugs and therapeutics committees.

The WHO Model List is useful to other UN agencies. Up to a decade ago, the WHO Model List was primarily used as a tool to flag medicines for government procurement, investing limited resources on carefully selected items that ensured the best return in terms of health gains. However, the concept has a far wider application, and the WHO Model List also serves as the starting point for reimbursement lists for public or private insurers in more complex health systems with purchaser-provider splits.



Practice point

An NEML is a list of carefully selected medicines intended to respond to priority needs of a country's population, and as such is a fundamental tool for achieving UHC. The availability and affordability of quality-assured essential medicines can be used to measure progress towards UHC at the national level. By linking selection to monitoring of medicines utilization and expenditure, an NEML can also serve to improve appropriate and rational prescribing and manage medicines spending.

Regardless of the terminology and level at which EMLs operate, there are common principles that should be applied in the evidence-based selection of medicines for these lists to prioritize the most effective and most important medicines.

This document provides guidance on the selection of essential medicines, summarizing key aspects of the evidence-based approach to medicines selection. Assessing effectiveness and safety, defining the therapeutic role through best available guidelines, considering resource implications, comparative costs and cost-effectiveness, addressing potential conflicts of interest and ensuring transparency in decision-making are dimensions that should inform addition or rejection of medicines. Evidence synthesis and its critical appraisal have a central role in recognizing the value of a medicine. It is not expected that all countries will have the capacity or need to adopt exactly the same processes, with full analysis of all these dimensions, even at national level. Nevertheless, transparency is essential to assuring an accountable medicines selection process. The WHO Model List serves as a reliable resource to support the processes put in place at national level.

In addition, this document describes strategies and processes to ensure successful implementation of NEMs. Without a commitment to using essential medicines as the basis for preferred procurement, reimbursement and clinical care, the efficiency goals of priority medicines selection are unlikely to be realized. Furthermore, selection should be followed by monitoring the use of these medicines, as actual clinical practice can show high variability and frequent inappropriate use.

In the 2017 Lancet Commission report on Essential Medicines for Universal Health Coverage,¹ the Commission described five necessary elements of essential medicines policies: paying for core set of essential medicines, making essential medicines affordable, assuring quality and safety of medicines, promoting quality use of medicines, and developing missing essential medicines. In addition, the Commission made a series of recommendations within each policy area that should be actioned as part of the global health and sustainable development agenda. Many of the recommendations are directly relevant to establishment and implementation of a NEM, including:

- ▶ that governments and health systems provide adequate financing to ensure inclusion of essential medicines in benefits packages provided by the public sector and health insurance schemes, and implement policies that reduce individual out-of-pocket spending;
- ▶ that governments and health systems routinely monitor data on price, availability and affordability of essential medicines across both the public and private sectors, and implement comprehensive policies to achieve affordable prices and equitable access;
- ▶ that governments and health systems develop national capacity to create medicines benefit packages that guide procurement and reimbursement of essential medicines;
- ▶ that payers and procurement agencies adopt good procurement practices that incorporate effective and transparent quality assurance mechanisms;

- ▶ that governments and the main public or private payers establish independent pharmaceutical analytics units to focus on generating information for action to promote quality use of essential medicines, to collaborate with stakeholders to identify medicine use problems, and to develop and implement relevant interventions for medicines use problems;
- ▶ that governments and national stakeholders develop and implement comprehensive national action plans to guarantee equitable access to new essential medicines.

Improving access and affordability of highly-priced essential medicines for both health systems and individuals are critical steps towards the achievement of UHC. The WHO Expert Committee has recognized that some medicines included on the Model List are highly-priced and that access and affordability are significant challenges for countries of

all income levels. The Expert Committee has identified a number of actions that can contribute to making essential medicines more accessible and affordable:

- ▶ the greater adoption of biosimilars, including expansion of the WHO Prequalification Programme to include biosimilars of biological medicines listed on the Model List;
- ▶ an expanded role for the Medicines Patent Pool to a wider range of patented essential medicines beyond its current remit;
- ▶ using pooled procurement and tendering activities to take advantage of market competition through application of the Model List's 'square box' concept;
- ▶ use of provisions providing public health flexibilities contained in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS);
- ▶ national medicines pricing and competition policies.

2. A committee process for selecting medicines for an essential medicines list

This section describes the WHO Expert Committee process for reviewing and updating the WHO Model Lists and suggests similar processes that can be put in place at national level.

WHO Expert Committees are highly regulated bodies convened by the Director-General for the purpose of reviewing or making technical recommendations on subjects relevant to the organization. The Expert Committee on the Selection and Use of Essential Medicines is responsible for providing recommendations to the Director-General regarding medicines on the WHO Model List of Essential Medicines. It meets every two years to consider applications for the addition, amendment or deletion of medicines on the Model List.

The regulations governing Expert Committees are set out in WHO's Basic Documents, and cover the selection, appointment and term of office of members, the international status of members and committee reporting requirements, among other things. Revised technical/scientific processes for updating the Model List were approved by

WHO's Executive Board in 2001, in acknowledgement of advances in the science of evidence-based decision-making. Other technical aspects, such as how to evaluate candidate medicines to the NEMs, the link between essential medicines and guidelines for clinical health care, and how to implement NEMs once selection is completed, are discussed in Chapter 3.

Using a committee of experts to select medicines to be included in an NEM, whether for procurement or reimbursement purposes, is a proven method used by many countries and is recommended by WHO. While it is acknowledged that the highly governed processes and regulations of WHO expert committees may not be feasible or applicable in many settings, they provide a useful procedural framework that can be adapted to suit national or regional needs and resources. What follows sets out some suggestions for the formation and function of an expert Selection Committee at national or regional level, based on the general processes and functions of the WHO Expert Committee on the Selection and Use of Essential

Medicines. For ease of reference, we will refer to the group of experts that does selection for the WHO Model List as the WHO Expert Committee, and to the group of experts that does selection at country level as the Selection Committee.



Practice point:

The ministry of health, or other relevant national or regional authority, should establish an expert “Selection Committee” to be responsible for the selection of medicines for inclusion on the NEML or reimbursement list. The Selection Committee should be independent and trustworthy, and its members required to declare any potential conflict of interest. Identified actual and potential conflicts of interest need to be proactively and transparently managed. The Selection Committee should be supported in its functions by a strong technical and administrative Secretariat.

2.1. Selection Committee membership and functions

The Selection Committee should be an official committee whose purpose, membership, functions, roles and responsibilities are well defined. Its roles, functions and procedures may be established in law, or may be managed administratively under the auspices of the ministry of health or authority responsible for the NEML. Clearly articulated and publicly available terms of reference can help to ensure transparency, fairness, con-

sistency and public confidence in the selection process.

The Selection Committee should be multidisciplinary and its members should possess relevant expertise and represent key medical, pharmaceutical and health system stakeholders. A multidisciplinary approach reflects the nature of health care and the health-care system. The membership of the Selection Committee may include, but need not be limited to:

- ▶ medical specialists, covering various clinical disciplines
- ▶ paediatricians
- ▶ pharmacologists
- ▶ pharmacists
- ▶ primary health-care providers, including nurses or physician’s assistants
- ▶ experts skilled in evidence synthesis and appraisal, evidence-based medicine and health technology assessment
- ▶ personnel from the ministry of health or other national, regional or local authority involved in procurement and supply of medicines, as well as in the development of national or regional policies and treatment guidelines
- ▶ national medical and/or pharmacist association representatives
- ▶ representatives of regional hospitals and primary care facilities
- ▶ representatives from patient groups, civil society organizations and/or international and nongovernmental organizations (optional).

A multidisciplinary committee with evidence appraisal skills serves to reflect the overall health-care process and a rigorous scientific approach.

The size and composition of the Selection Committee can vary, depending on needs, purpose, resources and availability of experts. A committee of 15–20 members is usually effective and manageable. In some cases fewer members may be more feasible, while in other cases more members may be required. However, larger committees can often be more complex to manage.



Practice point

The involvement of representatives from the pharmaceutical industry as members of the Selection Committee is not recommended. If the Selection Committee has responsibility or authority for setting prices or listing and reimbursement decisions, having industry representatives as members or observers could be problematic and introduce potential influences that should be avoided as they would weaken the committee's independence. Decisions to list medicines on an NEML are likely to be market-shaping.

Members of the Selection Committee should be competent in their areas of expertise and should possess critical appraisal and problem-solving skills and an understanding of the essential medicines concept (see Box 2). To ensure a high standard of integrity and to engender public confidence, prior to their involvement members of the Selection Committee should be required to disclose any direct or indirect circumstances that may, or may be perceived to, give rise to a conflict of interest (see 2.2 Managing conflicts of interest).

