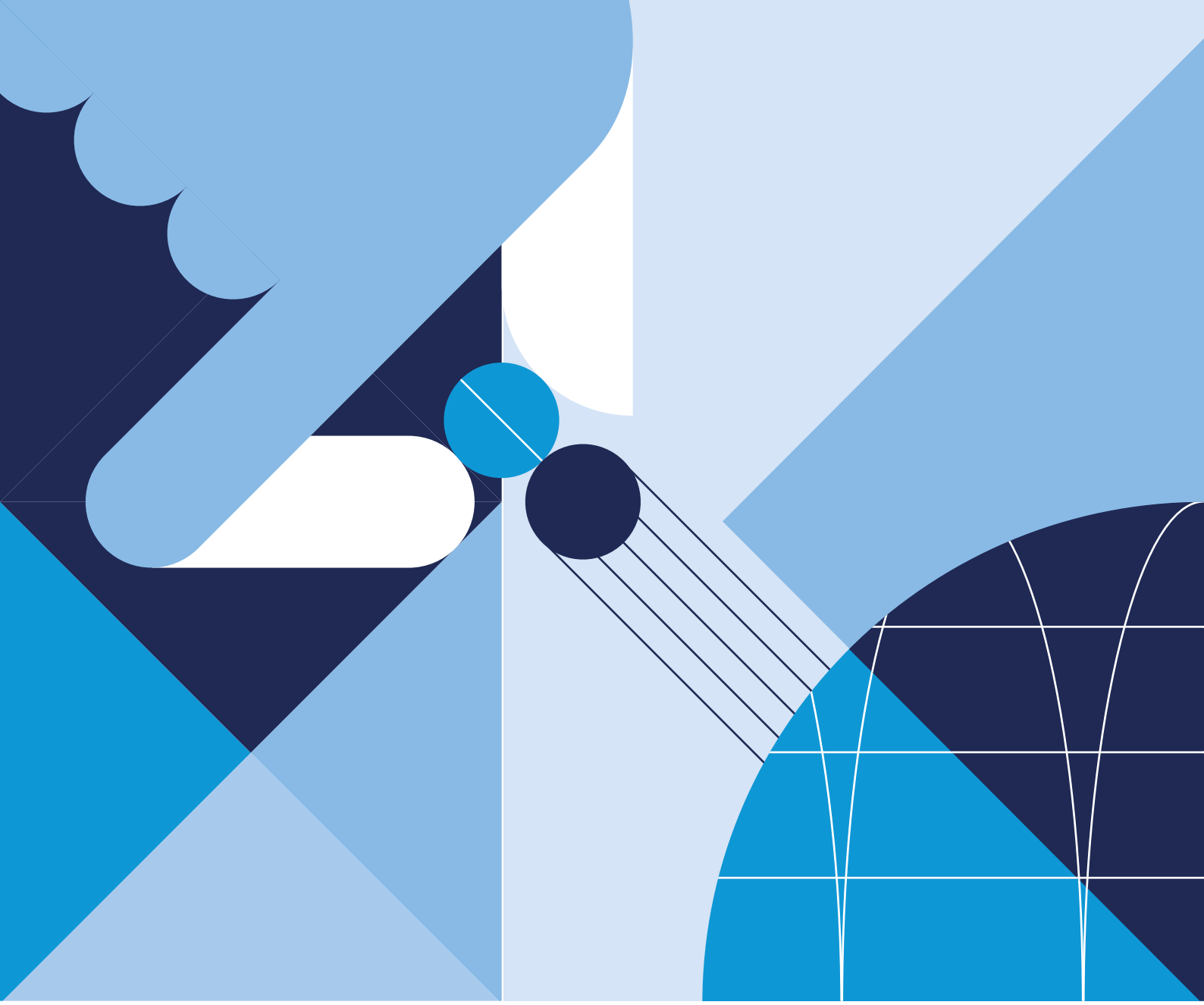

Policy and regulatory interventions to address antibiotic shortages in low and middle-income countries

GARDP

World Health Organization

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This document was prepared by

BCG (technical support), with contribution to all aspects by Kim Faure (SECURE Project lead, GARDP South Africa), Alexandra Cameron, Global Coordination and Partnership (GCP), AMR Division (AMR), WHO; Jennifer Cohn (Director Global Access, GARDP), Razieh Ostad Ali Dehaghi, Alireza Khadem Broojerdi, Regulation and Prequalification (RPQ), Access to Medicines and Health Products Division (MHP), WHO; Leslie Ong (Programme Specialist, Access and Delivery Partnership,HIV & Health Group, Bangkok Regional Hub, UNDP), Cecilia Oh (Programme Advisor, Access and Delivery Partnership, UNDP). Technical input was provided by the participants of the technical consultation:

- Alsayed, Najy (Menarini, Italy)
- Alimi, Yewande (Africa Centre for Disease Control, Ethiopia)
- Aboagye-Nyame, Francis (Management Sciences for Health, United States of America)
- Camara, Cheikh Sadibou (Agence sénégalaise de Réglementation pharmaceutique, Senegal)
- Chamdimba, Chimwemwe (New Partnership for Africa's Development, South Africa)
- Coulibaly, Koura (Agence sénégalaise de Réglementation pharmaceutique, Senegal)
- Custodio, Carolyn P. (Philippines Food and Drug Administration, Philippines)
- Desiere, Pieter-Jan (European Medicines Agency, Netherlands)
- Fafudi, Daphney (South African Health Products Regulatory Authority, South Africa)
- Hasbullah, Fadhilah (Malaysia National Pharmaceutical Regulatory Agency, Malaysia)
- Jamaloodien, Khadija K. (South African National Department of Health, South Africa)
- Kadir, Mdm. Salwati Abd. (Malaysia National Pharmaceutical Regulatory Agency, Malaysia)
- Kigen, Gloria (Kenya Mission for Essential Drugs and Supplies, Kenya)
- Khoo, Jacinda Mien Harn (Malaysia National Pharmaceutical Regulatory Agency, Malaysia)
- Ling, Dr. Phuar Hsiao (Malaysia National Pharmaceutical Regulatory Agency, Malaysia)
- Malhotra, Siti Kamilah (Malaysia National Pharmaceutical Regulatory Agency, Malaysia)
- Mucogo, Nerju Nancy (Kenya Ministry of Health, Kenya)
- Mugambi, Sabariah bt Pakeer Oothuman (Malaysia National Pharmaceutical Regulatory Agency, Malaysia)
- Mwalwisi, Yonah (Tanzanian Medicines and Medical Devices Authority, United Republic of Tanzania)
- Nik Salleh, Nik Shamsiah (Malaysia National Pharmaceutical Regulatory Agency, Malaysia)
- Nor, Noor Hidayah Mohd (Malaysia National Pharmaceutical Regulatory Agency, Malaysia)
- Poovan, Deon (South African Health Products Regulatory Authority, South Africa)
- Perrin, Jean-Baptiste (European Health Emergency Preparedness and Response Authority, HERA, Brussels)
- Querubin, Lanette Lee A. (Philippines Food and Drug Administration, Philippines)
- Rodríguez Alonso, Raquel (European Health Emergency Preparedness and Response Authority, HERA, Brussels)
- Srot, Luka (International Federation of Pharmaceutical Manufacturers & Associations - IFPMA, Switzerland)
- Sungusia, Victor (Tanzania Medical Stores Department, United Republic of Tanzania)
- Tay Szu Lynn, Charlene (Malaysia National Pharmaceutical Regulatory Agency, Malaysia)
- Zamudio, Melody M.(Philippines Food and Drug Administration, Philippines)

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Abbreviations

AMR	antimicrobial resistance
API	active pharmaceutical ingredient
ARP	Agency for Pharmaceutical Regulation
ASEAN	Association of Southeast Asian Nations
BCG	Boston Consulting Group
BfArM	Federal Institute for Drugs and Medical Devices
CHESSMEN	Coordination and Harmonisation of the Existing Systems against Shortages of Medicines – European Network
CMC	chemistry, manufacturing and controls
COVID-19	coronavirus disease 2019
EAC	East African Community
EMA	European Medicines Agency
EML	essential medicines list
EPICOR	Enterprise Resource Planning software used for resource planning EU European Union
EU	European Union
FDA	food and drug administration
GARDP	Global Antibiotic Research and Development Partnership
HCP	healthcare professional
HIC	high-income countries
LMIC	low- and middle-income countries
MAH	marketing authorization holder
Mfg	manufacturer
MSD	medical stores department
MSSG	Executive Steering Group on Shortages and Safety of Medicinal Products
NPRA	National Pharmaceutical Regulations Agency
NRA	national regulatory authority
PA	procurement agency
PPB	Pharmacy and Poisons Board
PQ	WHO prequalification
PTC	Pharmaceuticals and Therapeutics Committee
SAHPRA	South African Health Products Regulatory Authority
SRA	stringent regulatory authority
ToR	Terms of Reference
UNDP	United Nations Development Programme
USA	United States of America
WHO	World Health Organization
W&D	wholesaler and distributor
WLA	WHO listed authorities

Executive summary

Shortages of quality-assured antibiotics are a significant challenge to health systems and are a threat to combatting antimicrobial resistance (AMR). In high-income countries (HIC), antibiotic shortages have been a prominent political issue (1-3), mainly because of disruptions caused by the coronavirus disease 2019 (COVID-19) pandemic and geopolitical challenges. National regulatory authorities (NRAs) in several HIC have extended their mandates to find ways to anticipate and mitigate shortages.

In low and middle-income countries (LMIC), antibiotic shortages have, so far, received less attention. Several LMIC are, however, also experiencing shortages of various types of antibiotics and other drugs (e.g. cotrimoxazole in South Africa and cefazolin in India *(4)*) and have implemented measures to address them. As the health-care landscape evolves, antibiotic shortages are projected to become a greater concern in LMIC, and, as actual demand is better understood, gaps in the supply may become more obvious.

This document is based on a comprehensive review of measures initiated by NRAs in HIC, upper–middle-income countries and LMIC to address antibiotic shortages. A stepwise approach to addressing the problem, based on country contexts, is proposed.

The challenge of antibiotic shortages

Mitigating and preventing shortages are critical, as antibiotic shortages not only affect immediate treatment but have long-term consequences due to AMR. The types of shortages along the antibiotic chain include global shortages due to less attractive business cases for antibiotics and a fragile supply chain and national barriers, including unaffordable pricing or difficulty in accurate forecasting.

Antibiotic shortages in LMIC are often viewed as less urgent than in HIC, and only a few of the opinion leaders in LMIC who were interviewed recognized them as a major concern. This is due to gaps in available treatment being masked by a general higher frequency of stock-outs, and potentially, by the circulation of substandard or falsified medicines *(4)*. Certain measures are in place to combat shortages, but greater change is required. Many LMIC face persistent circulation of products of unknown quality, which do not meet NRA-approved quality requirements, and of falsified products, coupled with lack of stringent enforcement mechanisms and/or resources to stop their distribution.

As the health-care landscape evolves, antibiotic shortages are projected to become a larger concern in LMIC. Once effective enforcement mechanisms are in place, the market for substandard, unregistered and falsified products will be removed, and, with more information on actual demand, gaps in supply will become more obvious.

Definition: The WHO definition of medicine shortage is used in this document: “The supply of [approved and marketed] medicines, health products and vaccines identified as essential by the health system is considered to be insufficient to meet public health and patient needs”. This differs from stock-outs, which are defined as: “The complete absence of the medicine, health product or vaccine at the point of service delivery to the patient” *(5)*.

Multi-stakeholder action to reduce antibiotic shortages

Some HIC have extended the mandates of their NRAs to include the monitoring and mitigation of shortages of antibiotics and other drugs. Examples include establishment by the European Medicines Agency (EMA) of a Medicine Shortages Steering Group (MSSG) *(6)*, and, in the United States of America (USA), an executive order that gives more power to the Food and Drug Administration (FDA) *(7)* and the Coronavirus Aid, Relief, and Economic Security Act *(8)*.

In most of the LMIC consulted for this analysis, NRAs are not officially mandated to address shortages. Various measures to prevent major shortages in health-care systems have, however, been taken in LMIC by NRAs and other stakeholders, including ministries of health and procurement agencies. Although the project initially addressed only NRAs, its scope was broadened to include other stakeholders in the health system.

Four measures for addressing shortages of antibiotics

Measures to strengthen the basic capacities of NRAs are essential, including general registration and strengthening of quality assurance and enforcement. Countries have used four types of measure.

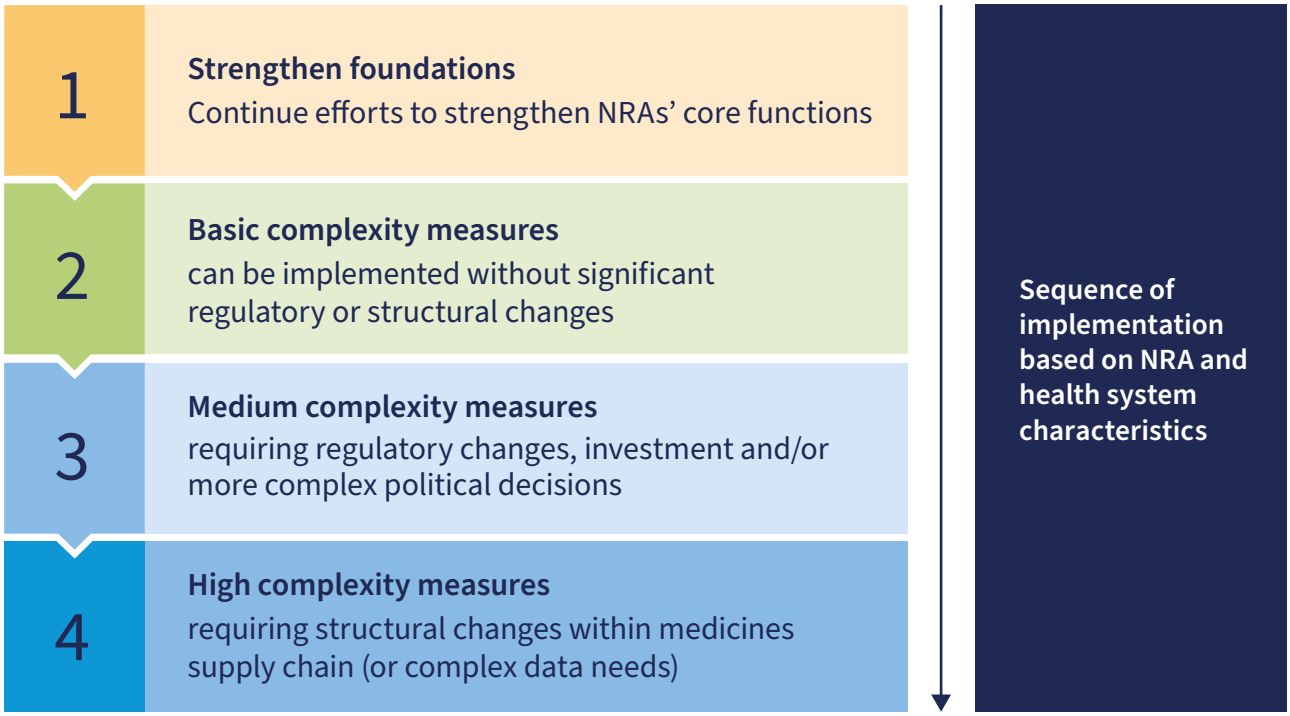
- Flexibility is necessary to address acute shortages, including of critical medicines. For instance, countries may react to shortages by temporarily allowing importation of products destined for other markets, allowing flexibility in expiry dates, package size, source of raw materials, the manufacturing site or temporary waiving of testing requirements. To increase supplies of substitute products, several countries identify alternatives and accelerate their approval.
- To strengthen sourcing of antibiotics that are often in short supply, measures such as a requirement to diversify suppliers or strengthening local manufacture of products have been used. NRAs, ministries of health or procurement officers also ensure the required buffer stocks, collaborate with manufacturers to increase the supply of products or create incentives for manufacturers to register such products. The feasibility of local production of antibiotics and further fragmentation of lots should be weighed against attempts to foster local production, which should be assessed on a case by case basis.
- To increase awareness of shortages, countries have established measures such as drawing up a register of shortages or mandating manufacturers to report upcoming shortages. More systemic measures include tracking and tracing systems to monitor demand and forecasting expected demand and supply. Such measures strengthen sourcing but require strong forecasting capability.
- Countries have also institutionalized collaboration through multi-stakeholder dialogue, providing guidance to health-care providers, a regional redistribution mechanism to exchange products and formation of a cross-sectoral stakeholder network for rapid action during emergencies. Long-term strategies include regional harmonization of regulatory requirements.

Way forward: a stepwise, country-specific approach

Local realities must be considered in assessing the impact and feasibility of implementation in LMIC. While NRAs might be able to assume accountability for some measures in HIC, they might not currently be equipped to do so in LMIC.

A stepwise approach to implementing measures to address antibiotic shortages is proposed, which should be tailored to the context of each country with respect to factors such as NRA capacity and health system infrastructure (Fig. 1).

Fig. 1. Stepwise approach to implementing measures to address antibiotic shortages



The first step is to strengthen the core functions of NRAs. Subsequent measures of basic complexity include policy implementation and structural changes or adjustments to existing regulatory systems, such as for procurement from private sector channels or flexibility in labelling. Measures of medium complexity include some regulatory changes and investment and more complex multi-stakeholder decision-making to improve the availability and quality of supplies, such as promoting high-quality local production and collaboration with manufacturers during a shortage. Highly complex measures require significant systemic changes to increase the visibility of products on the market by forecasting or track-and-trace systems (with high logistical hurdles and extensive financial and human resources) or harmonizing regulatory strategies in a region.