The Selection Committee should be chaired by a member appointed by the ministry or the authority involved, or selected by the committee members. As for all committees, it is important to select as the chair someone who possesses and has demonstrated leadership in similar situations, has experience working in committees, is tactful and fair, and has good communication skills.

The Selection Committee should include both experienced and new members. Active steps should be taken to ensure both continuity and succession planning for the Selection Committee. Consideration may be given to limiting the term of appointment and the number of times a member can be re-appointed (e.g. two-year appointments, maximum of three to five reappointments). This helps to ensure knowledge and consistency of processes, while also developing the skills and experience of new members.



Practice point

It is important that members of the Selection Committee be chosen on the basis of their technical expertise, critical appraisal skills and ability to evaluate complex clinical data from trials and other data sources. All committee members must be required to declare any interests that could potentially be perceived as a conflict of interest in making decisions on behalf of the government or institution.

The main function of the Selection Committee is to select medicines for inclusion on the NEML or reimbursement list. The methods

used should be based on transparent and accountable processes.

The criteria and processes for Selection Committee decision-making are discussed further in Chapter 3.



Practice point

A collaborative and consistently aligned approach between entities responsible for both medicines selection and financial coverage is recommended.

An aligned approach to decision-making, using the same evidence base and cost assumptions, serves to develop consistent medicines policies across the selection and reimbursement settings.

2.2. Managing conflicts of interest

Policies for managing conflicts of interest are critical to the good governance of health and pharmaceutical systems. Formal policies have been established only fairly recently (de facto declarations were introduced in late 1980s and early 1990s), and this practice was mostly initiated and put in place by leading medical journals.

The following definition provides an insight into several considerations that illustrate the nature of conflicts of interest:

A conflict of interest is a set of conditions in which professional judgement concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain). [...]

The primary interest is determined by the professional duties of a physician, scholar or teacher. [...] In their most general form, the primary interests are the health of patients, the integrity of research and the education of students.

The secondary interest is usually not illegitimate in itself, and indeed it may even be a necessary and desirable part of professional practice. Only its relative weight in professional decisions is problematic. The aim is not to eliminate or necessarily to reduce financial gain or other secondary interests (such as preference for family and friends or the desire for prestige and power). It is rather to prevent these secondary factors from dominating or appearing to dominate the relevant primary interest in the making of professional decisions.²

A 2009 report by the Institute of Medicine (US) Committee on Conflict of Interest in Medical Research, Education and Practice³ illustrates the relevance of conflicts of interest in medicine, stating that there exists “strong evidence that relationships with industry are pervasive in undergraduate, graduate and continuing medical education” and, “as is the case in medical research and education, evidence shows that relationships with industry are widespread among physicians in practice”. It also describes ways in which conflicts of interest can and should be managed – in expert working groups such as an NEML or a guideline committee – to improve transparency and accountability, and to increase trust in the overall system of research and evidence-based decision-making that has been put in place by WHO in

general and specifically by the WHO Expert Committee.

Members of the WHO Expert Committee are required to declare any circumstances that might be, or be reasonably perceived to be, a conflict of interest with respect to the work they undertake in reviewing applications for medicines on the Model List. This serves to ensure the highest levels of integrity and public confidence in the process and outputs.

A conflict of interest should be understood to mean any interest declared by a Selection Committee member that may affect, or be reasonably perceived to affect, the individual's objectivity and independence in providing advice to the ministry or other relevant authority, and/or create an unfair competitive advantage for the individual or persons or institutions with whom they have financial or business interests. Conflicts of interest exist on a spectrum of severity. In medical and pharmacy services, they can take many forms, for example accepting hospitality or gifts from for-profit vendors of health-related goods or services; awarding contracts to suppliers in which the decision maker has a personal or financial interest; and in the delivery of public services, where individuals or organizations assess service needs as well as provide the services. The development of a system to declare, evaluate, manage and report conflicts of interest of all those involved in a Selection Committee creates trust and gives credibility to the system.

It is important to remember that:

- ▼ conflicts are a condition and not a behaviour: conflicts can create a risk that decisions may be influenced, or perceived to be influenced, by a financial interest;
- ▼ conflicts are usually self-reported in a declaration of interests; and
- ▼ conflicts are legitimate but should be fully known and managed: once evaluated they can lead to exclusion from the committee or limited participation (e.g. participating in the discussion but being excluded from decisions that result in recommendations).



Practice point

Active management of conflicts of interest lends credibility to the overall system of medicines selection.

A system for assessing and managing potential conflicts of interest should be agreed on by the ministry or appropriate authority overseeing the work of the Selection Committee and the Secretariat.

Actual and/or perceived conflicts of interest may compromise the integrity of the medicines selection system and increase the risk that individuals will not perform their duties or obligations appropriately and consequently erode the evidence base for health-care decisions and efficient use of resources.

To ensure high standards of integrity and public confidence, Selection Committee members should be required to complete a declaration of interest and disclose any circumstances that could give rise to a conflict of interest related to their role in reviewing and/or updating the NEML and unduly influence their full and credible participation.



Practice point

Declarations of interest should be made at a number of different stages in the Selection Committee process:

- ▼ a detailed, written declaration prior to the initial appointment of a committee member, and annually thereafter;
- ▼ a written declaration prior to each meeting, specific to the agenda of the meeting; and
- ▼ a verbal declaration at the commencement of the meeting of any potential conflicts that may have arisen since the last written declaration.

Managing conflicts of interest requires that appropriate policies, resources and strategies be in place and adhered to. Appropriate management of conflicts of interest demonstrates good governance. Managing the participation of members in meetings in the event of possible conflicts of interest becomes an important part of the processes governing a Selection Committee. Written declarations of interest need to be reviewed by the Secretariat and/or the legal office within the ministry, and an individual's participation in a given meeting must be prevented if substantial conflicts are present. When minor conflicts are present they may be relevant, but can be managed by restricting participation. Financial conflicts of interest are considered the most important, and in particular individual financial conflicts of interest, which may prevent participation. Institutional conflicts of interest can often be managed by restricting participation.



Practice point

Options for restricting the participation of Selection Committee members with potential or perceived conflicts of interest include the following:

- ▼ members may recuse themselves or be excluded by the Secretariat from participating in both the discussion of and decisions on a given topic; and
- ▼ members' participation in the case of a minor conflict of interest can be limited to the discussion of a topic, without involvement in the decision-making process or formulation of the recommendations.

Useful resources

- ▼ Further information and relevant documents used by WHO for declarations of interest by experts, including members of the Expert Committee on Selection and Use of Essential Medicines, are available on the WHO website at: <http://www.who.int/about/ethics/en/#declarations>

2.3. Secretariat support for the Selection Committee

The ministry of health (or relevant national or regional authority) should establish a Secretariat for the Selection Committee to support it in its functioning. The Secretariat should have a strong technical role to support the Selection Committee in its decision-making, and should also be responsible for preparing and coordinating administrative activities.

The main functions of the Secretariat are outlined below.

Technical functions:

- ▼ reviewing recent updates to the WHO Model Lists and national treatment guidelines for comparison with the NEML or reimbursement list;
- ▼ identifying medicines for review by the Selection Committee and preparing or commissioning applications;
- ▼ reviewing received applications for suitability for consideration and completeness;
- ▼ appointing and supporting ad hoc working groups or subcommittees to provide additional advice to the Selection Committee on specialized areas such as cancer medicines, antibiotics, or rare or specific disease areas; and
- ▼ reviewing or conducting assessments of the cost-effectiveness of medicines and the budget implications of listing, based on confidence in estimates of long-term benefits and harms.

Administrative functions:

- ▼ scheduling and logistics of Selection Committee meetings;
- ▼ coordinating the appointment/reappointment processes of Selection Committee members;
- ▼ managing declarations of interest;
- ▼ taking receipt of applications for inclusion, amendment or deletion of medicines;
- ▼ preparing and distributing agenda materials;
- ▼ preparing, finalizing and distributing approved meeting reports and updated lists; and

- ▼ managing the website and other communications channels.

Options for structuring a Secretariat include the following:

- ▼ Identifying existing staff within the ministry or authority to take on the function.
- ▼ Appointing dedicated staff with relevant technical expertise whose function is to support the Selection Committee processes. Note that this is a more resource-intensive approach and may be better suited to countries with more mature and better-resourced pharmaceutical or insurance systems.



Practice point

It is highly desirable that a Selection Committee be supported by a functioning Secretariat with technical capacity in evidence appraisal and synthesis. This ensures that consistent and rigorous methods are applied to all considerations of the Committee and promotes consistency in decision-making over time.

2.4. NEML updating and timing

NEMLs should be reviewed regularly and updated as required. This process seeks to identify potential additions and deletions of medicines, and changes in formulations and doses. The WHO Expert Committee meets every two years to review and update the Model List. Thus, it would be appropriate for a formal check of the need to update an NEML to be undertaken by a country at least every two years, following the update to the

Model List. This would ensure that the decision on the need to update an NEML is based on the perceived current relevance of the changes made to the last published Model List. When the NEML and the Model List start to diverge, accumulating differences, a formal check of the need to update the NEML should be undertaken.

At country level, the possibility of having to wait up to two years before adding to or deleting medicines from the list might be a major limiting factor. National Selection Committees might therefore need to meet more frequently, depending on capacity and needs. The updates might concentrate on single chapters of the list, leading to more comprehensive review (e.g. cancer medicines) and policy actions at country level (e.g. antibiotics and the national action plan for addressing antimicrobial resistance). Nonetheless, given the number of medicines that

are considered for the WHO Model List every two years, the capacity needed for updating country lists is considerable. To address this, a number of options are available, including the following:

- ▶ defining sections of the NEML that need updating;
- ▶ identifying areas that require extension of therapeutic options, and areas that are no longer a priority; and
- ▶ planning concomitant updates of relevant clinical practice guidelines.



Practice point

Countries should be committed to regularly updating NEMLs. A formal check of the need to update an NEML should be undertaken by a country at least every two years following the update of the WHO Model List.

3. Guiding principles for evidenced-based evaluation and selection of essential medicines

3.1. Overview

Evaluation and selection of medicines are at the core of the WHO Model List and any NEML. The first part of this chapter describes the technical process at WHO. The second part presents suggestions for countries to enable selection of medicines based on a similar approach that can be adapted to local needs and capacity. It is important that the Model List and NEML share consistent guiding principles leading to similar decision-making and selection.

Medicines should be selected following a rigorous, transparent and evidence-based evaluation process. This rigorous process is governed by strict requirements for evidence appraisal, accountability, transparency and opportunities for public review.

3.2. The WHO Model List process

For the WHO Model List, essential medicines are selected “with due regard to disease prevalence, evidence on efficacy and safety,

and comparative cost-effectiveness”. Selection is based on an application dossier submitted to the WHO EML Secretariat for evaluation of the medicine(s).

The process of submitting an application to the Model List is open to all parties, including manufacturers, nongovernmental organizations, professional associations and patient advocates. There is full involvement of relevant WHO departments in the application in order to link medicines selection to clinical guidelines disseminated by WHO wherever possible.

Applications must give an evidence-based justification for inclusion, amendment (e.g. a new indication) or deletion of the medicine. A summary of the information to be included in an application is described in Box 3.

A stepwise process for the systematic review of applications for medicines on the Model List was endorsed by the Executive Board in 2002 and is described in Box 4.

BOX 3. Information to be included in a WHO Model List application

1. Summary statement of the proposal for inclusion, change or deletion.
2. Relevant WHO technical department
3. Name(s) of any organization(s) consulted or supporting the application.
4. The proposed medicine's International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code.
5. The dose form(s) and strength(s) of the proposed medicine.
6. Whether the listing is requested as an individual medicine or a representative of a pharmacological class with a "square box" (see below).
7. Details of the proposed therapeutic dosage regimen, treatment duration and any additional requirements associated with use of the medicine (e.g. diagnostic tests, specialized treatment facilities, administration and monitoring requirements, skill levels of health-care providers).
8. Information supporting the public health relevance of the request.
9. Evidence of clinical benefit.
10. Evidence of safety.
11. Data on comparative cost and cost-effectiveness.
12. Regulatory status and market availability of the medicine.
13. Availability of pharmacopoeial standards.

For full details, refer to: http://www.who.int/selection_medicines/committees/expert/22/EXPCOM22Information-for-Applicants.pdf?ua=1

3.3. Evaluating and selecting essential medicines at country level applying the WHO Model List process

The process used to establish the WHO Model List can be replicated at country level. However, countries can also adjust it based on their needs and resources, introducing or modifying key elements. The most important thing is to define what the different parties involved in evaluating and selecting essential medicines are required to do, so that responsibility and reasons for choices are well understood.

The Selection Committee should be in charge of defining the value of medicines for both patients and the health system at country level. Based on the value, medicines will be recommended for listing or rejected. The magnitude of benefit of a medicine should be the main driver when considering the value. These evaluations should inform other decisions such as pricing and reimbursement, or standard treatment guidelines, which may be the responsibility of other parties. However, in some cases, reimbursement decisions or guideline recommendations may be more integrated with the selection process (e.g.

BOX 4. Systematic review of applications for medicines on the WHO Model List

- ▼ Step 1: The EML Secretariat checks the application for completeness.
- ▼ Step 2: The application is posted on the WHO website for review and comments.
- ▼ Step 3: Specialist technical assessment(s) are made of the data presented in the application, in close collaboration with relevant departments at WHO.
- ▼ Step 4: Each application is peer-reviewed by at least two members of the Expert Committee, who formulate draft recommendations for consideration by the full committee during the meeting.
- ▼ Step 5: All reviews and comments received are published on the WHO website for full transparency.
- ▼ Step 6: Peer reviewers present their recommendations for each application to the full Expert Committee for discussion.
- ▼ Step 7: The Expert Committee reaches a decision for each application by consensus, documents the reasons for the decision and makes its recommendation to the Director-General.

1EB109/8 WHO medicines strategy. Revised procedure for updating WHO's Model List of Essential Drugs. Available at: http://apps.who.int/gb/archive/pdf_files/EB109/eeb1098.pdf

where the Selection Committee is entrusted with developing standard treatment guidelines).

3.4. Setting up evaluation of a medicine at country or regional level

The first step in evaluating a medicine at country or regional level should be to ascertain which of the following three categories the medicine falls under:

- ▼ The medicine has been evaluated by the WHO Expert Committee and is currently listed on the WHO Model List; OR
- ▼ The medicine has been evaluated by the WHO Expert Committee but:

- ▽ was not recommended for listing; or
 - ▽ was deleted from the WHO Model List;
- OR

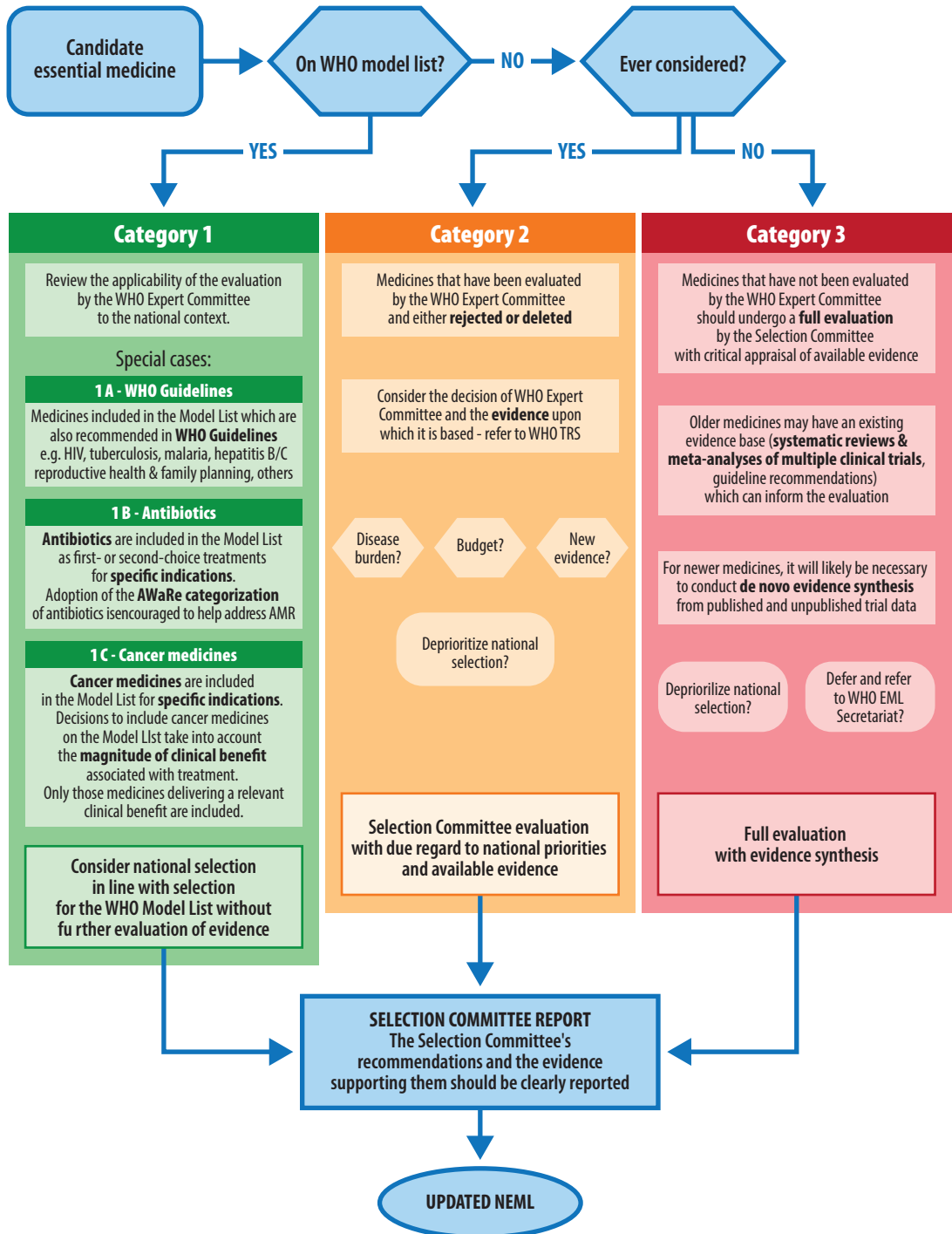
- ▼ The medicine has never been considered by the WHO Expert Committee.