Addressing antibiotic shortages as a joint effort and catalyst

Addressing antibiotic shortages goes beyond ensuring a stable supply and is a driver of broader enhancements in global health. Successful strategies to reduce antibiotic shortages also support global health objectives, by managing shortages of all drugs, strengthening regulatory frameworks, promoting domestic pharmaceutical production, eliminating substandard and falsified drugs and strengthening supply chains and health-care systems overall.

Exchanges among countries and collaboration among regions will be critical to address shortages. The role of regional organizations such as the Africa Centre for Disease Control, Africa's regional economic communities and the Association of Southeast Asian Nations (ASEAN) in the prevention or mitigation of shortages should be further explored. Beyond work towards regional regulatory harmonization, these organizations could support countries in implementing measures in the areas identified in this report, including pooled procurement, joint communications with suppliers to identify and address shortages and sharing best practices such as digitalizing supply chains and building procurement systems.

Caveats: The measures taken depend on the type of shortage, as regulatory and policy interventions cannot resolve all kinds. Shortages, stock-outs and lack of availability of antibiotics may be due to inadequate investment in research and development (not in the scope of this report), global shortages due to consolidated manufacture and lack of understanding of actual demand.

Policy and regulatory measures contribute to preventing and mitigating shortages, particularly at national level. Global issues such as fragile supply chains and lack of investment in novel products must be addressed by a wider group of stakeholders.

This report is based largely on data from HIC, where NRAs typically manage shortages, and a wider group of stakeholders will be required in other countries.

The report addresses measures adopted by regulatory authorities and the policies of ministries of health in both HIC and LMIC. In view of the different mandates and capacities of NRAs in LMIC, a wider group of both national and international stakeholders should be involved for effective anticipation of shortages, without compromising the independence of NRAs.

Addressing shortages requires strengthening core NRA capabilities, such as accelerating regulatory approval and enforcing quality assurance.

1. Introduction

1.1 Context and objectives

Antibiotics are fundamental to modern medical practice; however, the development of AMR is increasing faster than that of new drugs. A study on the global burden of bacterial AMR, published in The Lancet in 2022 *(9)*, provides empirical evidence. In 2019, AMR was solely responsible for approximately 1.27 million deaths and contributed to about 4.95 million deaths worldwide. The study further showed that about 70% of AMR-related deaths were linked to resistance against first-line antibiotics that are crucial for treating severe infections. Most of the deaths were attributed to six bacterial pathogens with a significant impact in LMIC, suggesting a correlation between AMR, socioeconomic factors and poor access to health-care services and therefore to antibiotics. In an updated version of the study in the WHO African Region *(10)*, the findings were corroborated by the high level of AMR in Africa, with 1.05 million deaths associated with bacterial AMR and about 250 000 deaths attributable to bacterial AMR.

The availability of quality-assured antibiotics is critical for public health; however, shortages of antibiotics are a recurring issue. For instance, 25 of the 27 Member States of the European Union (EU) reported a scarcity of some antibiotics to the EMA in 2022 *(11)*. In a survey of 29 national pharmacist organizations in 2022, 79% of respondents reported shortages of anti-infective agents such as antibiotics during the past year *(12)*. The shortages were due to a combination of the post-pandemic surge in infections, fragile global supply chains, geopolitical shocks and the presence of only a few manufacturers or producers of active pharmaceutical ingredients (API), in China and India *(13)*.

Shortages are not, however, restricted to HIC. For example, a representative of the National Pharmaceutical Regulatory Agency in Malaysia reported a shortage of six antibiotics in May 2022, and South Africa has reported shortages of benzathine penicillin G since 2015 *(14)*, indicating that antibiotic shortages also affect LMIC *(4,15)*, which are less well covered by the media. Further examples are shortages of cefazolin and cloxacillin in India and a shortage of cotrimoxazole throughout Africa *(4,16)*.

In some HIC, NRAs have extended their role of implementing and enforcing policies to ensure drug quality and safety to proactive monitoring and management of drug shortages by measures such as mandatory reporting of shortages, supply chain mapping, planning responses to shortages and domestic stockpiling. NRAs also coordinate responses, establish shortage alert systems and facilitate alternative sourcing by issuing special import licenses.

This report explores whether the approach taken by HIC NRAs can be used in LMIC by NRAs and other authorities who manage antibiotic shortages. After a comprehensive review of current activities to address antibiotic shortages in both HIC and selected LMIC in Africa and South-East Asia, a set of measures is proposed to improve the effectiveness of management of antibiotic shortages in LMIC. In view of the fragility of health-care systems in many low-income countries, which have fewer measures to prevent antibiotic shortages (with several notable exceptions, such as Burkina Faso), the report is based mainly on measures used in middle- and high-income countries.

This report has been developed as part of the SECURE initiative, with contributions from UNDP and the WHO Regulatory Systems Strengthening team. SECURE is an initiative of the Global Antibiotic Research and Development Partnership (GARDP) and the World Health Organization (WHO) *(17)* to increase sustainable, equitable, appropriate access to quality-assured antibiotics. The antibiotic portfolio will be adapted to national public health and clinical needs and will include both existing and new antibiotics to which access has been limited by lack of affordability, recurrent shortages in the global supply chain and market challenges. SECURE works to improve the ability of low- and middle-income countries (LMIC) to anticipate and avoid antibiotic shortages. The Global Antibiotic Research and Development Partnership (GARDP) *(18)* is a Swiss not-for-profit organization, registered under the legal name GARDP Foundation, that accelerates the development of new treatments to fight drug-resistant infections while working to ensure responsible use and sustainable access. While originally focused on NRAs, the scope was broadened to include other actors in health systems, such as ministries of health and procurement agencies, in addressing shortages in the LMIC surveyed.

1.2 Methods

This report was developed by the Boston Consulting Group (BCG) under the joint guidance and leadership of the World Health Organization (WHO), the Global Antibiotic Research and Development Partnership (GARDP), and the United Nations Development Programme (UNDP).

The first phase of the project was collection of information through desk research, including a review of the academic and grey literature, websites and publications of NRAs, legislative documents and newspaper articles.

The literature search was conducted using the following databases: PubMed, Scopus, and Web of Science. Publications in English, published between January 2010 and July 2024, were included in the search. Search terms related to antibiotic shortages included “antibiotic shortages,” “antimicrobial resistance,” “drug supply chain,” “substandard medicines,” and “falsified medicines.” Inclusion criteria were studies focused on antibiotic shortages, their causes, impacts, and any mention of substandard or falsified medicines. Exclusion criteria included articles unrelated to antibiotics or those focusing exclusively on clinical treatments without reference to supply chain issues. A total of 150 articles were retrieved, 120 were screened, and 45 were included in the final review.

A similar search was conducted for grey literature using Google Scholar and relevant organizational websites, including the World Health Organization (WHO) and the Global Antibiotic Research and Development Partnership (GARDP). The grey literature search focused on reports, policy briefs, and conference papers published within the same time frame and included the same search terms. A total of 30 grey literature sources were retrieved, 25 were screened, and 15 were included.

In addition, 30 semi-structured interviews were conducted with representatives of organizations (e.g. NRAs, Ministries of Health) in selected countries undertaking work on antibiotic shortages. Countries were selected based on prior engagements with the contributing organisations and where the literature review indicated that they have conducted work on shortages. Effort was made to create a representative sample across HIC settings (European Union, the United States of America) and LMIC settings (Burkina Faso, Ghana, Kenya, Malaysia, The Philippines, Rwanda, Senegal and the United Republic of Tanzania). Interviews were also held with regional and global health authorities, research institutes, nongovernmental organizations, pharmaceutical manufacturers and procurement organizations. Ethical clearance was not deemed to be needed in light of the nature of the interview questions. The organizations that provided interviews are listed in Annex 1.

The objective of the interviews was to obtain details of proactive regulatory approaches to mitigate antibiotic shortages and to identify steps for building the necessary capacity. The desk review and analysis resulted in a preliminary list of measures to address shortages, which were presented to the interviewees for assessment and contextualization. Follow-up interviews were conducted to validate and complement the findings. Interview findings were thematically analyzed in order to categorize information and insights into broader themes that capture the overarching interventions undertaken to mitigate and prevent shortages.

To identify available measures to address antibiotic shortages, interview findings were triangulated with the findings of the desk review. A set of measures is proposed for consideration by countries, with each measure evaluated according to its anticipated impact and effort required for implementation. See section 4.1 for a detailed description of the considerations included as part of anticipated impact and ease of implementation, respectively.

WHO, UNDP and GARDP then held a technical consultation, in which participants developed and refined the priorities to be considered by regulatory and other stakeholders in LMIC. Participants were primarily representatives of national agencies and institutions, intergovernmental and non-governmental organizations, as well as industry representatives, all participating as representatives of their organization. For one participant, a Declaration of interest (DOIs) was collected and reviewed following WHO standard operating procedures; this participant did not disclose any interests.

2. Background: AMR and shortages of antibiotics

2.1 Threat of AMR

AMR jeopardizes human health and global health security. WHO has categorized AMR as one of the top 10 global health threats *(19)*. A study in 2022 showed that AMR directly caused 1.27 million deaths and was associated with 4.95 million deaths worldwide in 2019 *(9)*. AMR is therefore a leading cause of death globally, with the highest rates observed in sub-Saharan Africa and South Asia. The study highlighted the high burden of AMR in LMIC, where, despite lower per-person antibiotic consumption, the AMR rates are higher than in HIC *(20)*.

By 2050, AMR is expected to contribute over eight times more deaths than today, most occurring in sub-Saharan Africa and Asia *(9)*. Poor access to quality-assured antibiotics, lack of formal stewardship programmes and other challenges increase the AMR burden and death rates in LMIC *(9)*.

2.2 Global status quo of antibiotic shortages

Shortages of quality-assured antibiotics is an issue throughout Europe and North America, attracting significant media, which has resulted in its recognition as a critical concern by national and supranational public health authorities *(3,20–24)*.

Countries, especially HIC and countries such as Brazil and South Africa, have recently experienced severe shortages of antibiotics due largely to disruptions in the global supply chain. An example is the scarcity of amoxicillin in Europe and of benzathine penicillin G in South Africa since 2015 *(4,14,16)*. Shortages have also been experienced in Canada and India for amoxicillin, in India and Japan for cefazolin, in Canada and the EU for ceftolozane-tazobactam, in Canada, the EU, India and the USA for cloxacillin, and a shortage of cotrimoxazole throughout Africa *(4)*.

The susceptibility of antibiotics to shortages is due to many factors, such as the low economic return on the manufacture of antibiotics, which has reduced the number of producers and concentrated the production of APIs. The situation is exacerbated by volatile demand patterns, such as unpredictable spikes after COVID-19, which cannot be forecast accurately.

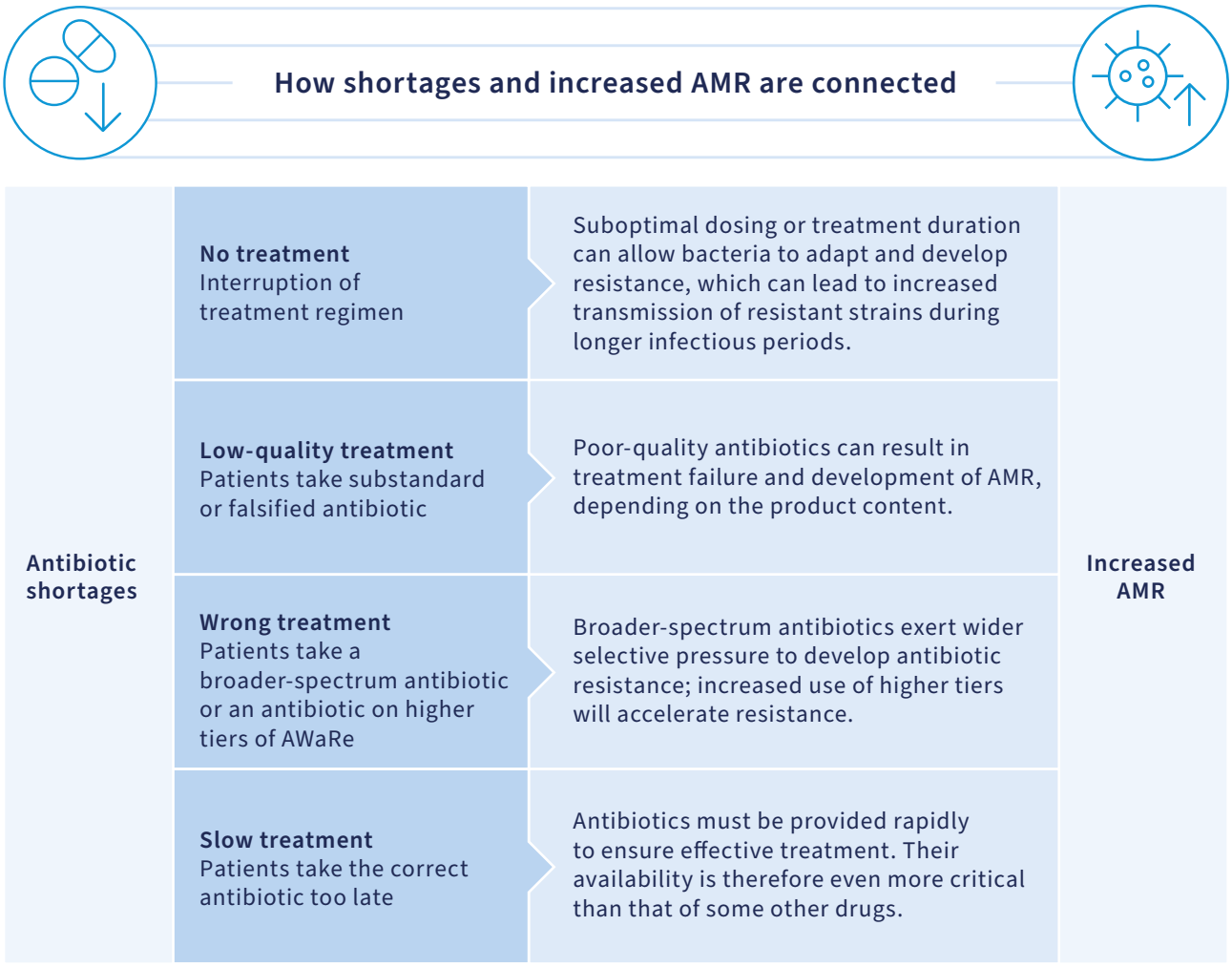
2.3 Antibiotic shortages and AMR

Mitigating and preventing shortages is critical, as they not only affect immediate treatment but have long-term consequences due to AMR *(4)*, such as when antibiotics are not available for treatment of illnesses such as pneumonia, diarrhoea and sepsis. Shortages can also result in incomplete or inappropriate treatment, including overuse of broad-spectrum antibiotics and prolonged infections, which can exacerbate AMR *(4)*. The risk is particularly high in Africa *(25)*, where the burden of bacterial infections and the prevalence of AMR are highest.

Antibiotic shortages accelerate AMR in various ways (Fig. 2):

- No treatment or interruptions in treatment regimens: Suboptimal dosing or treatment duration allow bacteria to adapt and develop resistance, leading to increased transmission of resistant strains over longer infectious periods.
- Poor-quality treatment of patients who take a substandard or falsified antibiotic: Poor-quality antibiotics can result in treatment failure and development of AMR, depending on the product content *(4)*. Treatment failure occurs when the API in drugs is inadequate to eliminate the bacterial infection.
- Wrong treatment of patients who take a broader-spectrum antibiotic or an antibiotic in higher tiers of the WHO AWaRe classification *(26)*: Use of antibiotics with a spectrum broader than that required can exert wide selective pressure, accelerating the emergence and spread of AMR. Furthermore, reliance on higher-tier antibiotics is not only more expensive but may reduce their effectiveness over time, creating a cycle of escalating resistance.
- Slow treatment of patients who take the correct antibiotic but too late: antibiotics must be provided rapidly to ensure effective treatment, making their availability even more critical than that of some other drugs.

Fig. 2. Antibiotic shortages contribute to AMR in various ways



Source: Access to Medicine Foundation *(21)*; US FDA *(27)*; Pulcini et al. *(28)*; Knowles et al. *(29)*; React Group *(30)*

The clear link between antibiotic shortages and exacerbation of AMR, especially in LMIC, highlights the urgency for action. If shortages of quality-assured antibiotics are not addressed, the effects will extend beyond individual patient health to global public health. The increase in AMR represents a significant global health challenge, necessitating immediate, coordinated action by NRAs, ministries of health in LMIC, suppliers and international health organizations *(31)*.