Different evaluation processes at country level can follow, depending on which of these categories applies to the medicine in question (see Figure 1).

These processes are described further in the following sections, including special cases for category 1 medicines:

- ▼ Medicines recommended in WHO Guidelines
- ▼ Antibiotics
- ▼ Cancer medicines.

FIGURE 1. Process for evaluating and selecting medicines for an NEML



Category 1: Medicines currently listed on the WHO Model List

The majority of deliberations of the Selection Committee on medicines for inclusion on a national list may be straightforward when comprehensive evaluations of available evidence have already been published. This is the case when the medicine under evaluation is already listed on the Model List for the indication being considered and the reasons that support its inclusion apply equally at country level. The formal process behind every deliberation regarding essential medicines on the WHO Model List ensures that countries have access to the evidence examined by WHO supporting the decision to list: a synthesis of the benefits and harms, feasibility and costs of the intervention. All key information is published in the reports of the Expert Committee as part of the WHO Technical Report Series.

Useful resources

- ▼ The technical reports of the WHO Expert Committee on Selection and use of Essential Medicines are available on the WHO EMP website at:
http://www.who.int/medicines/publications/essentialmeds_committeereports/en/
- ▼ A database linking currently and historically listed EML medicines with the relevant technical reports is available on the WHO EMP website at:
<http://apps.who.int/iris/bitstream/handle/10665/278038/WHO-MVP-EMP-IAU-2019.01-eng.xls>

If there are no substantial differences or major reservations about the positive impact that listing could have, the Selection Committee might consider adding the medicine to the national list, effectively adopting the Expert Committee's decision, without further evaluation of the evidence. If the Selection Committee has some reservations about the applicability of the Expert Committee's recommendation to the national context, a decision might be made to not recommend listing the medicine. It is important that the Selection Committee acknowledge the local conditions and interests that differentiate the NEML and WHO Model List, providing a transparent record of the reasons behind Selection Committee recommendations.



Practice point

Recommendations should be parsimonious, selecting medicines that are supported by strong evidence and avoiding listing when evidence is uncertain. It may be beneficial in the long term to take a conservative approach to listing new medicines with limited evidence, particularly in the absence of compelling unmet clinical need or supporting clinical guidelines.

Premature decisions to list medicines should be avoided. They may result in a need to delete soon afterwards, and this can damage the trust in the selection process and the NEML itself.

Special cases

Category 1A: Medicines recommended in WHO Guidelines

Integrating the NEML with clinical practice recommendations should also make the best use of WHO guidelines.

Among the goals of NEMLs is to support the appropriate use of essential medicines and help health professionals in their decision making. Guidelines are a key tool to achieve these goals. They complement NEMLs, better reflecting the way doctors approach information and providing a direct connection to clinical practice, covering relevant population details (e.g. age, severity and stage of disease), the intervention (eg. choice of drug, dosage, duration of treatment and most important harms) and outcomes that can be expected (eg. prolongation of survival, improvement in pain or disability).

WHO has a long tradition of developing high-quality guidelines on many health topics including communicable diseases, neglected tropical diseases, maternal and child health, and reproductive health and family planning. In these cases, countries might choose to adopt, contextualize or adapt the recommendations of the WHO Expert Committee and WHO guidelines as a combination guiding selection and use of essential medicines.



Practice point

The Selection Committee can:

- ▼ search the WHO website for WHO guidelines relevant to the disease area or topic of interest;
- ▼ review potential guidelines providing recommendations for medicines being considered for inclusion on the NEML;

- ▼ consider the specific recommendations and supporting evidence, including algorithms for diagnosis, treatment and monitoring;
- ▼ utilize WHO guideline recommendations and the evidence that underpins them to support selection decisions for the NEML and national treatment guidelines.

This approach would eliminate or reduce duplication of efforts in developing de novo guidance documents, and prevent or limit selection of these medicines without considering clinical practice. Furthermore, if in planning additions to the NEML, the Selection Committee is obliged to identify recommendations for clinical use, incorporating essential medicines into practice should be easier and faster.

Useful resources

- ▼ WHO Guidelines approved by the Guidelines Review Committee are available on the WHO website at: <https://www.who.int/publications/guidelines/en/>

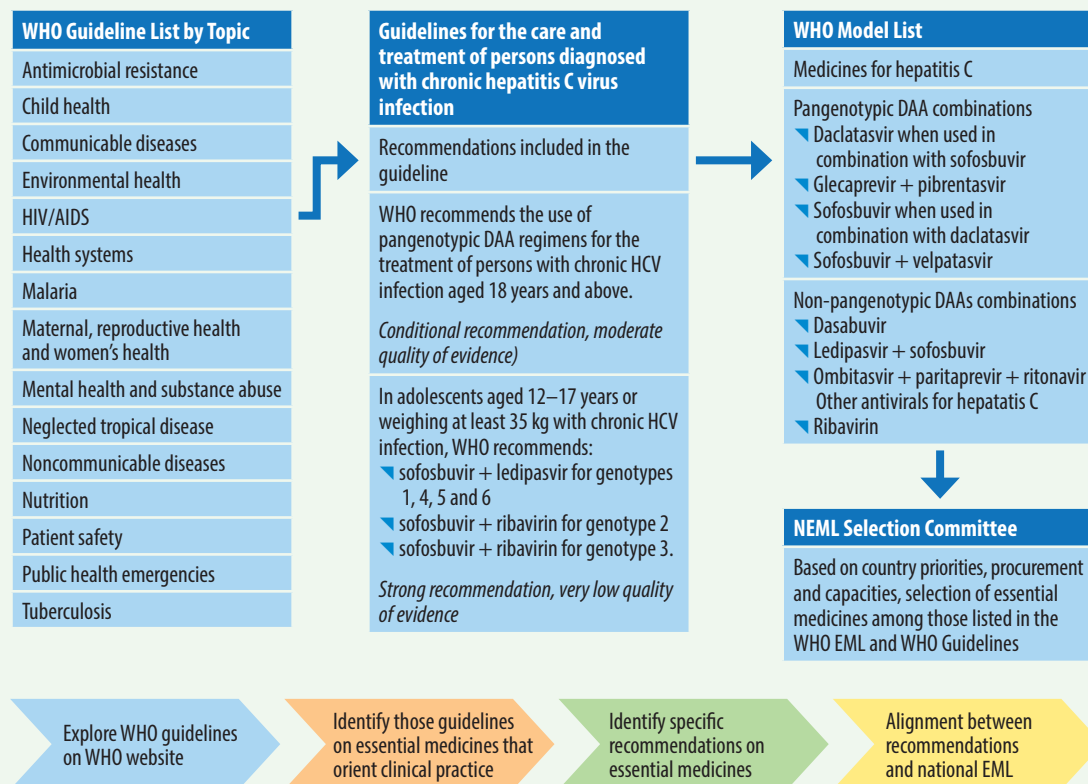
Category 1B: Antibiotics

In recent years, the WHO Expert Committee has undertaken a comprehensive review of antibacterials on the Model List for treatment of common, priority infectious syndromes.

Taking account of global recognition of the need for effective antimicrobial stewardship, as well as the need to ensure access to necessary antibiotics and appropriate prescribing, the Expert Committee has also endorsed the classification of antibiotics in-

FIGURE 2. Using WHO guidelines to support NEML selection

Conceptual framework describing the interplay between the WHO Model List of Essential Medicines and WHO Guidelines: an example focused on direct-acting antivirals (DAAs) for hepatitis C.



to three groups, Access, Watch and Reserve (the AWaRe classification) to emphasize the importance of their optimal use:

- Access** – antibiotics that have activity against a wide range of commonly encountered susceptible pathogens, while showing lower resistance potential than antibiotics in the Watch and Reserve groups;
- Watch** – antibiotic that have a higher resistance potential, including most of the highest priority agents among the Critically Important Antimicrobials (CIA) for

Human Medicine⁴ and/or antibiotics that are at relatively high risk of selection of bacterial resistance;

- Reserve** – antibiotics and antibiotic classes that should be reserved for confirmed or suspected infections due to multi-drug resistant organisms, and used mainly as “last-resort” treatment options.