2.4 Types of antibiotic shortages and their drivers

While this report focuses on shortages of antibiotics, some of its recommendations also apply to stock-outs, given the close interrelation. WHO defines a shortage as follows:

- A "shortage" occurs when the supply of medicines, health products and vaccines identified as essential by the health system is considered to be insufficient to meet public health and patient needs. This definition refers only to products that have already been approved and marketed, in order to avoid conflicts with research and development agendas. *(5)*

Stockouts can occur locally as a result of shortages or other factors. WHO provides the following definition of a stock-out:

- The complete absence of the medicine, health product or vaccine at the point of service delivery to the patient. *(5)*

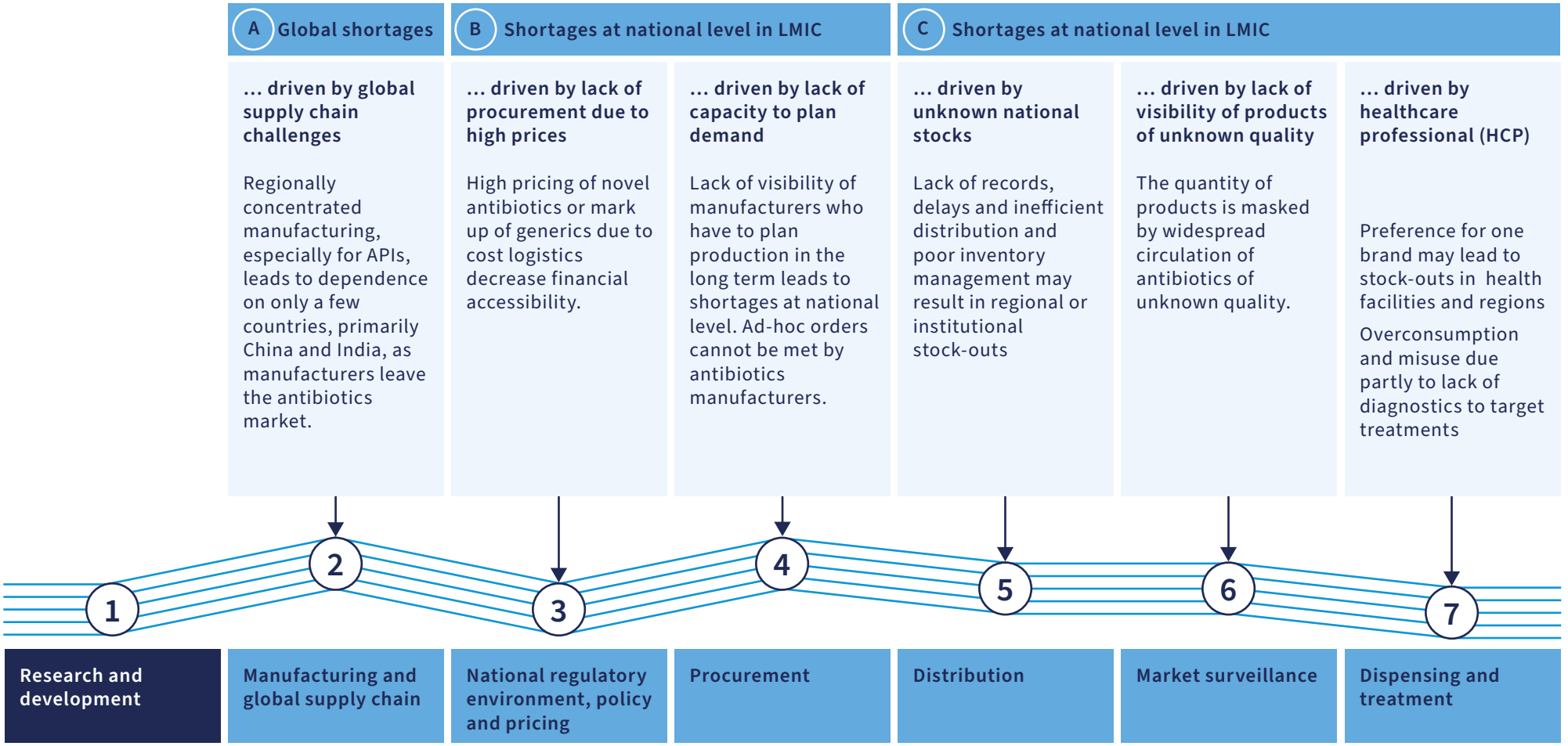
Shortages and stock-outs can arise at various points, each influenced by unique drivers and affecting different types of products. As illustrated in Fig. 3, there are three main categories of shortages in antibiotics: global, national and subnational.

Shortages in the global supply chain are due to concentrated, fragile supply chains for antibiotics (especially generics). Many antibiotics are produced by a very few manufacturers in China and India. Two scenarios are possible. First, new products may have few suppliers due to their small volumes. Secondly, low prices for generic product can result in concentration of suppliers. Further down the supply chain, shortages might arise because some major pharmaceutical companies have ceased marketing antibiotics altogether because of their low market attractiveness *(33)*.

Nationally, lack of access may be due to unaffordable prices for health systems or patients. The high prices of new, intellectual property-protected antibiotics often make them financially inaccessible in LMIC, given constrained health budgets. Even off-patent antibiotics may be unaffordable. In the public sector, high prices can result in little or no procurement. In the private sector, patients may be unable to afford a medication if out-of-pocket payment is required. Many countries lack the capacity for quantification, monitoring and forecasting to estimate demand for manufacturers, so that they can plan production. Antibiotics are produced in batches, which are carefully planned, and ad-hoc orders that require a switch of production lanes cannot be processed. Lack of information on the quality of products in circulation masks shortages of quality-assured products *(25)*. Because of limited monitoring and enforcement, many of the products in circulation are of unknown quality or are falsified. Available products may therefore not be quality assured.

At subnational level, stock-outs may be due to inefficient distribution of stock due to lack of proper surveys. These may result in regional or institution stock-outs *(5)* and delayed and inefficient distribution and inventory management, due, for example, to poor local infrastructure and transport networks.

Fig. 3. Types of shortages and stock-outs along the antibiotics value chain



Note: a shortage of a drug is defined as its lack of availability in the entire health system, while a stock-out is lack of availability at a point of care. Lack of availability due to the absence of research and development and of registration are not included, as this is not classified as a shortage.

2.5 Stakeholders

Ensuring that the right antibiotics reach the right patients at the right time is complex and requires collaboration among numerous stakeholders. NRAs in HIC have broadened their legislative mandates to include both the anticipation and mitigation of public health crises such as drug shortages. They are thus part of a larger group of stakeholders, whose roles vary from country to country but are essential to address antibiotic shortages.

NRAs

The remit of NRAs is primarily to oversee the regulation and supervision of pharmaceuticals and biological products and to ensure drug quality, safety and efficacy to protect the citizens of their country. While NRAs are independent entities in most countries, in others they are integrated into the ministry of health (e.g. in Egypt, Malaysia and the Republic of Korea).

Fig. 4 lists the core regulatory functions of NRAs, with a brief description by WHO, which include establishing a national regulatory system, registration and marketing authorization, vigilance, market surveillance and control, laboratory testing, oversight of clinical trials, lot release, licensing establishments and regulatory inspection. Some functions are more relevant for addressing drug shortages than others, including implementing and enforcing policies to maintain standards.

In some HIC or regions, NRAs have been directed to prevent and mitigate drug shortages through a legislative agency. For instance, in the USA, an executive order on drug shortages in 2011 directed the FDA to take additional steps, such as requiring manufacturers to provide advance notice of discontinuance of manufacture and accelerated regulatory review *(32)*. In Germany, a law passed in July 2023 strengthened the NRA's role in monitoring and mitigating drug shortages *(33)*. The EMA has taken various measures to prevent antibiotic shortages through its Executive Steering Group on Shortages and Safety of Medicinal Products (MSSG).

Fig. 4. Regulatory functions listed in the WHO Global Benchmarking Tool

	Overarching function: National regulatory system	• Provide framework to ensure quality, safety and efficacy of medical products. • Ensure accurate, relevant product information through competent oversight.
Functions with high relevance to address drug shortages	Registration and marketing authorization	• Evaluating, marketing authorization and registering medical products, especially these that are lacking, including alternatives, based on safety, efficacy and quality • Monitoring compliance and maintaining transparency of market authorization processes and decisions
	Licensing	• Issue and manage licenses for medical product facilities, wholesalers and distributors according to good manufacturing and distribution practices. • Maintain a public database of licensed products in the supply chain.
	Market surveillance and control	• Ensure that medical products on the market meet quality, safety and efficacy standards by continuous surveillance and import controls • Regulate and monitor medical product promotion to prevent falsified claims.
	NRA lot release	• Oversee lot release of biological products, ensuring their quality, safety and efficacy. • Implement lot release strategies for vaccines based on product characteristics and evidence of quality.
	Regulatory inspection	• Conduct inspections to enforce good practices throughout the medical product supply chain. • Manage quality control and decisions to establish licensing and product compliance.
	Vigilance	• Monitor and assess medical product safety to detect and prevent adverse effects. • Establish a reporting system for product-related issues and to harmonize vigilance activities.
	Laboratory testing	• Test the quality of medical products for market authorization and post-market surveillance. • Oversee laboratory operations, and ensure accurate reporting for regulatory decisions.
	Clinical trials oversight	• Authorize and monitor clinical trials for compliance with ethical and safety standards. • Review and approve trial protocols and data integrity.

Source: : WHO (31)

Stakeholders other than NRAs

Others are involved in securing the supply of antibiotics and addressing shortages (Fig. 5). They are particularly relevant in LMIC, as the NRAs in most countries do not address shortages.

- Ministries of health have an overarching role in policy-making and setting guidelines. They define essential medicines and guidelines for public drug procurement, develop treatment guidelines and policies on antibiotic use and resistance, allocate resources and funding for the procurement of antibiotics and oversee disease-specific public health programmes. Additionally, the ministry of health coordinates stakeholders to ensure a stable supply of high-quality antibiotics, to forecast and, often, to set drug prices.
- Procurement agencies are responsible for issuing tenders, purchasing drugs and managing stocks to prevent stock-outs. In some, the roles also include integrated services, such as storage and delivery. The structure of the procurement system may differ by country and health system. Public procurement agencies may also be responsible for public facilities, with private procurers for private, faith-based or not-for-profit health facilities and international donor-funded organizations.
- Ministries of finance allocate budgets for drug procurement and decide on extrabudgetary measures to address medicine shortages. The ministry may also be involved in tendering to ensure that it is free from corruption.
- Public and private payers determine rules for reimbursement of antibiotics, which influences their affordability and accessibility, and are sometimes involved in setting prices.
- Manufacturers produce antibiotics, either directly or through contract companies, ensuring a steady supply to meet market demand, and notify procurers and distributors of any disruptions.
- Customs offices and trade departments are responsible for inspecting and clearing imported antibiotics (according to requirements defined by the NRA), preventing the entry of falsified or substandard drugs and collecting relevant taxes and tariffs. They implement decisions on export restrictions related to shortages or waivers of import requirements decided by the NRA.
- Distributors and wholesalers facilitate the delivery of products and are responsible for transporting drugs to health facilities and pharmacies, ensuring proper storage and transport conditions and managing inventories to prevent shortages.
- Regional stakeholders, such as economic and political communities (e.g. Africa Centres for Disease Control, the East African Community [EAC], the Economic Community of West African States, ASEAN, EU), facilitate cross-border coordination of antibiotic supplies and regional regulatory harmonization.
- The recipients of antibiotics, including health facilities and pharmacies, administer antibiotics for patient care, manage stocks and storage conditions and order and monitor antibiotic use to prevent overuse and resistance. Pharmacies also dispense prescriptions for antibiotics and provide information and guidance to patients.

This network demonstrates the complexity and interdependence of the antibiotics supply chain, underscoring the necessity for coordinated efforts among the various stakeholders to anticipate and mitigate shortages.

Fig. 5. Network of stakeholders relevant to addressing antibiotic shortages

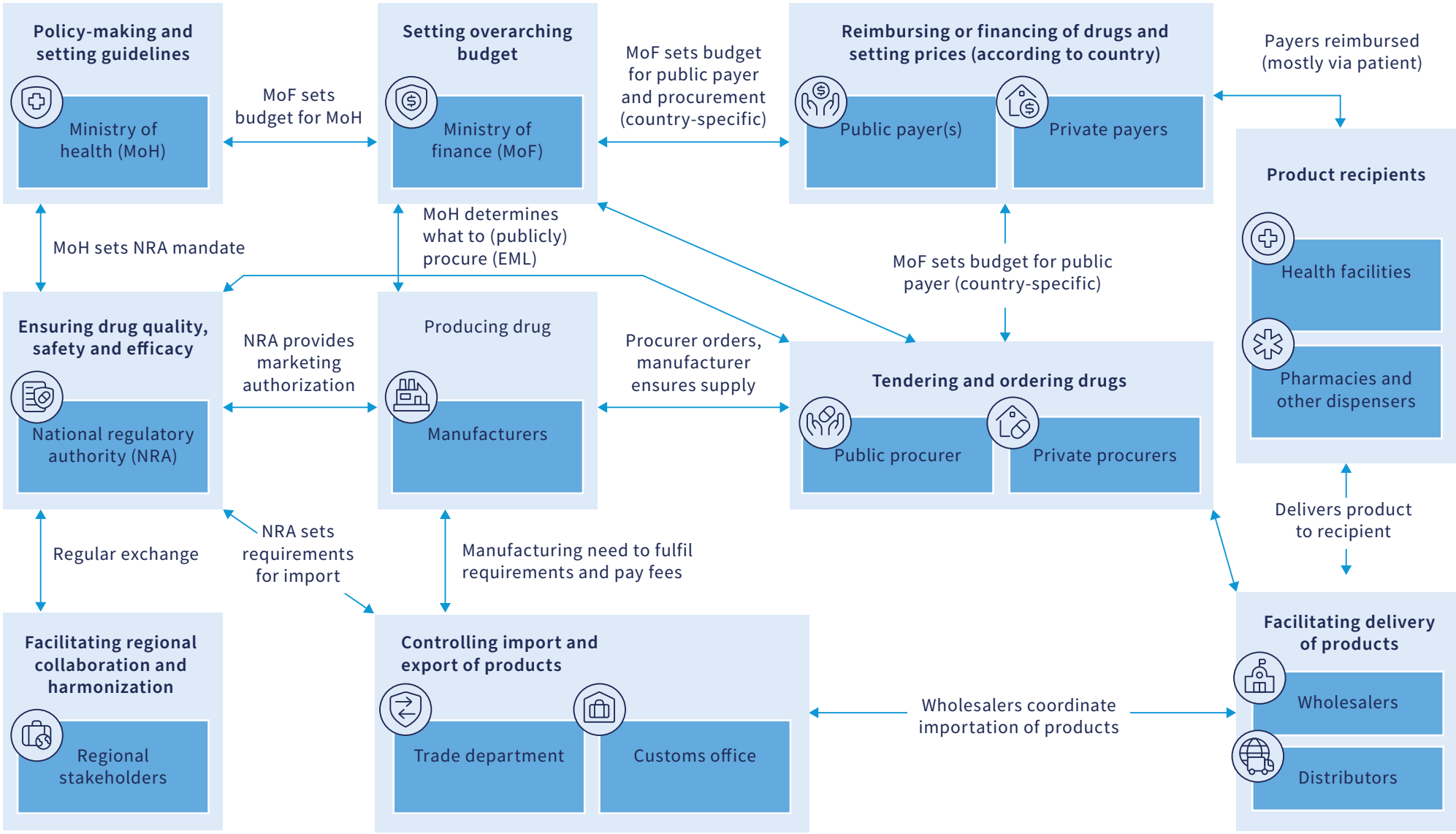


Fig. 5 (continued). Network of stakeholders relevant to addressing antibiotic shortages

National regulatory authority (NRA)

Core mandate: Implementing and enforcing policies to ensure drug quality, safety and efficacy

- **Registration and marketing authorization:** Approval and registration of drugs and withdrawal of substandard products
- **Vigilance:** Monitoring of adverse events
- **Market surveillance and control:** Control of quality, safety and efficacy standards in the market
- **Licensing establishments:** Issue and manage licenses according to good manufacturing practice and maintain public database of licenses
- **Regulatory inspection:** Inspection of manufacturing, distribution and retail sites (incl. wholesaler and distributors)
- **Laboratory Testing:** Test quality when necessary
- **Overseeing clinical trials:** Ensuring safety and efficacy
- **Lot release:** Implement release strategies

Extended mandate: Take measures to prevent and mitigate drug shortages, if directed to do so by a legislative agency (e.g. Germany: drug shortages law in 2023); USA: Executive Order on drug shortages in 2011

Ministry of health

Definition of policies and guidelines:

- **Definition of essential medicines list and resulting guidelines for public drug procurement**
- **Development of treatment guidelines and policies on use of antibiotics** and resistance
- **Allocation of resources and funding** for procurement of antibiotics
- **Oversight of disease-specific public health programmes and related antibiotics guidance** and funding (e.g. access to antibiotics by TB, HIV programmes)
- **Coordination of stakeholders** to ensure a stable supply of high-quality antibiotics
- **Setting prices of drugs** (depending on country, could be set by insurers in collaboration with public and private actors or solely by the manufacturer)

Oversight of NRA (sometimes with other bodies)

- **Definition of NRA mandate** and delegation of enforcement authority

Public procurers

- **Tendering and purchasing drugs** for public facilities
- **Managing stock levels and distribution** to prevent shortages
- **Sometimes also integrated services,** including storage and delivery

Private procurers

- **Procuring drugs for private and not-for-profit health facilities or outsourcing services for public sector**
- **Managing stock levels and distribution** to prevent shortages

Public payers

- **Determining reimbursement rules** for antibiotics, influencing their affordability and accessibility
- **Analysing data on medicines use and costs** for policy decisions, and manage expenses
- **Price setting** (in some countries)

Private payers

- **Determining reimbursement rules** for antibiotics, influencing their affordability and accessibility
- **Analysing data on medicines use and costs** for policy decisions, and manage expenses
- **Price setting** (in some countries)

Fig. 5 (continued). Network of stakeholders relevant to addressing antibiotic shortages

Ministry of finance

- **Allocating budget for procurement of drugs**
- **Decisions on any extrabudgetary measures to address medicine shortages,** e.g., allowing higher pricing or building stockpiles

Department of trade

- **Decisions on any export restriction or waiver of import requirements**

Regional stakeholders

- **Facilitating cross-border coordination** of antibiotics supply and **driving regional regulatory harmonization** (e.g. Africa CDC, EAC, ECOWAS, ASEAN, EU)

Customs office

- **Inspecting and clearing** imported antibiotics
- **Preventing entry of counterfeit or substandard drugs** and enforcing control if necessary (e.g. through sanctions)
- **Collecting relevant tariffs and taxes**

Manufacturers

- **Producing antibiotics** (directly or through contract manufacturers)
- **Ensuring a steady supply** to meet market demand
- **Notifying procurers and distributors** in cases of supply disruption

Wholesalers

- **Facilitating import and storage of drugs**
- **Ensuring proper storage and transport** conditions
- **Managing inventory** to prevent shortages

Distributors

- **Transporting drugs from wholesalers to health facilities and pharmacies**
- **Ensuring proper storage and transport** conditions and timely delivery
- **Managing inventory** to prevent shortages

Health facilities

- **Administering antibiotics** for patient care
- Ordering antibiotics through procurers
- **Managing stock and storage** conditions
- **Monitoring antibiotic use** to prevent overuse and resistance

Pharmacies

- **Dispensing antibiotics** as per prescriptions
- **Ordering antibiotics** through procurers
- **Providing information and guidance** to patients
- **Managing antibiotics stock and storage** conditions

Antibiotic shortages in LMIC

The perception of antibiotic shortages in LMIC differs from that in HIC. In the interviews conducted for this study, only a few NRA representatives and other stakeholders in LMIC identified disruptions to the global supply chain as the main concern for the availability of medicines. Issues such as circulation of products of uncertain quality or that are unregistered were of greater priority for both NRAs and other stakeholders.

While demand might appear to be met because drugs are available, the drugs could potentially be falsified, substandard or unregistered. Increased availability might be due to other reasons, such as several ports of entry, as in the Philippines, or limited capacity of the NRA. Further, as stock-outs are perceived as common in many LMIC, the situation appears less severe than in HIC. Because of lack of data on demand, available stock and products on order, countries often cannot differentiate between a shortage and a stock-out, nor can they predict, plan or manage it effectively. Although many LMIC face such challenges, they do not have stringent enforcement measures.

Many LMIC currently lack specific provisions to anticipate or address shortages. The key opinion leaders interviewed reported that managing shortages is currently not included in the mandate of NRAs but is considered the remit of procurement bodies or the ministry of health. In HIC such as Germany and the USA, legislative bodies have explicitly extended the responsibilities of NRAs to include management of shortages.

As the health-care landscape evolves, shortages of antibiotics are likely to become a more pressing concern in LMIC. As effective enforcement measures are increasingly successful in removing unregistered substandard or falsified products, gaps in supply and demand will emerge, and antibiotic shortages might become more critical. As HIC advance in addressing shortages, however, LMIC may fall behind.

2.6 Strengthening core NRA functions

As described in section 2.5, the remit of NRAs is primarily to oversee the regulation and supervision of pharmaceuticals and biological products. Strengthening their capacity to fulfil their core functions will enable uptake of the measures described in the next section. Core NRA functions must be backed by effective enforcement mechanisms to ensure high-quality practices and standards *(31)*. "Smart" solutions, such as serialization and barcoding, may increase the effectiveness of quality control mechanisms, which is often more difficult in LMIC due to porous borders and fewer resources.

In many LMIC, the approval of new products is lengthy due to limited capacity. To ensure an adequate supply of quality-assured products on the market, marketing approval must be accelerated. NRAs are establishing accelerated approval in situations such as health emergencies, shortages and for products for which there is urgent need. This will also increase the numbers of products available in the country. Countries could use various regulatory procedures for accelerated approval, which also reduce the burden on NRAs. They include the WHO collaborative registration procedure *(34-35)* and regional initiatives for joint assessments and work, such as ZAZIBONA *(36)*, the EAC and the Southern African Development Community.

NRAs in LMIC are also strengthening quality assurance and enforcement of sanctions for distribution of products of unknown quality and substandard or falsified products. In this analysis, substandard or falsified products and those of unknown quality was identified as an issue in most LMIC (with certain exceptions), which obscures the actual number of available products and shortages. Monitoring at ports of entry, which requires effective customs offices, and regular inspections, which require resources such as inspectors, are necessary to strengthen this function.

3. Measures to address shortages

3.1 Scope of analysis

While the measures investigated were initially those of NRAs, those of some ministries, regional organizations, research institutes, procurement organizations and manufacturers were later included to capture the full antibiotics supply chain ecosystem. Although the objective was to identify measures pertaining to antibiotics, the scarcity of specific initiatives led to inclusion of measures for ensuring the availability of other (essential) medicines.

3.2 Framework of measures to address shortages

Fig. 6 presents five categories of measures for addressing antibiotic shortages. Basic measures for strengthening systems form the foundation of the interventions proposed and are essential for preventing shortages and enabling rapid responses during crises. The measures can be used when shortages persist by increasing availability and facilitating a switch to alternatives.

Strengthen foundations: Continuation and enhancement of current measures to strengthen NRA core functions provide a strong basis for mitigating shortages. They include streamlining and improving regulatory approval processes to accelerate the availability of products of known quality, quality control to ensure that resources are used effectively and effective enforcement mechanisms. This should allow identification of products on the market and therefore more accurate demand and purchasing volumes. These measures will prevent shortages and prepare a country to act rapidly when necessary.

Institutionalize collaboration: Establishment of emergency plans and working relationships allows effective actions to address acute shortages in the future. The collaboration can be bilateral, ad-hoc conversations, formal steering committees or complex multi-stakeholder frameworks (Fig. 7).

Increase visibility: Measures to better understand the flow of medicines across a country and potential shortages to direct demand and supply, ensure timely identification of shortages and alert NRAs to implement their contingency plans for alternative supplies.

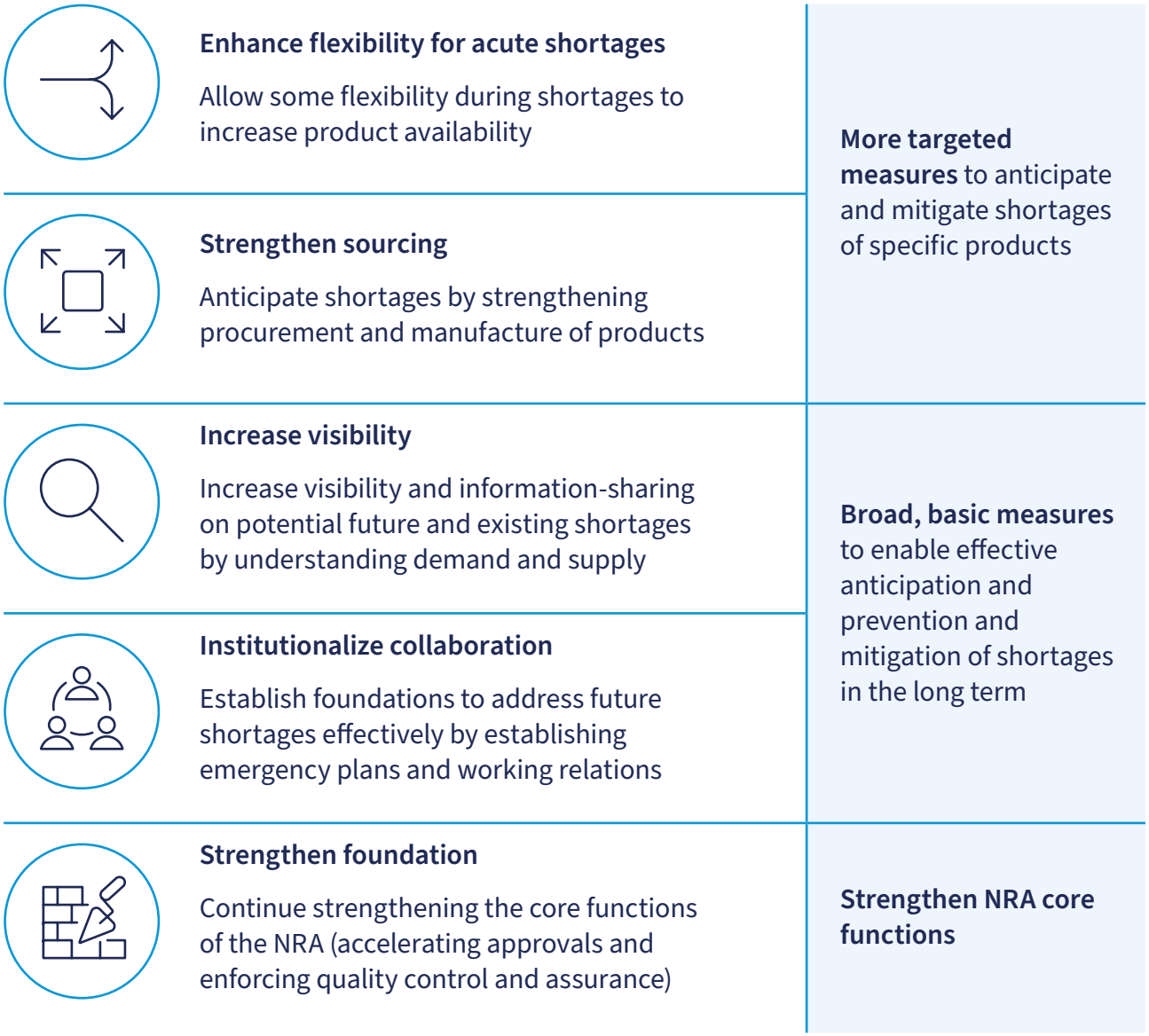
Targeted measures with a quicker effect, such as directly influencing the supply of products likely to be in short supply, include strengthening sourcing and greater flexibility. Strengthening sourcing includes measures to anticipate shortages by streamlining the procurement and manufacture of goods. Greater flexibility in public health emergencies increase the availability of products. Many short- and long-term measures can be combined. For example, the South African Health Products Regulatory Authority (SAHPRA) both provides temporary import permits and fast-tracks approval of medicines. Each category includes “quick wins”, which can be implemented readily, and long-term measures, which require structural changes or a change to the ecosystem. The measures to be taken first depend on the country’s context (see section 5).

3.3 Summary of measures observed in HIC and LMIC

The analysis resulted in a list of 42 measures in these categories, which were additionally classified into those for prevention and those for mitigation of acute shortages (Fig. 8). Almost all the measures were used in HIC and only about 25% in the African and Asian countries surveyed (Fig. 9).

To prepare for and prevent shortages, countries use buffer stocks, allow flexibility in labelling, introduce measures to increase the stability of demand to manufacturers, identify therapeutic alternatives and diversify the supplier base. Measures to identify potential shortages and to foresee demand and supply are essential to anticipate shortages Countries should plan and build a stakeholder network to prepare for potential shortages.

Fig. 6. Five categories of measures to prevent, anticipate and mitigate acute shortages of antibiotics



Measures should be planned to mitigate acute shortages. These include temporary measures to increase the short-term supply of products (e.g. waiving labelling requirements), reduction or restriction of product dispensing (e.g. rationing of medication) or use of alternatives. As shown in Fig. 10, measures to increase the supply of products likely to be or already in short supply or products already in shortage were most frequently described in interviews with key opinion leaders. The stakeholders who usually lead the respective interventions are listed in Fig. 10.

Differences in measures used in HIC and in LMIC were most evident for monitoring stock inventory, movement of drugs along the supply chain and identification of potential shortages. This corroborates the observation that shortages of quality-assured antibiotics in LMIC are hidden by the circulation of medicines of unknown quality. The conclusion is that NRAs and other institutions must implement and enforce policies for removing products of unknown quality and strengthen capacity to monitor stock and assess demand.

Fig. 7. Types of communication measures for addressing shortages

Increasing level of formalization; more explicit mandate

	Bilateral conversations	Working group	Steering committee	Multi-stakeholder ecosystem
Description and degree of formalization	**Regular exchange between two stakeholders (e.g. NRA and industry) on shortages and mitigation** Often ad-hoc, not formalized	**Regular exchanges among several stakeholders on shortages and mitigation** Degree of formalization can vary, often with no stringent terms of reference	**Formal multi-stakeholder group convened for discussions and decisions on shortage management** Decision-making power formalized in policies, terms of reference or other agreements	**Multi-stakeholder organization of partners for a specific mission related to shortage management, with clearly defined roles, responsibilities and processes** Formalized in policies, terms of reference or other agreements
Examples	**EU:** EMA in regular exchange with pharmaceutical companies to identify potential or existing medicine shortages	**Rwanda:** Rwanda FDA holds regular meetings with procurement and industry stakeholders to identify and mitigate medicine shortages (at no formal cadence)	**South Africa:** Pharmaceuticals and Therapeutics Committee (PTC) oversees medicines management system (based on National Policy for Establishment and Functioning of PTC) **Germany:** Advisory Council continuously monitors and evaluates the medicines supply (specified in the Medicinal Products Act)	**EU:** CHESSMEN[a] initiative established as coordinating mechanism for 22 EU NRAs; work in topic-specific subdivisions to achieve a harmonized response to shortages

ToR, terms of reference

[a] Coordination and Harmonization of the Existing Systems against Shortages of Medicines

Fig. 8. Measures identified in the desk review and interviews

Enhance flexibility for acute shortages	**1.1** Initiation of e-labelling	**Strengthen sourcing**	2.1 National buffer stock (manufacturers and pharmacies)
	1.2 Allowing import of unregistered product if approved by SRA, WHO PQ or reliant NRA		2.2 Centralized or pooled procurement (regional or national)
	1.3 Temporary permit to import products destined for other markets		2.3 Multi-year orders
	1.4 Temporary extension of expiry date, if safe		2.4 Work with manufacturers to increase supply of identified products
	1.5 Temporary flexibility in package size		2.5 Temporary permit to switch to alternative procurement channels such as private distributors
	1.6 Temporary flexibility in raw material source or manufacturing site		2.6 Requirement for diversification of suppliers
	1.7 Identification and communication of alternatives for shortage-prone antibiotics in advance		2.7 Requirement to purchase or include locally manufactured products
	1.8 Fast track of approvals (emergency) for substitute products		2.8 Incentives to manufacturers to register shortage-prone products (market exclusivity)
	1.9 Temporary waiving of testing requirements		2.9 New antibiotics reimbursement models (e.g. subscription model in HIC)
	1.10 Temporary allowance for price increases on products in shortage covered by public system		2.10 Requirements for diversification of API sources
	1.11 Reduced dosing or dose-sparing		
	1.12 Temporary export restrictions of locally produced products		
	1.13 Temporary rationing or prioritize populations in need		

Fig. 8 (continued). Measures identified in the desk review and interviews

Increase visibility	1.14 Temporary flexibility for batch releases	**Institutionalize collaboration**	4.1 Regional stockpiles
	1.15 Authorization of use of veterinary medicines		4.2 Harmonized labelling in countries or a region
	1.16 Authorization of use of magistral preparations		4.3 Regional harmonization of regulatory requirements (including chemistry, manufacturing and controls (CMC))
	3.1 Identification of essential drugs particularly prone to shortages (EML subcategory)		4.4 Country-specific risk management plan on addressing shortages
	3.2 Registries for manufacturers to report upcoming shortages (early warning system)		4.5 Regional collaboration to exchange products
	3.3 Establishment of forecasting system: match expected demand and supply to potential shortages		4.6 Use of regional fora and bodies to strengthen collaboration on shortages
	3.4 National tracking and tracing system to create visibility of demand		4.7 Bilateral meetings
	3.5 Public national shortages catalogue (sometimes combined with suggestions for alternatives)		4.8 Working groups
	3.6 Public regional shortages catalogue (sometimes combined with suggestions for alternatives)		4.9 Steering committees
	3.7 Provision of guidance to health-care providers and the public		4.10 Multi-stakeholder ecosystems
Strengthen foundation	0.1 Acceleration of general registration	0.2 Strengthening of quality assurance and control enforcement	

Prevention and anticipation Mitigation

Fig. 9. Measures used only in LMIC

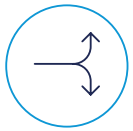
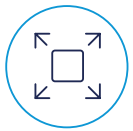
	Prevention and anticipation	Mitigation
 **Enhance flexibility for acute shortages**	**1.8 Fast track of approvals (emergency) for substitute products** e.g. Kenya, Malaysia, United republic of Tanzania	**1.2 Allow import of non-registered product if approved by SRA,** WHO PQ or reliant NRA, e.g. Burkina Faso, Philippines, United Republic of Tanzania.
 **Strengthen sourcing**	**2.1 National buffer stock (manufacturers/pharmacies)** e.g. Burkina Faso, Malaysia, Rwanda, Senegal, South Africa, United Republic of Tanzania	**1.3 Temporary permit to import products destined for other markets,** e.g. Burkina Faso, Malaysia, Rwanda, Senegal
	2.2 Centralized or pooled procurement (regional or national) e.g. Burkina Faso, United Republic of Tanzania, Viet Nam	**1.4 Temporary extension of expiry date, if safe** e.g. Senegal
	2.3 Multi-year orders e.g., South Africa, United Republic of Tanzania	**2.5 Temporary permit to switch to alternative procurement channels such as private distributors** e.g. Burkina Faso, Ghana, Rwanda, United Republic of Tanzania
	2.4 Work with manufacturers to increase supply on products identified e.g. Malaysia, Philippines	
	2.6 Requirement for diversification of suppliers e.g. Rwanda, Senegal, United Republic of Tanzania	
	2.7 Requirement for purchasing or inclusion of locally manufactured products e.g. Ghana, Kenya , Malaysia, Rwanda, South Africa, United Republic of Tanzania	

Fig. 9 (continued). Measures used only in LMIC

 **Increase visibility**	**3.2 Registries for manufacturers to report upcoming shortages (early warning system)** e.g. Malaysia, South Africa	
	3.4 National tracking and tracing system to create visibility of demand e.g. Malaysia, Senegal, South Africa	
 **Institutionalize collaboration**	**4.4 Country-specific risk management plan on addressing shortages** e.g. South Africa	
	4.6 Use of regional fora and bodies to strengthen collaboration on shortages e.g. Malaysia, Senegal	
	4.7/4.8 Bilateral conversations, working groups eg. Malaysia, Senegal, South Africa, United Republic of Tanzania	
	4.9 Steering committees eg. South Africa	
 **Strengthen foundation**	0. Continuous work to strengthen NRA core functions	All countries