Selected Access and Watch group antibiotics are included on the Model List as a first- or second-choice empiric treatment option for the clinical infectious syndromes reviewed

TABLE 1. EML-listed antibiotics by syndrome (2019)

	amikacin	amoxicillin	amoxicillin + clavulanic acid	ampicillin	azithromycin	benzathine benzylpenicillin	benzylpenicillin	cefalexin	cefazolin	cefixime	cefotaxime	ceftazidime*	ceftioxiime	cefuroxime	chloramphenicol	ciprofloxacin	clarithromycin	clindamycin	cloxacillin	doxycycline	gentamicin	meropenem	metronidazole	nitrofurantoin	phenoxymethylpenicillin	piperacillin + tazobactam	procaine benzylpenicillin	spectinomycin	sulfamethoxazole + trimethoprim	vancomycin oral	vancomycin IV
Community-acquired pneumonia (mild-moderate)	1	2																						1							
Community-acquired pneumonia (severe)			2							1	1					1															
Community-acquired pneumonia (severe - children)	1	1	1			1				1	1										1										
Pharyngitis	1						2																	1							
Pharyngitis (children)																2															
Sinusitis	1	1																													
Otitis media	1	2																													
Hospital-acquired pneumonia			1							1	1															1					
Sepsis in neonates / children	2	1	1		1					2	2						2			1											
Lower urinary tract infection	1	1																					1					1			
Pyelonephritis / prostatitis (mild-moderate)										2	2		1																		
Pyelonephritis / prostatitis (severe)	1									1	1																				
Meningitis	2	2			2					1	1	2																			
Meningitis (neonates)																					2										
Complicated intra-abdominal infections (mild-moderate)		1								1	1		2										3								
Complicated intra-abdominal infections (severe)										1	1											2	1		1						
Skin and soft tissue infections	1					2												1													
Invasive bacterial diarrhoea / dysentery				2				2		2	2		1															2			
Cholera																2				1											
Cholera (children)				1																2											
C. difficile infection																							1							2	
Gonorrhoea				3				2		1											2						2				
STI due to chlamydia trachomatis				1																1											
Trichomonas vaginalis																							1								
Syphilis					1	1																					2				
Syphilis (congenital)					1	1																					1				
Exacerbations of COPD	1	1					2														2										
Bone and joint infections		2					2	2	2								2	1													
Febrile neutropenia (low-risk)		1														1															
Febrile neutropenia (high-risk)	1																					2			1					2	
Severe acute malnutrition (uncomplicated)	1																														
Severe acute malnutrition (complicated)	1	1			1																1										
Enteric fever				1						1			1																		
Surgical prophylaxis		2					1						2								2	1									
Progressive apical dental abscess	1																							1							

1 = first choice; 2 = second choice; 3 = first and second choice; Green = Access group antibiotic; Orange = Watch group antibiotic.

*for the treatment of *Pseudomonas aeruginosa* infections resistant to gentamicin.

Adapted from the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children (2019).

BOX 5. **Expert Committee recommendations for otitis media (2017)**⁵**EML listings**

- Antibiotics proposed for both EML and EMLc unless specified

Endorsement indicates those antibiotics currently included on EML/EMLc

	First choice	Second choice
Watchful waiting, symptom relief and no antibiotic treatment should be considered as the first-line treatment option, unless a child is under 2 years of age with bilateral otitis media		
Endorsement	amoxicillin	amoxicillin + clavulanic acid

Committee recommendations

- The Expert Committee noted that the appropriate first-line treatment option for otitis media is watchful waiting, symptom relief and no antibiotic treatment, unless a child is under 2 years of age with bilateral otitis media.
- The Committee endorsed the inclusion of amoxicillin as first-choice therapy and amoxicillin + clavulanic acid as second-choice therapy in suspected bacterial otitis media.

by the Expert Committee. First choices are in general narrow spectrum agents with a low toxicity risk. Second choices are broader spectrum antibiotics which might have an increased risk of toxicity or resistance selection and should be used when first choice options are not available.

A summary of the recommended first- and second-choice EML-listed antibiotics for 35 clinical indications considered by the Expert Committee to date (2019) is presented in Table 1.

For example, after reviewing the evidence for antibiotic treatment of otitis media, the Expert Committee recommended watchful waiting, symptom relief and no antibiotic treatment be considered as first-line treatment in most cases. Where antibiotics are indicated, the Expert Committee recommended amoxicillin as first choice and amoxicillin + clavulanic acid as second choice (Box 5).

Selected Reserve group antibiotics are included on the Model Lists for the treatment of infections due to multi-drug resistant organisms when they have a favourable risk-benefit profile and proven activity against “Critical Priority” or “High Priority” pathogens identified by the WHO Priority Pathogens List.⁶

Useful resources

- Full details of the review of antibiotic treatment for priority infectious syndromes can be found in the Technical Reports of the 2017 and 2019 meetings of the Expert Committee on Selection and Use of Essential Medicines. Access the reports (TRS 1006 and TRS 1021) at: http://www.who.int/medicines/publications/essentialmeds_committeereports/en/

Antibiotics included on the Model List represent a parsimonious, evidence-based selection of essential empiric treatment options for the clinical infection syndromes reviewed by the Expert Committee. They are a small proportion of all globally available antibiotics and should be prioritized for selection on national EMLs.

The AWaRe classification of antibiotics, however, extends beyond the antibiotics included on the Model List to 180 of the most commonly used antibiotics globally, including those listed on the Model List, to better support antibiotic monitoring and stewardship activities at country level.

Useful resources

- ▶ The AWaRe Classification Database can assist policy makers in adopting AWaRe as a tool to support setting performance targets and guide optimal use of antibiotics at country level and inform the development of antibiotic treatment guidelines.
- ▶ The database can be downloaded from: <https://apps.who.int/iris/bitstream/handle/10665/327957/WHO-EMP-IAU-2019.11-eng.xlsx>



Practice point

When considering antibiotics for inclusion on the NEML, the Selection Committee is encouraged to adopt the Model List's approach to specifying the indications for which the medicines are recommended as essential first- and second-choice treatment selections and the AWaRe categorization.



Practice point

The AWaRe categorization takes into account the impact of different antibiotics on antimicrobial resistance. It is a useful tool for monitoring antibiotic consumption, defining targets and monitoring the effects of stewardship policies that aim to ensure optimal antibiotic use and curb antimicrobial resistance.

The WHO 13th General Programme of Work 2019-2023 includes a country-level target of at least 60% of total antibiotic consumption being Access group antibiotics.

This AWaRe-based indicator is intended to monitor access to essential medicines and progress towards universal health coverage. It also serves as a common global target to reduce AMR.

Category 1C: Cancer medicines

Medicines used as part of cancer treatment regimens are listed on the Model List with the indications for which they are considered essential and deliver a clinically relevant benefit. This listing approach followed a comprehensive review of the cancer medicines chapter in 2015 and ongoing work in 2019. The guiding principles adopted by the Expert Committee in considering cancer medicines for inclusion on the EML have ensured that the most treatable tumours and the medicines required to treat them were identified and recommended as essential.

Guiding principles for inclusion of cancer medicines on the WHO Model List

- ▶ consideration must be given to the magnitude of clinical benefit associated with treatment. The observed benefit must be clinically meaningful, patient-relevant and of public health relevance:
 - a threshold for benefit of at least 4-6 months survival gain must be met for new cancer medicines to be considered for EML inclusion;
 - ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) scores should be taken into consideration for new cancer medicines. To be eligible for EML consideration, cancer medicines should have a ESMO-MCBS score of A or B in the curative setting and of 4 or 5 in the non-curative setting.
- ▶ a decision to include a cancer medicine on the Model List must be supported by clinical evidence of comparative efficacy and safety, with due attention given to the overall quality of evidence:
 - clinical data from more than one trial is required;
 - data from high quality randomized trials is considered the most important, and must be mature in order to adequately assess the impact of the medicine on overall survival, and to show consistent results across different trials;
 - randomized trials should compare efficacy of new regimens to current best standard of care, rather than to available but sub-optimal comparators;
 - trials that define the need for and length of maintenance therapy can be informative. Shorter treatment durations that compromise efficacy only

marginally or not at all may substantially reduce outlays and allow more patients access to treatment;

- ▶ consideration should be given to disease stage and line of therapy. The efficacy of cancer medicines is usually less in more advanced stages of disease, and when used in advanced lines of treatment. Medicines that are effective in the first-line treatment setting are more clinically meaningful and therefore highly desirable;
- ▶ consideration must be given to the overall feasibility of treatment, including diagnostic, testing and monitoring requirements, care requirements (including management of adverse effects) and cost.