Note: Verification with informants pending for some countries

Fig. 10. Measures used and frequency

		High-income countries						Africa							Asia					
		THE UNITED KINGDOM	THE USA	EUROPEAN UNION	SWEDEN	DENMARK	GERMANY	KENYA	UNITED REPUBLIC OF TANZANIA	GHANA	RWANDA	BURKINA FASO	SENEGAL	SOUTH AFRICA	MALAYSIA	PHILIPPINES	VIET NAM	THAILAND	SINGAPORE	INDONESIA
Enhance flexibility foracute shortages	1.1 Initiation of e-labelling			✓																
	1.2 Allowing importation of non-registered product if approved by SRA, WHO PQ or reliant NRA							✓	✓			✓		✓		✓				
	1.3 Temporary permit to import products destined for other markets	✓		✓	✓	✓		✓			✓	✓	✓	✓	✓	✓				
	1.4 Temporary extension of expiry date, if safe		✓	✓		✓							✓							
	1.5 Temporary flexibility in package size	✓		✓	✓	✓	✓													
	1.6 Temporary flexibility in raw material source or manufacturing site		✓	✓																
	1.7 Identification and communication of alternatives for shortage-prone antibiotics in advance			✓	✓															✓
	1.8 Fast track approval (emergency) of substitute products	✓	✓	✓				✓	✓				✓	✓	✓	✓	✓			
	1.9 Temporary waiving of testing requirements							✓												
	1.10 Temporary allowance of price increases on products in shortage covered by public system	✓					✓					✓								
	1.11 Reduced dosing or dose sparing	✓		✓																

Fig. 10 (continued). Measures used and frequency

		High-income countries						Africa							Asia					
		THE UNITED KINGDOM	THE USA	EUROPEAN UNION	SWEDEN	DENMARK	GERMANY	KENYA	UNITED REPUBLIC OF TANZANIA	GHANA	RWANDA	BURKINA FASO	SENEGAL	SOUTH AFRICA	MALAYSIA	PHILIPPINES	VIET NAM	THAILAND	SINGAPORE	INDONESIA
Enhance flexibility for acute shortages	1.12 Temporary export restrictions on locally produced products	✓																		
	1.13 Temporary rationing or prioritizing of populations in need			✓																
	1.14 Temporary flexibility for batch releases	✓	✓	✓																
	1.15 Authorization of use of veterinary medicines			✓																
	1.16 Authorization of use of magistral preparations	✓		✓					✓											✓
Enhance sourcing	2.1 In-country buffer stock (manufacturers/pharmacies)	✓		✓		✓	✓		✓		✓	✓		✓	✓					
	2.2 Centralized or pooled procurement (regional or national)			✓					✓			✓					✓			
	2.3 Multi-year orders								✓					✓						
	2.4 Work with manufacturers to increase supply of identified products		✓	✓											✓	✓				
	2.5 Temporary permit to switch to alternative procurement channels e.g. private distributors								✓	✓	✓	✓			✓					

Fig. 10 (continued). Measures used and frequency

		High-income countries						Africa							Asia					
		THE UNITED KINGDOM	THE USA	EUROPEAN UNION	SWEDEN	DENMARK	GERMANY	KENYA	UNITED REPUBLIC OF TANZANIA	GHANA	RWANDA	BURKINA FASO	SENEGAL	SOUTH AFRICA	MALAYSIA	PHILIPPINES	VIET NAM	THAILAND	SINGAPORE	INDONESIA
Enhance sourcing	2.6 Requirement for diversification of suppliers								✓		✓		✓							
	2.7 Requirements to purchase include locally manufactured products			✓				✓	✓	✓				✓	✓		✓			
	2.8 Incentives to manufacturers to register shortage-prone products (market exclusivity)			✓				✓												
	2.9 New antibiotics reimbursement models (e.g. subscription model in HIC)				✓		✓													
	2.10 Requirement for diversification of API sources			✓			✓													
Increase visibility of use	3.1 Identification of essential drugs particularly prone to shortages (EML sub-category)	✓		✓			✓											✓		
	3.2 Registries for manufacturers to report upcoming shortages (early warning system)	✓	✓	✓	✓	✓	✓							✓	✓			✓		

Fig. 10 (continued). Measures used and frequency

		High-income countries						Africa							Asia					
		THE UNITED KINGDOM	THE USA	EUROPEAN UNION	SWEDEN	DENMARK	GERMANY	KENYA	UNITED REPUBLIC OF TANZANIA	GHANA	RWANDA	BURKINA FASO	SENEGAL	SOUTH AFRICA	MALAYSIA	PHILIPPINES	VIET NAM	THAILAND	SINGAPORE	INDONESIA
Increase visibility of use	3.3 Establishment of forecasting system: match expected demand and supply for potential shortages	✓	✓	✓			✓	✓												
	3.4 National tracking and tracing system to create visibility of demand																			
	3.5 Public national shortages catalogue (sometimes combined with suggested alternative)		✓	✓	✓	✓	✓							✓	✓			✓		
	3.6 Public regional shortages catalogue (sometimes combined with suggested alternative)			✓	✓	✓														
	3.7 Provision of guidance to health-care providers and the public	✓	✓	✓															✓	✓

Fig. 10 (continued). Measures used and frequency

		High-income countries						Africa							Asia					
		THE UNITED KINGDOM	THE USA	EUROPEAN UNION	SWEDEN	DENMARK	GERMANY	KENYA	UNITED REPUBLIC OF TANZANIA	GHANA	RWANDA	BURKINA FASO	SENEGAL	SOUTH AFRICA	MALAYSIA	PHILIPPINES	VIET NAM	THAILAND	SINGAPORE	INDONESIA
Institution-alize collabora-tion	4.1 Regional stockpiles			✓																
	4.2 Harmonized labelling among countries or in a region	✓		✓									✓							
	4.3 Regional harmonization of regulatory requirements (including CMC)			✓																✓
	4.4 National risk management plan on addressing shortages		✓	✓										✓						
	4.5 Regional redistribution mechanism to exchange products	✓		✓						✓			✓							
	4.6 Use of regional fora and bodies to strengthen collaboration on shortages			✓	✓	✓							✓		✓					
	4.7 Bilateral discussions		✓	✓		✓	✓		✓		✓	✓		✓	✓					✓
	4.8 Working groups		✓	✓		✓	✓		✓		✓	✓		✓	✓					
	4.9 Steering committees		✓				✓							✓						
	4.10 Multi-stakeholder ecosystem			✓																

Measures in place ✓

3.4 Typical roles and responsibilities in identified measures

Distinct roles and responsibilities were identified for stakeholders in the antibiotic supply chain (as detailed in section 3.5) for each measure. These are organized into a matrix (Responsible, Accountable, Consulted and Informed) in Fig. 11, each term representing a different level of stakeholder engagement. The assignment of roles and responsibilities will depend on the context of each country; thus, there is no "correct" or "incorrect" allocation. Furthermore, regional stakeholders may play a role in some measures. For simplicity, the matrix shows only the primary stakeholders involved in each measure. Roles and responsibilities were assigned according to desk research and internal analysis.

Fig. 11. Typical roles and responsibilities in identified measures

Category	#	Measure	NRA	MoH	PA	Mfg	W & D	Other relevant stakeholders
Enhance flexibility for acute shortages	1.1	Initiation of e-labelling[a]	A/R	A/R	I	I	I	Pharmacies, health facilities, health-care providers, patients: I
	1.2	Allow import of non-registered product if approved by SRA, WHO PQ or reliant NRAa	A/R		R		R	Custom office: I
	1.3	Temporary permit to import products destined for other markets	A		R		R	Custom office: R
	1.4	Temporary extension of expiry date, if safe[a]	A/R	C	I		I	Pharmacies, health facilities. Health-care providers: I
	1.5	Temporary flexibility in package size[a]	A/R	C	I	I	I	Pharmacies: R
	1.6	Temporary flexibility in raw material source or manufacturing site[a]	A/R	C		R		
	1.7	Identification and communication of alternatives for shortage-prone antibiotics in advance	R	A				Professional association: Health facilities, pharmacies, health-care providers:
	1.8	Fast track of approvals (emergency) for substitute products[a]	R/A			R		
	1.9	Temporary waiving of testing requirements[a]	A/R	C				
	1.10	Temporary allowance for price increases on products in shortage covered by the public system[a]		A				Public payers: R
	1.11	Reduced dosing or dose-sparing[a]	R	A				Pharmacies, health facilities, health-care providers: R
	1.12	Temporary export restrictions on locally produced products[a]		A/R	I	I	I	Ministry of trade: A/R Customs office: I

Fig. 11 (continued). Typical roles and responsibilities in identified measures

Category	#	Measure	NRA	MoH	PA	Mfg	W & D	Other relevant stakeholders
Enhance flexibility for acute shortages	1.13	Temporary rationing or prioritization of populations in need	R	A				Pharmacies, health facilities, health-care provders: R
	1.14	Temporary flexibility for batch releases[a]	A/R	C				
	1.15	Authorization of use of veterinary medicines	A/R	I				
	1.16	Authorization of use of magistral preparations	A/R	I				
Strengthen sourcing	2.1	National buffer stock (manufacturers/pharmacies)[a]		A	R	R	R	Pharmacies and health facilities: R
	2.2	Centralized or pooled procurement (regional or national level)[b]		A	R	I	I	Regional health authority: A
	2.3	Multi-year orders		A	R	I	I	
	2.4	Work with manufacturers to increase supply of identifiedproducts	R	A		R		
	2.5	Temporary permit to switch to alternative procurement channels, e.g. private distributors		A	R			Pharmacies and health facilities: I
	2.6	Requirement for diversification of suppliers		A	R			
	2.7	Requirement to purchase or include locally manufactured products[a]		A	R			Ministry of trade: A Payers: R
	2.8	Incentives to manufacturers to register shortage-prone antibiotics (market exclusivity)	A/R	C		I		
	2.9	New antibiotics reimbursement models (e.g. subscription model in HIC)		A		I		Payers: R
	2.10	Requirements for diversification of API sources	C	A	R			Payers: R

Fig. 11 (continued). Typical roles and responsibilities in identified measures

Category	#	Measure	NRA	MoH	PA	Mfg	W & D	Other relevant stakeholders
Increase visibility	3.1	Identification of essential drugs particularly prone to shortages (EML subcategory)[a]	R	A/C	R			Specialist associations: C
	3.2	Registries for manufacturers to report upcoming shortages (early warning system)[a]	A		A[1]	R	R	Technical provider: R
	3.3	Establishment of forecasting system: match expected demand to supply to identify potential shortages	R	A	C	R	R	Technical provider: R
	3.4	National tracking and tracing system to create visibility of demand	A	R	R	R	R	Pharmacies, health facilities, payers: R
	3.5	Public national shortages catalogue (sometimes combined with suggestion for alternative)	R	A				Pharmacies, health facilities, health-care providers: I
	3.6	Public regional shortages catalogue (sometimes combined with suggestion for alternative)	R			R		Regional health authority: A/R
	3.7	Provision of guidance to health-care providers and the public	C	A/R				HCP: I

Fig. 11 (continued). Typical roles and responsibilities in identified measures

Category	#	Measure	NRA	MoH	PA	Mfg	W & D	Other relevant stakeholders
Institution-alize collaboration	4.1	Regional stockpiles[b]	A/R	A/R	R	R	I	
	4.2	Harmonized labelling among countries or in a region[a]	A/R	A/R	I	R	I	
	4.3	Regional harmonization of regulatory requirements (including CMC)[b]	A/R	A/R	I		I	Regional stakeholder: R & C
	4.4	National risk management plan on addressing shortages	A/R	A/R				Pharmacies, health facilities, healthcare providers, payers: I
	4.5	Regional redistribution mechanism to exchange products	A/R	A/R			R	Pharmacies, health facilities: R
	4.6	Use of regional fora and bodies to strengthen collaboration on shortages[b]	A/R	A/R				Regional health authority: R
	4.7	Bilateral discussions	A/R	A/R	C	C	C	May be initated by regional organizations and include a broad range of other stakeholders, e.g. healthcare providers, pharmacists or patient associations
	4.8	Working groups	A/R	A/R	C	C	C	
	4.9	Steering committees	A/R	A/R	C	C	C	
	4.10	Multi-stakeholder ecosystems[b]	A/R	A/R	C	C	C	

Responsible R Accountable A Consulted C Informed I

[a]Task of stakeholders depend on country's context

[b]Regional organizations play a relevant role

Note: PA, procurement agency; Mfg, manufacturer; W&D, wholesaler and distributor; MoH, Ministry of Health.

3.5 In-depth analysis of measures

This section provides in-depth analyses of the measures identified. For each measure, the following dimensions are analysed:

- lead stakeholder of those identified in section 3.4 in the countries surveyed;
- occurrence in HIC or LMIC as observed in this study;
- type of shortage addressed of those identified in section 3.4 (shortages in the global supply chain, limited access, difficulty in forecasting and difficulty in delivery);
- qualitative advantages of each measure (expected or actual); see also section 4, in which measures are rated according to their anticipated impact;
- requirements for implementing the measure to estimate the work necessary and the regulatory, infrastructural, financial and logistical complexity; and
- selected examples and observed frequency to illustrate concrete applications of the measure, described in more detail in section 3.5 and Annex 2.

Enhancing flexibility for acute shortages

E-labelling	Pharmaceutical products bear an electronic label that contains all information on the product, which can be adjusted flexibly (e.g. to change language or expiry date). Stakeholders can access the electronic label by scanning a barcode (e.g. a QR code)
	• lead stakeholder: NRA or ministry of health (depends on country) • observed in: HIC • type of shortage addressed: problems in the global supply chain, lack of registration, lack of demand planning, lack of quality control • advantages: allows rapid adjustments in response to changes in market demand (e.g. shortages) and obviates changes to physical labels, resulting in cost savings. Can encourage manufacturers to enter markets, as label requirements are easy to implement. Improves quality assurance as it provides standardization, traceability and real-time updates to product information. • requirements: digital infrastructure and regulation on use of electronic labels. Selected example: EU: The EMA and the European Medicines Regulatory Network conducted a pilot study on use of electronic product information for human medicines in July 2023. The goal is to use authorized, statutory product information for medicines (including product characteristics, package leaflet and labelling) in an electronic format *(37)*. Note: LMIC may lack infrastructure and mechanisms for reading e-labels, especially outside health facilities.
Importation of non-registered products if approved by a stringent regulatory authority (SRA), WHO prequalification (PQ) or reliant NRA	NRAs allow faster marketing authorization or direct import of unregistered medications if they are approved by an SRA/WHO listed authorities (WLA) *(38)*, have WHO PQ or are already registered by an SRA in another country.
	• lead stakeholder: NRA • observed in: LMIC and HIC • type of shortage addressed: lack of demand planning or of national stock-taking • advantage: rapid, direct access to medications that are limited or unavailable for a short time • requirements: regulations allow faster importation and robust monitoring and reporting of adverse events Selected examples: Kenya: Grants faster marketing authorization and inspection of products from SRA/WHO listed authorities (WLA), . Rwanda: Allows faster approval of products that are registered in other countries with which it has agreements (e.g. Ghana and the United Republic of Tanzania, both of which have an NRA at maturity level 3) Note: This measure resolves shortage of only one product at a time.

Temporary permit to import products destined for other markets	NRAs can grant concessions for flexible importation of foreign products, for example by accepting the labels and standards of other countries, even if they have different language or graphics. • lead stakeholder: NRA • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning or of national stock-taking • advantage: rapid, direct access to medications with limited or no availability for a short time • requirements: regulatory flexibility to accept foreign labelling and packaging standards and streamlined processes for rapid approval of imported drugs Selected example: United Kingdom: The Medicines and Healthcare products Regulatory Agency can grant temporary exemption of legislative labelling or leaflet requirements (for national, mutual recognition or decentralized procedures and centrally authorized medicines) for a maximum of 6 months during severe shortages of a medicine.
Temporary extension of expiry date, if approved	NRAs can grant extension of the shelf-life of released batches of a medicine, if the extension is approved. • lead stakeholder: NRA • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning or national stock-taking • advantage: rapid, direct access to medications with limited or no availability for a short time • requirements: scientific capacity to assess the safety of extended shelf lives and regulations for rapid approval of extensions Selected example: USA: The US FDA can mitigate shortages by reviewing requests for extensions of expiration dates if safe for patients.
Temporary flexibility in package size	NRAs can grant concessions to pharmacies or hospitals to dispense packages of different sizes, if deemed safe. • lead stakeholders: NRA, pharmacies • observed in: HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning and national stock-taking • advantage: rapid, direct access to medications with limited or no availability for a short time • requirements: adaptive regulatory processes to permit variations in package sizes, and effective communication with manufacturers and health-care providers Selected example: Germany: since 2023, pharmacies are authorized to dispense a medication different from that prescribed but with the same API but different package size or different strength of API when the medication cannot be supplied by two pharmaceutical wholesalers within a reasonable time *(39)*.
Temporary flexibility in source or manufacturing site of raw material	NRAs can grant concessions for manufacturers to source raw materials from different suppliers or manufacturing sites. • lead stakeholder: NRA • observed in: HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning and national stock-taking • advantage: rapid, direct access to medications with limited or no availability for a short time • requirements: robust regulatory oversight to ensure quality and safety when the sources of raw materials or the manufacturing site are changed, and efficient approval of changes Selected example: EU: In 2023, the MSSG endorsed a recommendation on tools for addressing shortages of medicinal products. The MSSG may recommend flexibility in facilitating changes to alternative sources of raw materials, manufacturing site or manufacturing equipment to enable increased production and to support sparing use of the product.