Useful resources

- ▶ The ESMO-MCBS Scale may be used as a screening tool to identify cancer treatments that have therapeutic value sufficient to be considered for inclusion on the NEML. More information, including score cards for new cancer medicines is available at: <https://www.esmo.org/Guidelines/ESMO-MCBS>

The EML Expert Committee has reviewed treatment regimens for 40 specific cancers in both adults and children. The individual cancers reviewed have been those with high incidence whose treatment produces a clinically relevant survival benefit, and cancers (irrespective of incidence) for which the goal of treatment is cure or long-term remission. A summary of the EML-listed cancer medicines and the specific cancers for which they have been recommended as essential is presented in Table 2.

TABLE 2. EML-listed cancer medicines by cancer type (2019)

	arsenic trioxide	asparaginase	bendamustine	bleomycin	calcium folinate	capecitabine	carboplatin	chlorambucil	cisplatin	cyclophosphamide	cytarabine	da carbazine	daclotromycin	daunorubicin	docetaxel	doxorubicin	etoposide	fludarabine	fluorouracil	gemcitabine	hydroxycarbamide	ifosfamide	irinotecan	melphalan	mercaptopurine	methotrexate	oxaliplatin	paclitaxel	pegaspargase	procarbazine
Acute lymphoblastic leukaemia		•							•	•			•		•	•									•	•			•	
Acute myeloid leukaemia										•				•																
Acute promyelocytic leukaemia	•									•			•													•	•			
Burkitt lymphoma						•			•	•						•	•													
Cervical cancer							•		•																			•		
Chronic lymphocytic leukaemia			•					•	•									•												
Chronic myeloid leukaemia																					•									
Chronic myeloid leukaemia (imatinib-resistant)																														
Diffuse large B-cell lymphoma										•						•														
Early stage breast cancer							•		•						•	•			•							•		•		
Early stage breast cancer (HER2 positive)																														
Early stage colon cancer						•	•												•								•			
Early stage rectal cancer						•	•												•											
Epithelial ovarian cancer							•														•							•		
Ewing sarcoma										•						•	•					•								
Follicular lymphoma			•							•						•														
Gastrointestinal stromal tumour																														
Gestational trophoblastic neoplasia						•			•			•					•									•				
Head and neck cancer								•																						
Hodgkin lymphoma			•						•	•						•	•												•	
Kaposi sarcoma			•													•												•		
Metastatic breast cancer						•			•						•	•												•		
Metastatic breast cancer (HER2 positive)																														
Metastatic castration-resistant prostate cancer																														
Metastatic colorectal cancer						•	•													•				•			•			
Metastatic melanoma																														
Metastatic prostate cancer															•															
Multiple myeloma										•						•									•					
Nasopharyngeal cancer							•		•											•								•		
Nephroblastoma													•			•														
Non-small cell lung cancer							•		•								•				•							•		
Non-small cell lung cancer (EGFR mutation positive)																														
Osteosarcoma						•	•		•							•							•			•				
Ovarian germ cell tumours				•					•								•						•				•			
Retinoblastoma							•										•													
Rhabdomyosarcoma									•			•											•							
Testicular germ cell tumours				•				•									•						•							
Febrile neutropenia (prophylaxis)																														
Tumour lysis syndrome																														
Malignancy-related bone disease																														

Adapted from the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children (2019).

The cancer medicines listed on the Model List represent just a small proportion of the total number of cancer medicines approved and marketed worldwide. This limited selection of cancer medicines on the Model List supports national policy makers and programme managers to distinguish cancer medicines that should be prioritised for national listing and procurement, from those which provide marginal or no benefit.

Useful resources

- Full details of the reviews of treatment regimens for specific cancers can be found in the Technical Reports of the meetings of the Expert Committee on Selection and Use of Essential Medicines. Access the reports at: http://www.who.int/medicines/publications/essentialmeds_committeereports/en/



Practice point

When considering cancer medicines for inclusion in the NEML, the Selection Committee is encouraged to adopt the Model List's approach to specifying the indications for which the medicines are recommended as essential. It is necessary to consider the full treatment regimen for each cancer, which usually involves multiple medicines.

Category 2: Medicines that have been evaluated but not recommended for listing, or that have been deleted from the Model List

It is important to note that only medicines that were recommended for inclusion by the Expert Committee appear on the Model List. Medicines that were deleted, rejected or for which recommendations were deferred are not reported on the Model List. Information about medicines considered and deleted, rejected or deferred is covered in the technical reports of the Expert Committee.

Useful resources

- Medicines that have been deleted from the Model List can be tracked using the EML history database. The database links to the relevant technical reports for information on the Expert Committee's recommendation to delete. The database can be downloaded from: <http://apps.who.int/iris/bitstream/handle/10665/278038/WHO-MVP-EMP-IAU-2019.01-eng.xls>

Countries should identify whether medicines being considered for NEML selection were rejected by the Expert Committee. If a medicine that has been considered by the Expert Committee and not recommended for the Model List is considered for inclusion on the NEML, the national Selection Committee should conduct an evaluation with due regard to national priorities and relevant evidence. Reviewing the application presented to the Expert Committee and reasons for the decision not to include it on the Model List may help in the assessment at national level.

Useful resources

- ▶ A searchable, interactive online database of the Model List is in development and is scheduled for launch in 2019. This will include all medicines recommended and rejected by the Expert Committee.
- ▶ The WHO EML Secretariat can assist countries with information about whether particular medicines have been considered and rejected for inclusion on the Model List.

When a national Selection Committee decides to include on the NEML a medicine that has been evaluated and rejected for inclusion, or deleted from the Model List, justification for the decision should always be reported, including a description of the evidence evaluated and its interpretation. A balanced review of the available evidence on the size and likelihood of benefits and harms is usually the key to making the right judgement. Selection Committees have a moral and scientific duty to evaluate all the available data and to come to an informed decision.



Practice point

Medicines rejected by the WHO Model List can provide important insight into what may not be relevant for patients and health-care systems, and should not be prioritized for selection on NEMLS. When a Selection Committee uses a different evidence base, the Committee should clarify the most important studies contributing to deliberations, explicitly distinguishing differences in studies selected for review and their interpretation compared with the evidence base used by the WHO Expert Committee.

Category 3: Medicines that have not been considered by the WHO Expert Committee

Medicines that have not been considered by the WHO Expert Committee should undergo a full evaluation by the Selection Committee. They can be categorized into the following groups:

- ▶ new, recently approved medicines for which more limited evidence is available (e.g. original clinical trial); and
- ▶ older medicines for which a substantial evidence base exists (e.g. multiple clinical trials, systematic reviews and meta-analyses).

It is important to recognize that before any new medicine is labelled as essential, it must go through extensive clinical research to demonstrate the benefits associated with its use.

The safety and efficacy of potential new medicines should preferably be investigated in multiple clinical trials. A single study, particularly when it provides evidence of benefit on surrogate outcomes, might be sufficient to grant regulatory or marketing approval for a medicine, but usually does not provide compelling evidence to list a medicine as essential. Consequently, when a new medicine is approved, its risk–benefit ratio is often poorly defined.

In some cases, the ability to evaluate effectiveness for relevant long-term outcomes is limited, particularly for newly approved medicines where approval was based on studies with small patient numbers. Such medicines might represent a lower priority for the Selection Committee and could be

considered at a later date, when (and if) better data become available. Furthermore, postponing evaluation of such medicines at national level may be an option if the WHO Expert Committee is expected to evaluate the same medicine within the context of the WHO Model List, to avoid duplicating effort.



Practice point

General recommendations for using existing studies in deciding selection of essential medicines include the following:

- ▼ Do not rely only on studies' conclusions, but also examine quantitative results such as effect estimates and assess their coherence with interpretation.
- ▼ Rely on pre-specified and relevant primary outcomes.
- ▼ Comment on the relative and absolute effect sizes and nature of benefits and harms.
- ▼ Examine components of composite outcomes, prioritizing single estimates of hard outcomes such as mortality;
- ▼ Do not use a subgroup analysis as a basis for recommendations unless pre-specified and strongly supported by findings.
- ▼ Consider also the extent to which the evidence reported is applicable to the national setting.