Advance identification and communication of alternatives for antibiotics prone to shortages	NRAs collaborate with scientists, manufacturers and other stakeholders to define and recommend alternatives to drugs in short supply. Another version could be identification of a combination of products, decreased dosage of the product in short supply, while maintaining efficacy (e.g. reduced intake of antibiotics when combined with other medicinal products) • lead stakeholder: NRA (responsible), ministry of health (accountable) • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain and in local access • advantage: improves the preparedness of a country for shortages • requirements: scientific and clinical collaboration to identify effective alternatives and communication systems to inform procurement agencies and health-care providers Selected example: Sweden: The Swedish MPA evaluates whether drugs are pharmaceutically equivalent and selects substitutes according to various criteria, including cost. The principles for substitution are: products that contain the same active substance in the same amount and are otherwise medically equivalent to be substituted for the least expensive reimbursed pharmaceutical.
Fast track of approvals for acute shortages of substitute products	NRAs can fast-track approvals to authorize substitutes for products in short supply or during public health emergencies and for products that are urgently required. The approval depends on the information required (e.g. data from a clinical trial) and can be given if another mechanism is in place (e.g. WHO PQ). Authorization can be temporary, with certain requirements such as subsequent provision of data. Reliance can significantly accelerate local approval. • lead stakeholder: NRA • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain, lack of registration or national stock-taking • advantages: faster access to medications or alternative treatments during shortages due to quicker introduction of products onto the market; rapid reaction in crises • requirements: regulatory frameworks for expedited approval and systems to ensure continuous monitoring of safety and efficacy Selected example: Kenya: The Pharmacy and Poisons Board (PPB) is authorized to approve fast-tracking of use of any unregistered medicinal substance to meet acute shortages during public health emergencies.
Temporary waiving of testing requirements	NRAs can waive or be flexible about certain testing requirements, such as sterility and the cold chain, for importation or registration of a medication during emergencies (for instance, the results of tests for sterility may take up to 4 weeks) • lead stakeholder: NRA • observed in: LMIC • type of shortage addressed: problems in the global supply chain, lack of demand planning and national stock-taking • advantage: rapid, direct access to medications with limited or no availability for a short time • requirements: regulatory and logistical capability to ensure that quality and safety standards are maintained under flexible testing requirements Note: Although this measure was discussed in many of the interviews, none of the countries consulted had used this measure because of concern about the risk to quality. The Kenya PPB is allowed, in emergencies such as war or threats from chemical, biological, radiological or nuclear sources, to issue acute approval of limited clinical trial data when no standard treatment or diagnostic tool is available.
Temporary price increases on products in short supply covered by a public system	Government entities can grant exceptions to permit higher pricing or reimbursement by national health insurance funds for medications in short supply, even if the prices are normally fixed.

	• lead stakeholder: ministry of health or insurance fund • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning, lack of visibility of in-country stock • advantage: rapid, direct access to medications with limited or no availability for a short time • requirements: regulatory and economic measures to manage and approve price increases (i.e. payers or procurement agencies should be able to influence pricing), financial capacity for price increases and systems to monitor effects on affordability and access Selected example: Germany: The Federal Institute for Drugs and Medical Devices (BfArM) may authorize the Federal Ministry of Health, after consultation with the Federal Association of Health Insurance Funds, to increase the price of essential medicines by a fixed amount or up to 50% when they are on the list of critical active substances. This list includes several antibiotics, such as amoxicillin and meropenem.
Reduced dosing or dose sparing	NRAs or similar competent entities can permit pharmacies to dispense a medicine at a lower dose if it has the same effect as at higher doses. • lead stakeholder: ministry of health • observed in: HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning or national stock-taking • advantage: rapid, direct access to medications with limited or no availability for a short time • requirements: clinical and scientific expertise to determine the safety and effectiveness of reduced-dose protocols and channels to inform health-care providers Selected example: United Kingdom: The Department of Health and Social Care issues “serious shortage protocols” that allow community pharmacies to dispense specific alternative products or quantities (e.g. a smaller amount). Note: This measure is not applicable to antibiotics because of the increased risk of AMR.
Temporary export restrictions on locally produced products	The ministry of health or of trade or a similar competent entity imposes temporary restrictions on the exportation of locally manufactured medications or molecules to increase the supply in the country. • lead stakeholder: ministry of health or of trade • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning or national stock-taking • advantage: ensures direct access to the medication by the local population during a shortage • requirements: local manufacturing capacity for relevant drugs, legal and enforcement framework for imposing and monitoring export restrictions, weighing national need and the impact on global markets Selected example: United Kingdom: The Department of Health and Social Care and the Medicines and Healthcare Products Regulatory Agency regularly update a list of medicines that may not be exported to safeguard the supply for patients in the United Kingdom, particularly during critical shortages. Updates to the list are communicated to the World Trade Organization secretariat and published on its website. In its response to the COVID-19 pandemic, Indian authorities imposed various restrictions on exports, including bans, to prevent any shortage of medical supplies considered to be essential. Note: This measure can increase pressure on global and national markets and is therefore not included in the global recommendations.

Temporary rationing, prioritization of certain populations	Ministries of health and NRAs can provide detailed guidelines or instructions to health-care providers and pharmacies to ration medicines (such as prioritization of high-risk patient groups or front-line workers) or to propose alternative preparations (e.g. intradermal or intramuscular administration, injection or tablet). • lead stakeholder: ministry of health, NRA • observed in: LMIC (e.g. for COVID-19 vaccines) and HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning and national stock-taking • advantage: ensures treatment of patients at greatest need when availability is limited • requirements: systems for prioritizing patient groups, effective distribution mechanisms and transparent communication with health-care providers and the public Selected example: EU: In 2023, the MSSG endorsed recommendations for tackling shortages of medicinal products. The MSSG may recommend controlled distribution by rationing the stocks of pharmacies and hospitals and prioritizing patients in greatest need. For example, in LMIC, administration of yellow fever vaccine intradermally rather than intramuscularly, injection of iron supplements for pregnant women rather than distributing tablets.
Temporary flexibility for batch releases	NRAs or similar competent entities can grant exceptions for the release of individual batches that do not fulfil all the requirements of the NRA, if certain conditions such as strict oversight can be assured • lead stakeholder: NRA • observed in: HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning or national stock-taking • advantage: rapid, direct access to medications with limited or no availability for a short time • requirements: regulatory discretion to evaluate and approve the release of batches that do not fully meet quality standards while ensuring that patient safety is not compromised Selected example: USA: The US FDA can exercise temporary regulatory flexibility and discretion for use of medically required products of questionable quality. In 2022, this measure was used to supply a filter to remove particulate matter from some products *(40)*. Note: This measure should be weighed carefully against quality concerns.
Authorization of use of veterinary medicines in humans	NRAs or similar competent entities can allow use of veterinary medicines in humans after evaluation of safety. This measure is taken only in cases of extreme shortages. • lead stakeholder: NRA • observed in: HIC • type of shortage addressed: problems in the global supply chain and local access • advantage: rapid, direct access to medications that contain the same API but are unavailable for a limited time • requirements: regulatory processes for assessing and authorizing safe use of veterinary medicines for human use in emergencies Selected example: EU: In 2023, the MSSG endorsed a recommendation for addressing shortages of medicinal products. The MSSG may recommend use of medicines (the same active substance, suitable strength and pharmaceutical form) authorized for veterinary use to address critical shortages of medicinal products for human use in exceptional circumstances. Note: This measure is used only exceptionally and if safety, quality and efficacy can be guaranteed

Authorization of magistral preparations	NRAs or similar competent entities can evaluate options for safe use of magistral preparations (medical products prepared in a pharmacy for an individual patient) or small-scale preparations if other medications are not available or are in short supply. • lead stakeholder: NRA • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain or in local access • advantage: conservation of scarce medicines to ensure access by the largest number of people possible • requirements: systems for approving and monitoring small-scale pharmacy drug preparations to ensure their quality and safety Selected example: EU: In 2023, the MSSG endorsed recommendations for addressing shortages of medicinal products. The MSSG may suggest use of pharmaceutical preparations, such as magistral or officinal formulations, as suitable alternatives to medicines that are not available or at risk of shortages.

Strengthen sources

National buffer stocks (manufacturers and pharmacies)	A government entity builds a stockpile of critical medicines, and/or manufacturers, pharmacies, health-care professionals and wholesalers are mandated to maintain buffer stocks for unforeseen emergencies. This ensures a supply of essential medications for a specified period, such as 1–6 months (usually 2–3 months). The size of the buffer stock depends on shelf life and appropriate distribution channels for both inpatient and outpatient use. Smaller buffer stocks reduce the risks but may increase the likelihood of shortages. • lead stakeholder: ministry of health • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain, lack of national stock-taking • advantage: prevents short-term stock-outs of (essential) medicines • requirements: adequate working capital to maintain stockpiles in the country and for manufacturers, pharmacies, health-care providers and wholesalers. Selected example: Germany: Since 2023, by law *(39)*, pharmacies and hospitals must maintain a mandatory stockpile of drugs classified by the Ministry of Health as prone to shortages, holders of market authorization for rebated drugs (6-month supply) and wholesalers for paediatric drugs (4-week supply). Note: The predictability of demand during, for example, each 12-month period allows manufacturers to manage their capacity. Studies on the practice of extending shelf-life could be encouraged to ascertain the long-term viability of medical products.
Centralized or pooled regional or national procurement	System or formal arrangement for national or regional entities to jointly purchase pharmaceutical products on behalf of an individual purchasing authority • lead stakeholder: ministry of health, regional health authority • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain and affordability • advantages: results in economy of scale to reduce the cost of scarce medicines and can result in more efficient re-allocation during shortages • requirements: identification of unmet treatment needs and national or regional trends, financial and organizational capacity and political will to create centralized procurement systems or agreements for joint procurement Selected examples: EU: In 2023, the MSSG endorsed recommendations on addressing shortages of medicinal products. The MSSG may recommend facilitation of central negotiations and purchases of medicines by Member States of the EU and of the European Economic Area. In the United Republic of Tanzania, public procurement is pooled and conducted through the Medical Stores Department (MSD).

Multi-year orders	A contract is issued by a governmental entity or procurement agency for purchase of specific quantities of medicines from manufacturers over several years (usually three), obviating annual contract renewal. • lead stakeholder: ministry of health, procurement agency • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain and of affordability • advantages: increases the willingness or capacity of a manufacturer to supply, facilitates production planning by manufacturers and may improve relations with manufacturers • requirements: identification of national and regional treatment requirements and trends, financial and forecasting capacity to commit to a multi-year procurement contract and agreements with manufacturers Selected examples: South Africa and the United Republic of Tanzania: The National Department of Health in South Africa and the MSD, the public procurer in the United Republic of Tanzania, issue bids for supplies of pharmaceutical products, including antibiotics, antiretrovirals and vaccines for up to several years.
Work with manufacturers to increase supplies of identified products	Government entities collaborate with manufacturers to increase production to meet forecasts or to address shortages. Production can be coordinated among different manufacturers through the governmental entity. • lead stakeholder: ministry of health • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning and national stock-taking • advantage: rapid identification of manufacturers that can increase production • requirements: effective communication and collaboration between authorities and manufacturers, substantial market for bargaining power with manufacturers Selected example: EU: The European Commission, the heads of medicines agencies and the EMA issued recommendations to prevent shortages of key antibiotics in the winter of 2023–2024. The recommendations are based on demand in past seasons. The MSSG forecast the demand for the winter of 2023–2024 and developed action plans to address potential gaps. The EMA and the European Health Emergency Preparedness and Response Authority will continue to collaborate with the heads of medicines agencies to increase the production of certain intravenous antibiotics for next autumn and winter. The forecast was also used in drawing up an EU list of critical medicines.
Temporary permit to switch to alternative procurement channels, such as private distributors	Government entities can grant exceptions to allow public health facilities to procure medicines from private distributors if public facilities or procurers experience stock-outs • lead stakeholder: ministry of health • observed in: LMIC • type of shortage addressed: lack of demand planning and national stock-taking • advantage: rapid, direct access to medications with limited or no availability for a short time • requirements: regulatory and logistical capacity for procurement from alternative channels while maintaining quality and safety standards Selected example: Rwanda: Public hospitals can order supplies directly from private wholesalers when there is a shortage.

Requirement for diversification of suppliers	Ministries of health or similar competent entities oblige procurement agencies and similar bodies to procure the same type of product from several suppliers to diversify their sources and reduce dependence on one supplier. • lead stakeholder: ministry of health • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain • advantage: improves the preparedness of the country for shortages, as the manufacturers that supply the national market reduce their risk of dependence on one API supplier • requirements: regulatory requirements and capacity to assess and monitor the quality of sources, financial capacity for meeting potential additional costs Selected examples: Rwanda: The national drug store is obliged to maintain at least three prequalified suppliers in their procurement plan to prevent shortages. United Republic of Tanzania: MSD, the public procurer, is required to have contracts with three suppliers per product and molecule to diversify risks.
Requirement to purchase and include locally manufactured products	The ministry of health or of trade may impose import restrictions on specific medications or molecules to ensure that procurement agencies purchase products locally. In countries with a national health insurance fund, the ministry of health or similar competent body can favour national or regional manufacturers by setting higher reimbursement rates for their products. This report acknowledges that local production might have an adverse effect on affordability but recognizes that localization of production can strengthen a country's supply chain. Discussion of when and whether to localize manufacture is beyond the scope of this report, as many factors would have to be considered for each context. • lead stakeholder: ministry of health • observed in: LMIC and HIC • type of shortage addressed: lack of registration, poor affordability, lack of demand planning • advantage: encourages manufacturers to establish national or regional production and therefore improves the preparedness of countries by decreasing their dependence on the global market • requirements: sufficient local manufacturing capacity and systems to assess and ensure the quality of locally produced drugs Selected example: Ghana: The country restricts importation of certain medicines, such as amoxicillin capsules (250 mg, 500 mg) and amoxicillin suspensions (125 mg/5 mL, 250 mg/5 mL) in favour of local manufacturers and to decrease dependence on the global market. United Republic of Tanzania: MSD, the public procurer, prioritizes bids issued by local manufacturers and pays 15% more for local products if they are in competition with international manufacturers. MSD currently supplies about 80% of the international market, as there are about 10 reliable local manufacturers.

Incentives to manufacturers to register shortage-prone products (market exclusivity)	NRAs or similar competent entities encourage manufacturers to register products through incentives such as reduced fees, longer market exclusivity for registering medications prone to shortages, such as novel antibiotics. • lead stakeholder: NRA • observed in: LMIC and HIC • type of shortage addressed: insufficient research and development, lack of registration • advantage: enables and diversifies access to shortage-prone medications by providing incentives to manufacturers to register medical products for the national market; market exclusivity ensures a certain profit, making production financially attractive to a manufacturer • requirements: financial and regulatory capacity to commit to market exclusivity, and systems to monitor market dynamics and drug availability Selected example: EU: Offers 10-year market exclusivity for orphan medicines after authorization, preventing similar products for the same indication from entering the market. Note: This approach should be nuanced as it risks restricting entry of competitors' products onto the market, which could lead to shortages in the long term. Furthermore, there is a risk that the incumbent could abuse its dominant position by increasing prices or restricting supplies. Careful consideration and strong mitigation strategies are therefore required (e.g. by enforcing a competition policy to prevent excessive pricing).
New reimbursement models for antibiotics (e.g. subscription model in HIC)	Countries introduce new antibiotic reimbursement models, such as the subscription model, in which reimbursement is based not on volume but on maintaining a stock of antibiotics. • lead stakeholder: ministry of health • observed in: HIC • type of shortage addressed: insufficient research and development, lack of affordability • advantage: provides an incentive for manufactures to maintain production of essential medicines by preventing gaps in supplies and to invest in research and development of new antibiotics for a consistent, predicable revenue stream • requirements: substantial financial capacity and political will to invest in long-term access to antibiotics • limitation: likely to be applicable only in HIC Selected example: Sweden: The new reimbursement subscription model (31 December 2023) maintains a buffer stock of off-patent antibiotics.
Requirement for diversification of sources of APIs	NRAs or similar competent entities oblige manufacturers to use APIs from several local sources or from other countries to diversify their sources and reduce dependence on the global API market. • lead stakeholder: ministry of health • observed in: HIC • type of shortage addressed: problems in the global supply chain • advantage: decreases the risk of shortages due to location or manufacturers' failure to supply, and diversifies API production • requirements: information on source of API (usually confidential), regulation and capacity to assess and monitor the quality of sources of APIs, financial capacity for potential additional costs Selected example: Germany requires antibiotics produced with APIs made in Europe for public procurement.

Increase visibility

Identification of essential drugs particularly prone to shortages (subcategory of lists of essential medicines)	NRAs or equivalent entities proactively identify drugs or molecules on the list of essential medicines that are prone to shortages. This allows implementation of targeted measures to ensure the availability of these drugs and their inclusion in risk plans. • lead stakeholder: ministry of health (enablers: NRA and procurement agency) • observed in: LMIC and HIC • type of shortage addressed: lack of registration and of demand planning • advantage: enables country to identify products to which measures should be applied (e.g. where to diversify supply or to seek alternative products) • requirements: data analysis to identify at-risk drugs and systems for continuous monitoring and updating of essential drugs lists Selected example: Germany: The BfArM publishes a list of essential paediatric medicines after consulting its advisory council and a list of supply-critical APIs (§ 52b paragraph 3c) *(39)*.
Registries for manufacturers to report expected shortages (early warning system)	NRAs or equivalent entities are required to establish and maintain an early warning system based on national registries that tracks all expected or current shortages and discontinuations of products. Manufacturers or marketing authorization holders (MAH) are legally obliged to notify authorities though dedicated portals a certain time in advance when they plan to discontinue a product or are experiencing problems in the supply chain. The information is shared with relevant stakeholders • lead stakeholder: NRA (in some countries: procurement agency) • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning • advantage: improves targeted action by NRAs to fill shortages, such as diversifying the supplier base, warning health-care professionals or recommending alternatives • requirements: regulatory mandates for reporting, sufficient bargaining power with the manufacturer (implying substantial market size) and infrastructure for effective data collection and dissemination Selected example: Denmark: The Danish Medicines Agency requires MAHs to notify them of any predictable or unpredictable supply shortages within no more than 2 months (unless special circumstances apply). The shortages include temporary shortages or cessation of marketing (notification is always mandatory even if a generic exists).