After having reviewed and summarized the best available evidence, the Selection Committee should make a recommendation to list or not list the candidate medicine. To ensure transparency of the process, a report of the committee's deliberations and deci-

sions should be prepared. For each medicine considered, the report should include the committee's decision either for or against inclusion, with a concise statement about the main reason(s) supporting the decision. The committee's assessment of the strength or quality of evidence, the consistency of findings across studies in different settings, the applicability and feasibility of use in the local setting, cost-effectiveness, costs and expected budget impact should also be reported. In the case of a medicine not recommended for inclusion, the report should highlight the reason(s) for such a decision, for example where there is a lack of evidence; evidence for a lack of effect (note that lack of evidence and evidence for a lack of effect are two different concepts); or another issue such as applicability, acceptability, feasibility or cost.



Practice point

When adding a medicine that has NOT been evaluated for inclusion on the WHO Model List, the Selection Committee should undertake a full assessment and critical appraisal of available evidence. The amount of available evidence will differ depending on whether the medicine is a newly approved medicine, for which only limited clinical data are available, or an older medicine, for which there may be considerable clinical data (e.g. multiple clinical trials, systematic reviews and meta-analyses).

Key considerations include the following:

- ▼ Is there sufficient evidence, in terms of quality and applicability, to form a judgement?

- ▼ What is the estimated magnitude of effect and associated measure of uncertainty (i.e. confidence intervals)?
- ▼ Is the evidence applicable to the national population and needs and feasible within the national health-care system?

For medicines that have not been considered by the WHO Expert Committee, the national Selection Committee might consider deferring a decision, referring evaluation to the WHO EML Secretariat.

The WHO EML Secretariat welcomes feedback on medicines that have not been evaluated by the Expert Committee, but are seen as priority medicines for countries. This feedback can inform future priorities for the Model List. It is important that efficient processes be in place for transferring the burden of evaluation of these medicines from countries to the WHO EML Secretariat, so that country decisions can be supported.

Useful resources

- ▼ The WHO EML Secretariat is available to support countries and their national Selection Committees. Contact the EML Secretariat via email at: emlsecretariat@who.int

Practice point

Selection Committees may use different criteria for decision-making. Common, important criteria may include:

- ▼ consideration of comparative benefits and harms of a medicine proposed for inclusion versus other

interventions (e.g. the currently listed option, usual care or no intervention);

- ▼ the extent to which a proposed medicine represents a clinically meaningful advance in therapy or prophylaxis in terms of efficacy, safety and/or ease of use;
- ▼ the potential total cost and budget impact, including cost per cure to the health insurance or government health budget;
- ▼ assessment of the cost-effectiveness of a medicine, based on confidence in estimates of clinically meaningful benefits and harms;
- ▼ the scope for use of the medicine beyond any restriction for use or subsidy and hence the risk of diversion from the intended use;
- ▼ the potential for adverse outcomes arising from availability with subsidy (e.g. it may be prudent to limit subsidized access to certain antibiotics to limit the development of resistant organisms);
- ▼ clinical need, particularly for conditions for which there are no, or few, treatment options; and
- ▼ the affordability of the medicine for patients in the absence of coverage or subsidy.

4. Relationship with treatment guidelines

4.1. Linking selection to guidelines

Ideally, the recommendations of national treatment guidelines should be aligned with the selection of essential medicines and vice versa. If a medicine is listed as an essential medicine, it is likely that the same medicine is considered by the local guideline development group within the key proposed recommendations. Ideally the information and reasons that support the inclusion of the medicine in the Model List or NEML should be used as an evidence base for guideline recommendations.

Early planning is essential to identify how the guideline will be updated to expand recommendations to include new NEML deliberations and data that support these deliberations. Significant new evidence on effectiveness, safety or a change in costs should be considered if the medicine falls within the scope of the guideline. When possible, staff from the Selection Committee and guideline development group should discuss together how to better revise and discuss evidence, agreeing on appropriate actions. For multiple

medicine appraisals, the Selection Committee and guideline development group should consider working together to ensure that there is no unnecessary duplication of effort and that the appraisal and decisions are fully consistent.



Practice point

Modifying an NEML should involve consultation with the relevant stakeholders in charge of developing related treatment guidelines.

The NEML and related guidelines should be aligned in terms of methodology and outcomes. Adopting common standards between guidelines and NEMLs in evidence evaluation and managing conflicts of interest should be a shared responsibility.

The adoption of published guidelines should be accompanied by adaptation to local contingencies and critically appraised for methodology.

5. Applying the Model List's square box concept to selection at national level to support procurement strategies

Markets are filled with thousands of medicines: many are generic or biosimilar duplicates or similar pharmaceutical analogues of others, and offer only minimal, if any, additional clinical benefit. It is unrealistic to think that any public sector or health insurance system could afford to supply or reimburse every available medicine. Consequently, it is important to have systems to facilitate selection of a limited number of essential medicines from the plethora of pharmaceuticals available on the market.

The same principle of limited selection of essential medicines can also be applied to medicines within a pharmacological class and can help to improve access and deliver better value procurement through competitive tendering.



Practice point

Selecting a single medicine from within a pharmacological class of therapeutically equivalent medicines can result in better value procurement, improved access and more rational prescribing.

Where reimbursement systems are in place, a wider range of comparable medicines may be covered, with a maximum reimbursement price stipulated. Nonetheless, the potential impact on out-of-pocket payments needs to be considered.

The WHO Model List uses the “square box” concept as a means of indicating that medicines within a pharmacological class can be considered therapeutically equivalent. The presence of a square box alongside a medicine in the Model List indicates that the listed medicine is a representative of the pharmacological class to which it belongs and that other medicines within that class can be assumed to be therapeutically equivalent in terms of efficacy and safety.

A square box listing on the Model List is intended to signal to countries that they are at liberty to select a medicine (or medicines) from within the pharmacological class that best suits local needs, based on availability and resources, for inclusion on the national list. However, this mechanism can also be

used to identify options for reimbursement, where procurement is not relied upon.

5.1. Unrestricted and restricted square box listings on the Model List

In most cases, square box listings on the WHO Model List are unrestricted. That is, there is no qualifying note or recommendation to limit the choice of medicine within the pharmacological class. For example, omeprazole appears on the WHO Model List with a square box as representative of the pharmacological class of proton pump inhibitors (PPIs). In deciding whether to include a PPI on an NEML, the Selection Committee can consider the other PPIs within this class and select the most appropriate one for the national setting. This may or may not be omeprazole.

In some circumstances, a square box listing on the WHO Model List may be qualified by a note to indicate that acceptable alternatives within the pharmacological class are restricted to specific medicines. These qualifying notes may be recommended by the Expert Committee when there is evidence to suggest within-class differences between medicines, or when there is limited clinical evidence for some medicines in the class. For example, the Model List includes enoxaparin with a square box as the representative low-molecular-weight heparin, and restricts alternatives to nadroparin and dalteparin. The absence of sufficient evidence on the relative efficacy of other agents in this pharmacological class in conditions other than prevention or treatment of ve-

nous thrombosis drove this decision by the Expert Committee.

Restricted square box listings aim to inform and support rational, evidence-based medicine selection decisions at country, regional or hospital level, and tacitly discourage selection of unspecified medicines.

5.2. Identifying therapeutically equivalent medicines

Restricted square box listings on the Model List clearly specify the alternative medicines determined by the Expert Committee to be therapeutically equivalent. Countries should make their selection from among the specified medicines.

For unrestricted square box listings on the Model List, therapeutically equivalent alternatives are not specified, but can be determined using the ATC classification system. In addition to its application for drug utilization studies, the ATC classification system for medicines can be used to identify therapeutically equivalent medicines and can help inform medicine selection decisions at national or regional level.

The ATC classification is a five-level system that classifies medicines according to the anatomical system on which they act, and their therapeutic, pharmacological and chemical properties. The fifth level identifies individual medicines with a unique code. Individual medicines within a pharmacological class with an assigned defined daily dose (DDD) represent the alternatives from which selection can be made when a medicine from that class is listed with a square box on the WHO Model List.

Some examples of medicines listed on the Model List with a square box (unrestricted and restricted) and their therapeutically equivalent alternatives for the purposes of national selection are shown in Table 3.



Practice point

The fourth-level ATC classification can be used to identify the pharmacological class represented by a medicine listed with a square box on the WHO Model

List. The corresponding fifth-level ATC classification lists the individual medicines that can be considered as suitable alternatives for selection at national, regional or hospital level. Recognition of therapeutic equivalence should be a guiding principle for pooled procurement and tendering at national, regional or hospital level, and can result in significant savings.