Establishment of a forecasting system and matching the expected demand with potential shortages	NRAs or equivalent entities are required to establish a system for forecasting demand and supply, for example for the next winter season. Forecasts are based on data on past and present supply and demand from manufacturers or MAHs. MAHs are legally obliged to share data on shortage-prone medications. • lead stakeholder: ministry of health, NRA, procurement agency • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning and national stock-taking • advantage: authorities can anticipate gaps in supply and demand rapidly. The data can be used to plan supply requirements for specific periods (e.g. waves of influenza), to develop regulations to prevent possible shortages and to plan orders. As, according to basic economic theory, supply usually follows demand, accurate forecasts could attract pharmaceuticals manufacturers to enter the market. • requirements: data analysis capacity for forecasting demand and supply, requiring cooperation with suppliers for access to data and national supply and drug consumption. Selected examples: EU: European Commission, Health Emergency Preparedness and Response Authority and EMA collected data on supply and demand from manufacturers to forecast supply and demand for key antibiotics for respiratory infections in the autumn and winter of 2023–2024, including specific paediatric formulations. United Republic of Tanzania: the MSD issues tenders that are based on the annual procurement plan prepared by the quantification team in the Ministry of Health. The plan is based on data on demand from public health facilities to forecast the demand for the following year.
National tracking and tracing system to predict demand	Ministries of health, procurement agencies and others develop a comprehensive tracking and tracing system for medications, by monitoring them from production to dispensing. Specific codes are assigned at various stages (serialization), which are validated at dispensing points such as pharmacies to ensure the authenticity of the medication and the integrity of the supply chain. • lead stakeholder: ministry of health (in some countries: procurement agency) • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning, national stock-taking and quality control • advantage: allows data-based decisions for efficient distribution to areas most in need; increases the transparency of the supply chain, ensuring legitimate sourcing, preventing falsification and smuggling and identifying products of unknown quality; helps procurers to identify the location of products to facilitate redistribution; faster, more accurate product recall and faster reimbursement of pharmacies by reimbursement agencies • requirements: ideally, one or only a few centralized procurement or distribution agents in the country, advanced digital infrastructure for tracking and tracing drugs, capacity for data analysis and decision-making Selected example: Türkiye: The Ministry of Health uses a full pharmaceutical track-and-trace system to secure the country's pharmaceutical supply. The system validates medicine packages at dispensing points with codes assigned during manufacture (Global Trade Item Number; serial number). Expiration date and batch number are also stored. The principles of the drug-tracking system are specified in "Packaging information of medicinal products for human use" *(41)*. MAHs, wholesalers, distributors, pharmacies and health facilities notify the system when a product is sold, exported or returned. Registration or importation must be done by the MAH. Patients using the drug can find its origin on an app. The system helps to identify products of unknown quality, which saves the country US$ 1 billion annually. It also provides inventory levels and ensures that drugs are sold only for accurate reimbursement systems *(42)*.

Public catalogue of national shortages (sometimes with suggested alternative)	NRAs or equivalent entities establish a national list of shortages that is accessible by various stakeholders, including manufacturers, pharmacies, health-care providers, and patients. MAH are legally required to inform the authorities in advance through dedicated portals if they plan to discontinue a product or encounter problems in the supply chain. • lead stakeholder: ministry of health, NRA • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning and national stock-taking • advantage: allows oversight of regional supply to inform health-care professionals, pharmacies and patients about shortages and availability • requirements: awareness of possible shortages or acute supply chain failures for regular updating and dissemination of information to the public and health-care providers Selected example: Sweden: The Swedish MPA publishes a list of upcoming and current shortages (with dates of the start and expected duration, cause of shortage, product identification numbers, package identification number, contact for the company, possible alternatives). Manufacturers are obliged to report upcoming shortages and discontinuation of products to the MPA.
Public catalogue of regional shortages (sometimes with suggested alternative)	Regional entities or international initiatives draw up lists of shortages in regions, providing a comprehensive overview for manufacturers, pharmacies, health-care providers and patients. The lists include the name of the product, the cause of shortage and the start date and expected duration. They are compiled from national data or directly from manufacturers and MAHs in the event of a shortage or discontinuation. Depending on the legal mandate of the regional entity, manufacturers and MAHs may be required to report anticipated disruptions, such as product discontinuation or supply chain issues, in advance through dedicated portals, which are a single point of contact, thus streamlining communication • lead stakeholder: regional health authority • observed in: HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning • advantage: allows oversight of regional supply and awareness of shortages among health-care professionals, pharmacies and patients; enabler for other regulatory measures • requirements: awareness of upcoming shortages, systems for regular updating and disseminating information to the public and health-care providers Selected example: EU: Established a single-point-of-contact working party to track shortages in EU countries and assess information on medicine shortages in more than one Member State. The shortages are published in a catalogue that includes the reason, the status of the shortage (ongoing or resolved), the extent of the shortage, information for patients and health-care professionals and links to relevant related documents.

Provision of guidance to healthcare professionals and the public	The ministry of health makes transparent, reliable announcements about the current situation and the future outlook. Direct guidance is given to health-care providers by including prescription guidelines, rationing strategies, use of magistral preparations and other measures • lead stakeholder: ministry of health • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain, lack of national stock-taking, poor affordability, preferences of health-care professionals • advantage: optimization of prescribed medication by health-care professionals and helps to shape the behaviour of health-care professionals and the public, e.g. avoiding hoarding • requirements: scientific and public health expertise and capacity, communication to provide timely, accurate guidance to health-care professionals during shortages Selected example: EU: In 2023, the MSSG endorsed a recommendation on addressing shortages of medicinal products. The MSSG may recommend news announcements to inform the public and health-care professionals about critical shortages and measures taken in the EU.

Institutionalize collaboration

Regional stockpiles	A regional entity builds a stockpile of critical medicines for unforeseen emergencies in the region, ensuring that countries have the medications for a specific time (e.g. 1–6 months). The size of the buffer stock is context-specific for factors such as shelf-life and the availability of appropriate distribution channels for both inpatient and outpatient use. Smaller buffer stocks reduce risks but may increase the likelihood of shortages. • lead stakeholder: ministry of health and/or NRA • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain • advantage: prevents short-term stock-outs of (essential) medicines • requirements: regional cooperation and funding to establish and maintain stockpiles Selected example: EU: For reserve capacity in disasters or emergencies, the European Commission upgraded the EU Civil Protection Mechanism to create a fully funded EU rescue plan, which includes a stockpile of medical items.
Harmonized labelling among countries in a region	The labels of pharmaceutical products contain standardized information about the product, which complies with the health authority regulations and industry standards of all countries in the region. • lead stakeholder: ministry of health and/or NRA • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain, lack of registration • advantage: enables rapid redistribution among countries and regions in the event of a shortage, with reduced bureaucracy and logistics; can encourage manufacturers to enter markets. • requirements: regulatory capacity to introduce and enforce agreements on standardization and regulatory alignment for consistent product labelling Selected example: EU: the EMA and the European Pharmacopoeia jointly set standards for pharmaceutical products and their ingredients, ensuring consistent quality throughout Europe. This also ensures that all Member States adhere to unified standards for the safety and efficacy of pharmaceuticals. In LMIC, the Southern African Development Community has launched an initiative to harmonize package labelling, although the project still requires legislative work before finalization *(43)*. ASEAN has provided guidelines on labelling requirements for traditional medicines *(44)*.

Regional harmonization of regulatory requirements (including on chemistry, manufacturing and controls)	NRAs in various countries align their standards (including for chemistry, manufacturing and controls) for registration. This can significantly reduce the cost to manufacturers of entering a market. • lead stakeholder: ministry of health and/or NRA • observed in: LMIC (under way) and HIC • type of shortage addressed: lack of registration • advantages: diversifies access to shortage-prone medications, as it encourages manufacturers to enter the markets in several countries by reducing financial and bureaucratic burdens • requirements: political will, collaborative regulatory frameworks among regions and mechanisms for aligning standards and approval Selected example: EU: The EMA revised evaluation of human medicines for the treatment of bacterial infections to contribute to reducing AMR. Regulators in the EU, Japan and the USA have agreed to align data requirements as much as possible so that the design of clinical trials includes the evidence required by several regulatory agencies. The African Medicines Regulatory Harmonization Agency is establishing guidance and standards for its member states and promoting adoption of similar standards for timely approval and joint assessment procedures. It provides models for authorization of medicines during acute shortages. The Agency collaborates with procurement agencies to ensure that registered products are included on lists of essential medicines.
Country-specific risk management plan for addressing shortages	The ministry of health, the procurement agency and the NRA develop a risk management plan to address shortages of essential medicines. This plan may include mandates, regulations for managing shortages or preventive measures such as diversifying the sources of medication to ensure a stable supply. NRAs therefore require manufacturers to report shortages and to develop risk management plans to identify potential risks in the supply chain. Risk management plans are included in the WHO Global Benchmarking Tool *(31)*. • lead stakeholder: ministry of health and/or NRA • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning and national stock-taking • advantage: streamlines coordination and ensures focused resource allocation in the event of a shortage; enabler for other regulatory measures • requirements: strategic planning capability and cross-sectoral collaboration Selected example: EU: The EMA issues recommendations on good practices for industry for the prevention of human medicinal product shortages *(37)*, which provide guidance on the flow of information, strengthening the supply chain and meeting the needs of patients.

Regional redistribution mechanism to exchange products	During shortages, a ministry of health may mandate redistribution of pharmaceutical products among regions or stakeholders. This requires assessment of the availability of essential medications and reallocation of supplies to areas or entities facing acute shortages. The aim of the strategy is to ensure equitable access to medications in regions or groups that are disproportionately affected by the shortage. • lead stakeholder: ministry of health and/or NRA • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning and national stock-taking • advantage: fast, short-term access to medications during shortages • requirements: agreements and logistics for sharing products among regions, a responsible coordinating body Selected example: EU: Introduced a voluntary solidarity mechanism to ensure that member states of the EU and the European Economic Area could obtain medicines during critical shortages. The mechanism is overseen by the MSSG. In 2023, the MSSG endorsed a recommendation for addressing shortages of medicinal products. The MSSG may recommend lifting of national export restrictions and other measures to ensure fair distribution of medicines.
Use of regional forums and bodies to strengthen collaboration on shortages	Use of regional forums to improve a region's preparedness for medicine shortages. Regular meetings are essential to discuss joint strategies for shortages and to increase the visibility of the collaboration. • lead stakeholder: ministry of health and/or NRA • observed in: LMIC and HIC • type of shortage addressed: problems in the global supply chain, lack of demand planning capability, national stock-taking and quality control, preferences of health-care professionals • advantage: establishes strong relations that can be activated rapidly during crises to discuss potential means for preventing shortages • requirements: platforms for regional collaboration, information exchange with manufacturers: sufficient market size to attract investment by manufacturers Selected example: Nordic countries: Denmark, Finland, Norway and Sweden have established a working party of the Nordic Council on exchange of pharmaceutical information to find solutions to supply problems. In 2016, the Nordic Council of Ministers for Health and Social Affairs and for Food and Agriculture formed a cross-sectoral strategy group to prevent local and international AMR. This group, advised at regular meetings of field experts, recommends priorities.
Dialogue	Regular exchanges between two groups (e.g. NRA and industry) on shortages and mitigation measures, often ad-hoc, not formalized • lead stakeholder: ministry of health, NRA and/or regional organization • observed in: LMIC and HIC • type of shortage addressed: all types mentioned • advantage: establishes strong relations that can be activated rapidly during crises; creates awareness among stakeholders and discussion of potential solutions • requirements: no strict requirements, pre-existing working relations are beneficial Selected example: EU: EMA holds regular exchanges with pharmaceutical companies on potential or current shortages of medicines.

Working groups	Establish regular exchanges among stakeholders on shortages and mitigating measures at various levels of formality, often with no stringent terms of reference. • lead stakeholder: ministry of health, NRA and/or regional organization • observed in: LMIC and HIC • type of shortage addressed: all types of shortage mentioned • advantage: establishes strong relations that can be activated rapidly during crises; raises awareness among stakeholders and discussion of potential solutions • requirements: pre-existing working relations are beneficial, a responsible coordinating body Selected example: Rwanda: the Ministry of Health holds regular meetings (no formal frequency) with procurement and industry stakeholders to identify and mitigate shortages of medicines.
Steering committees	Formal multi-stakeholder groups to be convened for discussions and decisions on management of shortages. Decision-making power is usually formalized through policies, terms of reference or another agreement. • lead stakeholder: ministry of health, NRA and/or regional organization • observed in: LMIC and HIC • type of shortage addressed: all types of shortages mentioned • advantage: establishes strong relations that can be activated rapidly in crises, creates a strategy for preventing drug shortages • requirements: pre-existing working relations are beneficial; a responsible coordinating body Selected example: South Africa: Pharmaceuticals and Therapeutics Committee oversees the medicines management system
Multi-stakeholder organization	Organization of partners working on a specific mission for management of shortages, with clearly defined roles, responsibilities and processes formalized in policies, terms of reference or other agreements. • lead stakeholder: ministry of health, NRA and/or regional organization • observed in: HIC • type of shortage addressed: all types of shortages mentioned • advantage: establishes strong relations that can be rapidly activated during crises, creates a strategy for prevention of drug shortages • requirements: pre-existing working relations beneficial; a responsible coordinating body Selected example: EU: Coordination and Harmonisation of the Existing Systems against Shortages of Medicines – European Network initiative was established to coordinate 22 EU NRAs. Topic-specific subdivisions result in a harmonized response to shortages and improve collaboration.

3.6 Country examples

This section demonstrates the diversity of measures in place in different countries. The country examples illustrate problems in each country and measures taken to address them

Additional country profiles are available in Annex 3.

Burkina Faso

Context

National regulatory authority: Direction Générale de la Pharmacie, du Médicament et des Laboratoires

Classification: Maturity level 1/2

About the Direction Générale de la Pharmacie, du Médicament et des Laboratoires:

- Has the mandate to ensure availability of effective, safe and high-quality health products and their compliance with regulations and standards
- Includes four directorates: (1) Pharmaceutical Regulation and Licensing (DRLP); (2) Pharmaceutical Supply Security (DSAP); (3) Medicine and Pharmacopeia (DMPT); and (4) Laboratories (DL)[1]

Health system:

- National procurement agency CAMEG (Central d'Achat des Médicaments Essentiels Génériques et des Consommables Médicaux).

Shortage situation: No widespread shortages reported at the national level. Unavailability of reserve antibiotics due to a lack of registration of specific molecules, attributed to the small market size and registration challenges for manufacturers. Additionally, subnational stock-outs are observed, stemming from forecasting challenges faced by the national procurement agency, Central d'Achat des Médicaments Essentiels Génériques et des Consommables Médicaux (CAMEG).

[1] Ministère de la Santé et de l'Hygiène Publique, 2024 (*45*)

The country has adopted an essential medicines list, updated every three years, which includes the WHO AWARE classification to guide antibiotic usage. The NRA has introduced flexibility in product registration, particularly for reserve antibiotics and third-line products that are not yet registered. Furthermore, the NRA allows manufacturers to independently set prices for these products. In emergency scenarios, the NRA can authorize private wholesalers to import drugs that are in short supply. Additionally, it grants temporary waivers for labeling requirements; however, these labels must be in French. An emergency response framework is in place but requires further refinement as it has yet to function effectively.

Further measures highlighted by experts to combat shortages at the sub-national level are focusing on strengthening of sourcing. The Ministry of Health commits to ensuring an 80% availability of vital drugs in hospitals, with wholesalers encouraged to stock a similar percentage of the essential medicines list. However, enforcement mechanisms are needed to ensure compliance by wholesalers. The country is also part of pooled procurement initiatives supported by the EMA, aiming to centralize purchasing and distribution of medicines, including antibiotics, tailored to each country'' needs.

In 2021, with WHO support, Burkina Faso initiated a significant project to increase visibility by introducing an e-procurement system for the Ministry of Health . This system will feature capabilities for handling inquiries, bid preparation, and submission digitally. The project entails setting regulatory and functional requirements as well as technical specifications for the procurement agencies. Economic indicators defined through this system will enhance the monitoring and quality reporting of public procurement operations, allowing for adaptive policy-making and decision-making in the event of identified supply shortages. The data gathered will also support electronic modules such as e-planning, e-tendering, and e-contract management, alongside standard procurement performance reports, ultimately saving time and effort while ensuring quality in reporting.

Furthermore, Burkina Faso is continuously improving its measures to institutionalize collaboration. The NRA, Ministry of Health, wholesalers, and importers have regular exchanges at which they discuss issues of shortages.

Burkina Faso | Key learnings

Leveraging e-procurement for enhanced supply chain management: Using e-procurement systems can bolster supply chain transparency and efficiency and can be used for demand and supply forecasts as well as to improve visibility of counterfeit or falsified medicines.

Commitment to drug availability by the Ministry of Health is a first step to improve medicine availability: The Ministry of Health has committed to ensuring 80% availability of vital drugs in hospitals. This highlights the government's proactive approach and can be a first step within the country to prevent drug shortages.

Enforcement mechanisms are essential to guarantee stocking of medicines: Defining clear commitments and setting explicit targets for drug availability is crucial but must be supported by robust enforcement mechanisms to ensure these commitments are fully realized.