TABLE 3. **Square box listings on the WHO Model List and therapeutically equivalent alternatives for national selection**

Square box listing on the WHO Model List	Alternatives for selection	ATC code	DDD (RoA)
EXAMPLES OF UNRESTRICTED LISTINGS			
Omeprazole Representative of the pharmacological class of PPIs	Omeprazole	A02BC01	20 mg (O); 20 mg (P)
	Pantoprazole	A02BC02	40 mg (O); 40 mg (P)
	Lansoprazole	A02BC03	30 mg (O)
	Rabeprazole	A02BC04	20 mg (O)
	Esomeprazole	A02BC05	30 mg (O); 30 mg (P)
	Dexlansoprazole	A02BC06	20 mg (O)
Enalapril Representative of the pharmacological class of ACE (angiotensin-converting-enzyme) inhibitors	Captopril	C09AA01	50 mg (O)
	Enalapril	C09AA02	10 mg (O); 10 mg (P)
	Lisinopril	C09AA03	10 mg (O)
	Perindopril	C09AA04	4 mg (O)
	Ramipril	C09AA05	2.5 mg (O)
	Quinapril	C09AA06	15 mg (O); 15 mg (P)
	Benazepril	C09AA07	7.5 mg (O)
	Cilazapril	C09AA08	2.5 mg (O)
	Fosinopril	C09AA09	15 mg (O)
	Trandolapril	C09AA10	2 mg (O)
	Spirapril	C09AA11	6 mg (O)
	Delapril	C09AA12	30 mg (O)
	Moexipril	C09AA13	15 mg (O)
	Temocapril	C09AA14	10 mg (O)
	Zofenopril	C09AA15	30 mg (O)
	Imidapril	C09AA16	10 mg (O)

Square box listing on the WHO Model List	Alternatives for selection	ATC code	DDD (RoA)
EXAMPLES OF RESTRICTED LISTINGS			
Morphine (Alternatives are limited to hydromorphone and oxycodone).	Morphine	N02AA01	0.1 g (O); 30 mg (P); 30 mg (R)
	Hydromorphone	N02AA03	4 mg (R); 4 mg (P); 20 mg (O)
	Oxycodone	N02AA05	30 mg (P); 75 mg (O)
Erythropoiesis-stimulating agents (The square box applies to epoetin alfa, beta and theta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta, and their respective biosimilars).	Erythropoietin <i>Epoetin alfa</i> <i>Epoetin beta</i> <i>Epoetin theta</i>	B03XA01	1 TU (P)
	Darbepoetin alfa	B03XA02	4.5 mcg (P)
	Methoxy polyethylene glycol-epoetin beta	B03XA03	4 mcg (P)
	Enoxaparin (Alternatives are limited to nadroparin and dalteparin).	Enoxaparin	B01AB05
Dalteparin		B01AB04	2.5 TU (P)
Nadroparin		B01AB06	2.85 TU (P)

RoA = route of administration; O = oral; P = parenteral; R = rectal; TU = therapeutic unit.

6. Monitoring utilization and expenditure on essential medicines

6.1. Using medicines utilization and expenditure data to support decision-making

Medicines utilization and expenditure can be used to increase understanding of how medicines are being used in practice and to prioritize interventions. These approaches have been applied to:

- ▼ describe overall expenditure using top 20 medicines products by sales as a driver of priority setting to increase fair spending;
- ▼ describe the extent of use of a medicine or group of medicines and trends over time;
- ▼ examine patterns of medicine use and the extent to which alternative medicines are being used within a class;
- ▼ compare patterns of medicine use for the treatment of a certain disease with current recommendations or guidelines;
- ▼ provide feedback to prescribers on their prescribing practices compared with other similar prescribers or compared with national averages;
- ▼ relate the number of case reports about a medicine's adverse effects to the number

of patients exposed to assess the potential magnitude of the problem; and

- ▼ evaluate regulatory effects on prescribing patterns.



Practice point

Analysis of medicines utilization and expenditure can be useful in providing information about whether medicines use aligns with expected population health needs, whether spending on medicines is within budget and in identifying medicines which are responsible for the largest budgetary impact.

Medicines utilization analysis is an important tool in supporting decision-making for essential medicines selection: to assess appropriate and intended use, identify medicines with high rates of use, predict budgetary effects of new listings and review the effects of previous decisions to list.

Medicines expenditure and its proportion of the health-care budget are important public health indicators for UHC programmes at

country level. Medicines expenditure and the medicines responsible for the majority of expenditures should be easily identified and can inform reviews and ensure optimal coverage.



Practice point

Top 20 lists of medicines by volume and/or expenditure can be a useful starting point in identifying priority actions of a national Selection Committee.

Medicines utilization studies typically use the ATC classification system and the DDD as a unit of measurement. The ATC/DDD methodology facilitates the presentation and comparison of medicines consumption statistics at international, national and regional levels despite differences in nomenclature (both branded and generic), packing sizes, pricing and customary dosages.

Useful resources

- WHO endorses the ATC and DDD methodology as the gold standard for drug utilization monitoring and research. WHO has produced an ATC/DDD Toolkit that is a comprehensive online resource, available at: <http://www.who.int/medicines/regulation/medicines-safety/toolkit/en/>

6.1.1. Measures of medicines utilization

Medicine utilization data are typically adjusted for population size, such as number of DDD per 1000 inhabitants per day. This provides a measure of exposure or therapeutic intensity in a defined population, allowing comparisons across various time periods and population groups. Other measures such as DDD per inhabitant per year or DDD per 100 bed-days, can be used depending on the context.

6.1.2. Sources of medicines utilization/ expenditure data

A variety of sources of information at national, regional or local facility level can be used to derive medicines utilization data. These sources include:

- sales data obtained from importers, wholesalers or local manufacturers;
- dispensing data from reimbursement systems (claims data) or computerized pharmacies;
- health facility data: e.g. hospital consumption data; and
- procurement data: e.g. from national medicines stores or hospitals.



Practice point

The ATC/DDD classification is a dynamic system that provides annual updates to both ATC codes and assignment of DDD values. When producing and presenting longitudinal trends in utilization and expenditure data, it is important that the data for different years all be presented using the latest ATC/DDD version.

6.2. Practical applications

Evaluating top-selling and top-used drugs

A study of highest expenditure on medicines, usually starting with top 20 drugs by expenditure, can offer meaningful insights on the overall quality of prescribing practice. This will require access to financial records on medicines purchases at national, regional, local or facility level. High levels of expenditure on medicines not on the priority list should be investigated further.

The ATC/DDD methodology can be applied to determine highest volumes of use of

medicines. The list of top-used drugs in terms of quantity and exposure offers a very different perspective and may suggest areas requiring further investigation.

Monitoring antimicrobial medicines consumption

Antimicrobial monitoring is now a priority to reduce the burden of antimicrobial resistance and to inform programmes for more appropriate uses. WHO uses the ATC/DDD methodology to describe and summarize data on antimicrobial medicines consumption.

Useful resources

- Further details on the WHO methodology for a global programme on surveillance of antimicrobial consumption are available at: http://www.who.int/medicines/areas/rational_use/WHO_AMCsurveillance_1.0.pdf?ua=1

Deriving measures that reflect quality use of medicines

It has long been recognized that prescribers tend to use a limited formulary of medicines that covers the clinical needs of the majority of their patients. There will be situations when patient-specific factors and other comorbidities will affect usual treatment choices. This same principle can be applied to aggregate or population-level data where DDD data can be used to determine the number of different agents that comprise 75 or 90% of prescribing, often referred to as DU75% or DU90%. These metrics can be applied at the level of class of drug, for example which NSAIDs (non-steroidal anti-inflammatory drugs), ACE inhibitors or antibiotics are used. The medicines used in practice can then be compared with preferred medicine

choices, guideline recommendations, least expensive medicine choices and so forth.

Providing feedback to prescribers

Medicines utilization data can be fed back to prescribers. This is particularly useful when the prescribing patterns by a particular individual can be compared with some form of gold standard or best practice, and with the average prescriptions in the relevant country, region or area.

Comparing prescribing choices to guideline recommendations or prescribing protocols

An examination of medicines utilization data may indicate the extent to which medicines recommended in guidelines and prescribing protocols are actually being used in practice. Some medicines are specific for their indication (such as anti-diabetes drugs), whereas others may be used for more than one clinical indication. For example, medicines used in hypertension can also be used on other cardiovascular conditions such as heart failure, angina and arrhythmias. Medicines utilization data are good at determining volumes of use, though they are usually not helpful in defining the appropriateness of use in a specific patient. To monitor guidelines, it will be necessary to perform audits or cross-sectional studies.

Useful resources

- WHO has published a manual of methods for analysing drug utilization and expenditure as a tool to support countries in their evidence-based decision-making processes for selecting essential medicines at national, regional and facility level. The manual is available online at: <http://apps.who.int/iris/bitstream/handle/10665/274282/9789241514040-eng.pdf?ua=1>

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