Malaysia

Context

National regulatory authority: Malaysian National Pharmaceutical Regulations Agency (NPRA)

Classification: Maturity level 3 according to WHO Global Benchmarking *(38)*

About the NPRA:

- mandated to regulate the quality, safety and effectiveness of medicines and vaccines
- is integrated into the Ministry of Health *(46)*

Health system:

- dominated by the public sector, covering ~65% of the population *(47)*
- public procurement managed by the Pharmacy Practice and Development Division in the Ministry of Health

Shortage situation: Malaysia experienced a shortage of six antibiotics in 2022, due to disruptions in the global supply chain, including amoxicillin and ampicillin sulbactam. (According to the NPRA, the shortages were resolved in July 2023.)

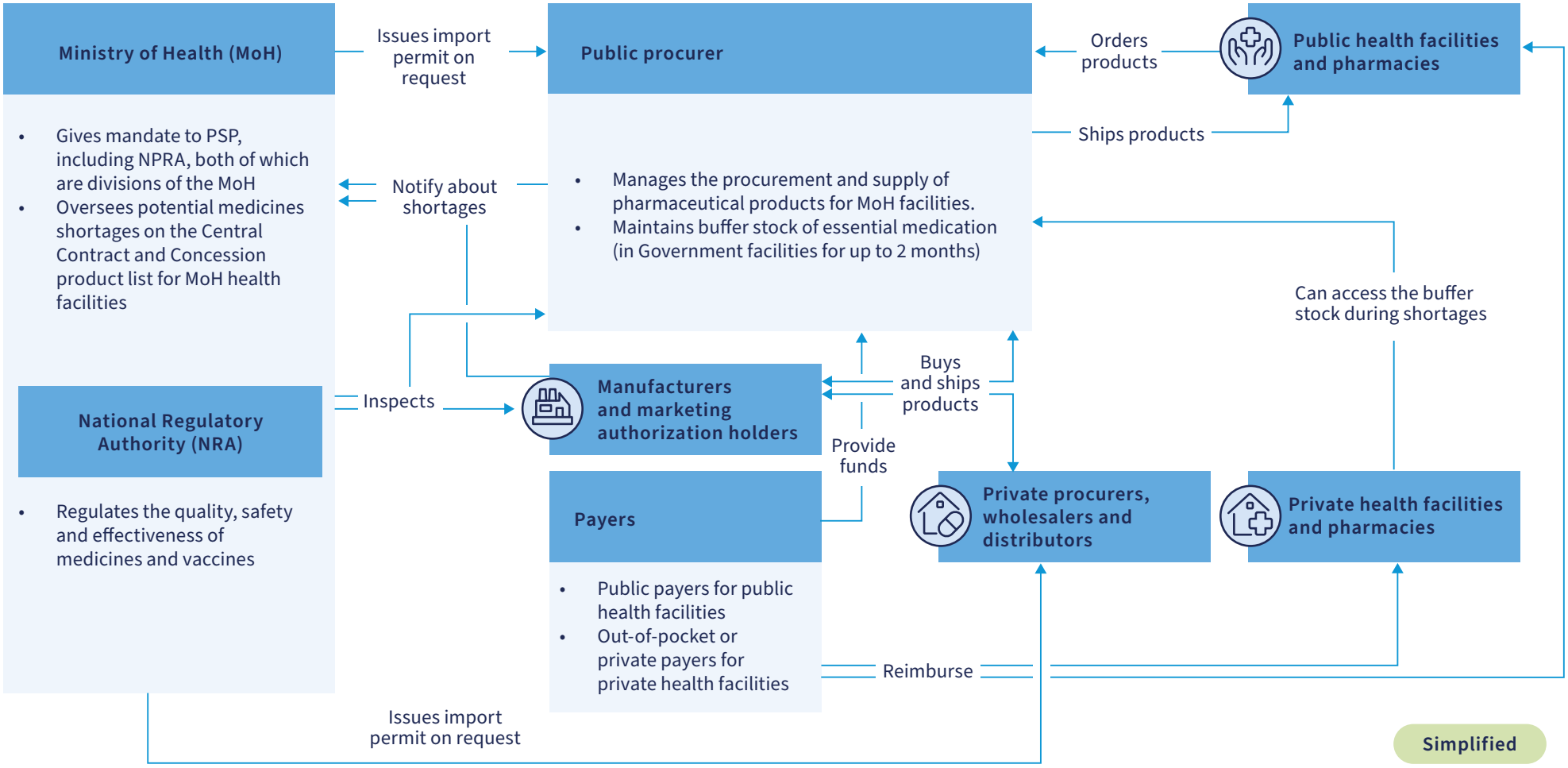
To prevent shortages in Malaysia, the measures in place include regulatory flexibility, such as accelerated approval of imports and manufacture during emergencies. A supply chain expert interviewed for this analysis observed that increasing reliance on registration waivers risks compromising quality by bypassing the NRA's procedures. It is recommended that, instead of waivers, flexibility measures be included in the NRA policy framework, clearly defining situations in which they can be used and appropriate risk mitigation measures. The NPRA maintains a list of medications, including possible alternatives, that are eligible for fast-track approval. The speed of such approval depends on the integrity of the dossier and the product type (e.g. a maximum approval time of 100 working days for generics). In addition, the NPRA allows flexibility in registration and approval in emergencies by issuing approvals for additional manufacturers. Flexibility in labelling can also be used during emergencies (e.g. labels from other countries or outdated labels or specifications are accepted). Such labelling exemptions are applicable only within 6 months of approval of the product registration. According to experts at the NPRA, accelerated approval was the most effective measure for addressing shortages.

To increase transparency, the NPRA requires public hospitals and community pharmacies to report stocks of products on the drug shortage list every second month. According to NPRA experts, there is an electronic document in which health facilities report any shortages. They noted, however, that there is currently no legislation to enforce reporting of shortages, although discussions are under way.

Malaysia | Summary of measures

Increase flexibility for emergencies	• temporary permit to import products destined for other markets • temporary permit to switch to alternative procurement channels such as private distributors • fast-track approval of substitute products in acute shortages • requirement to purchase or include locally manufactured products
Strengthen sourcing	• national buffer stock held by manufacturers and pharmacies • work with manufacturers to increase the supply of identified products
Increase transparency	• registries for manufacturers to report upcoming shortages (early warning system) • public catalogue of national shortages, sometimes combined with suggestions for alternatives
Institutionalize collaboration	• use of regional forums and bodies to strengthen preparedness for shortages • dialogue • working groups

Malaysia


Ministry of Health (MoH)
Issues import permit on request
Public procurer
Orders products
Public health facilities and pharmacies
Gives mandate to PSP, including NPRA, both of which are divisions of the MoH
Oversees potential medicines shortages on the Central Contract and Concession product list for MoH health facilities
Notify about shortages
Manages the procurement and supply of pharmaceutical products for MoH facilities.
Maintains buffer stock of essential medication (in Government facilities for up to 2 months)
Ships products
Can access the buffer stock during shortages
National Regulatory Authority (NRA)
Inspects
Manufacturers and marketing authorization holders
Buys and ships products
Provide funds
Regulates the quality, safety and effectiveness of medicines and vaccines
Payers
Private procurers, wholesalers and distributors
Private health facilities and pharmacies
Public payers for public health facilities
Out-of-pocket or private payers for private health facilities
Reimburse
Issues import permit on request
Simplified

To strengthen sourcing, the Pharmaceuticals Services Programme is required to keep buffer stock of essential medicines for up to 3 months. Buffer stocks are released when there are shortages, when the stocks can be bought by both public and private facilities. An example was observed in May 2022, when a shortage of paracetamol in over 220 private health-care facilities was resolved by releasing part of the buffer stock. Other initiatives include collaboration between the NPRA and local manufacturers to increase their production capacity during shortages.

The Malaysian Government has introduced several measures to institutionalize national and international collaboration. Several round-table discussions have been held with representatives of the pharmaceutical industry, health-care professionals and others in the private and public health sectors to devise strategies to reduce the impact of shortages of medicines on the public within the Malaysian National Medicines Policy *(48)*.

Malaysia leads the ASEAN Drug Security and Self-reliance initiative and participates in the ASEAN Vaccine Security and Self-reliance initiative *(49)* to ensure sustained, uninterrupted access to medicines and vaccines, including during acute shortages.

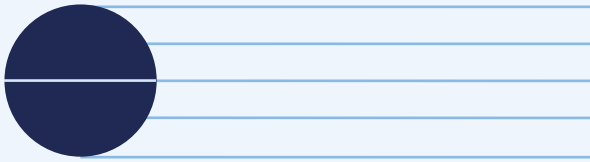
Collaboration among stakeholders and enforcement of quality control are essential in addressing antibiotic shortages. To illustrate use of these effective strategies, Rwanda is cited for collaboration and South Africa for use of measures to enforce quality control. Both countries also use measures to anticipate and mitigate shortages.

Malaysia | Key learnings

Cross-institutional collaboration and clear division of tasks: Collaboration between the Ministry of Health and the NRA, with clear allocation of roles and responsibilities, is essential.

Aim for progress over perfection: Malaysia uses pragmatic solutions, such as use of simple tools such as an online platform for reporting, instead of waiting for sophisticated systems to be developed.

Cross-borders alliances and regional collaboration: To strengthen core regulatory functions, Malaysia is engaging in capacity-building with other Asian countries and is part of the ASEAN Drug Security and Vaccine Reliance initiative.



Rwanda

Context

Collaboration in addressing antibiotic shortages:

- Antibiotic shortages are addressed by several bodies within the health system to safeguard a continuous supply of medicines. Networks and collaborations should be organized before shortages occur to ensure a rapid, effective response in a crisis.
- Various organizational and geographical levels of communication are necessary to address different types of shortage. Regular exchanges between the public and private sectors are useful for preventing or alleviating shortages. Regional collaboration ranges from bilateral dialogue to more complex measures such as redistribution and shared stockpiles.
- Regional harmonization of regulatory requirements will be the solution in the long term, which will require effective collaboration. More flexible redistribution of products, providing manufacturers with incentives to register products and harmonization, can prevent or mitigate shortages.

Best practices in collaboration:

- Rwanda FDA is rapidly developing an NRA. The Rwanda FDA, established in 2018, quickly achieved WHO maturity level 2 and is working to reach level 3 *(38, 50)*.
- Rwanda is facing shortages of several antibiotics and other drugs, and the situation was exacerbated by COVID-19, when shortages, particularly of specific doses of amoxicillin, occurred in the public sector *(51)*. Rwanda has no domestic drug production and depends on suppliers in China and India, with significantly disrupted supply chains at that time *(52)*.

Rwanda | Key learnings

- Collaboration is necessary for a rapid response to acute shortages. The Rwanda FDA has memoranda of understanding with the more mature NRAs of Ghana and the United Republic of Tanzania *(50,53)*. Recognition of products that had been inspected by either of the two NRAs accelerates registration in Rwanda and allows the country to source alternative products when there are acute shortages. The Rwanda FDA participates in the EAC Medicines Regulatory Harmonization programme, which has developed a common technical document for drug registration and established a mutual recognition framework for drug approval *(54)*. Rwanda can therefore increase drug supplies during shortages by granting regulatory flexibility and enabling imports from partners. This process creates larger, more attractive markets for manufacturers, thereby strengthening sourcing by diversification of suppliers. Rwanda's Ministry of Health holds regular meetings with the national procurement organization (Rwanda Medical Supply) to discuss potential and current shortages.
- Collaboration to build capacity and skills. Collaboration with other NRAs also facilitates transfer of knowledge and building capacity to support the objective of the Rwanda FDA of achieving WHO maturity level 3.
- Collaboration to strengthen general regulatory functions. Collaboration between the Rwanda FDA and law enforcement agencies ensures enforcement of quality assurance by removing non-compliant medical products *(55)*. This will significantly reduce the circulation of unregistered, substandard and falsified drugs and therefore facilitate identification of actual shortages

South Africa

Enforcement of quality control in addressing antibiotic shortages

Effective quality control signals actual shortages of quality-assured medicines. Falsified, substandard and counterfeit drugs* are prevalent in LMIC: WHO reports that 1 in 10 medical products in LMIC are falsified or substandard *(57)*, with major effects on health and the economy. In sub-Saharan Africa, such drugs are estimated to be the cause of 116 000 deaths annually and of an additional US$ 38.5 million in costs for care *(58)*. A study of 312 drug samples in South Africa, including common medications such as amoxicillin and paracetamol, showed that only 55.4% met all the necessary standards for quality *(59)*. Removal of falsified and substandard drugs allows evaluation of the supply of quality-assured drugs that are to be listed in a catalogue of shortages. If falsified, substandard or counterfeit antibiotics are not removed, because of ineffective quality control, the risk for AMR is increased, as treatment is insufficient, inducing resistance. Effective enforcement of quality control is a core function of NRAs and may the basis for extending their mandate to management of shortages. Strengthening of this function will therefore allow an NRA to address shortages through targeted measures. A strong NRA can enforce its mandate to ensure the quality of products in the country by removing falsified and substandard drugs.

Best practices in quality control in South Africa

South Africa has a health-care system dominated by public health and a mature NRA. The system serves 84% of the population, and the NRA, SAHPRA, is at WHO maturity level 3 *(38, 61)*.

SAHPRA has a dedicated inspection unit for enforcing its mandate *(62)*, which is to inspect both national and international segments of the supply chain of medicines and vaccines sold in South Africa by entering and inspecting relevant locations, taking samples and seizing necessary data *(63)*.

WHO terminology: falsified, substandard and counterfeit medicines* *(56)*

Falsified: Medical products that deliberately or fraudulently misrepresent their identity, composition or source

Substandard (also known as "out of specification"): Authorized medical products that fail to meet either their quality standards or their specifications or both

Trademark counterfeit: Products, including packaging, bearing without authorization a trademark that is identical to the trademark validly registered in respect of such product, or which cannot be distinguished in its essential aspects from such a trademark, and which thereby infringes the rights of the owner of the trademark in question under the law of the country of importation

South Africa | Key learnings

- Create public awareness about products of assured quality: Collaborative initiatives between the general public and law enforcement agencies in addressing counterfeit, falsified, and low-quality products can raise awareness about these products. The aim of SAHPRA's public education campaign *(67)* on avoiding falsified and substandard drugs is part of the national strategy to raise awareness, strengthen public–police cooperation and reduce the demand for these drugs. The campaign:
  - raises awareness of the problem by training pharmacists;
  - explains the dangers of falsified and substandard drugs;
  - shows how to identify a problematic product;
  - provides advice on action to be taken if a problematic product is found; and
  - offers strategies for avoiding such drugs.
- Ensure strict enforcement and hold pharmacists accountable: To uphold NRA quality standards, SAHPRA issues licenses to holders of certificates of registration, who are responsible for the quality of imported and domestically manufactured drugs. The principle of personal responsibility is also enforced in pharmacies, where a designated pharmacist is personally accountable for ensuring compliance with the Medicines and Related Substances Act *(64)* and the Pharmacy Act *(65)*. The penalties stipulated by the Acts include imprisonment for up to 10 years and removal from the pharmacist register. The South African Pharmacy Council is mandated by the Pharmacy Act to inspect and grade pharmacies according to their compliance with good pharmacy practice. Further inspections of the pharmacies depend on their grade: Grade A pharmacies are inspected after 3 years, grade B after 2 years and grade C after 1 year *(66)*. Pharmacies that are no longer in operation, have closed or have relocated without informing the authorities are in Grade D.
- Form a multidisciplinary expert team to ensure quality: The national pharmaceutical "crime task" team meets quarterly to devise strategies to prevent falsified and substandard drugs. Its members represent a wide coalition of public and private stakeholders:
  - SAHPRA: the NRA, responsible for regulation of health products intended for human and animal use and licensing of manufacturers, wholesalers and distributors of medicines and medical devices;
  - the Directory for Priority Crime Investigation, a police directorate responsible for investigation and prevention of national priority crimes, such as serious organized crime, serious commercial crime and serious corruption;
  - the Institute of Commercial Forensic Practitioners, which regulates the commercial forensic profession in South Africa by providing a regulatory framework and a code of conduct for detection and deterrence of commercial crime and other forms of exploitation of commercial systems;
  - "clicks group": A South African retail group that includes a pharmaceutical wholesaler;
  - Adcock Ingram, a South African pharmaceutical company; and
  - the Companies and Intellectual Property Commission, an agency of the Department of Trade responsible for registration of companies, cooperatives and intellectual property rights (trademarks, patents, designs and copyright).
- Collaborate globally to remove falsified drugs: Most falsified drugs originate from China and India *(67)* and reach South Africa primarily through its land borders, posing a significant challenge. South Africa therefore participates in the African Pharma Crime Task Team, comprising 22 African countries that discuss pharmaceutical crimes and facilitate cross-border enforcement *(68)*. South Africa is also involved in Operation Pangea, an Interpol operation against illicit drugs *(68)*. The latest activity led to 72 arrests, seizure of drugs worth more than US$ 7 million and closure of 1300 criminal websites.

United Republic of Tanzania

Context

National regulatory authority: Tanzania Medicines & Medical Devices Authority

Classification: Maturity level 3 according to WHO Benchmarking *(38)*

About the Direction Générale de la Pharmacie, du Médicament et des Laboratoires:

- among the most mature NRAs on the African continent
- first African NRA to be certified as at level 3 maturity, in 2018 *(69)*

Health system:

- relatively evenly divided between the public (55%) and private (45%) sectors *(70)*
- has a public procurement agency, MSD, which is an autonomous department under the Ministry of Health and the largest buyer of medical commodities; procures, stores, distributes and, to a smaller extent, manufactures medical products *(71)*.

Shortage situation: The United Republic of Tanzania appeared to be less affected by global antibiotic or drug shortages than the other countries surveyed, although anecdotal evidence points to antibiotic shortages in hospitals. Any shortages are due mainly to national factors such as disruption of the supply chain or budgetary limitations.

The MSD has undergone several reforms to address and prevent shortages and stock-outs *(72)* to increase transparency. Because of frequent stock-outs of antiretroviral drugs in the early 2010s, MSD sought support from the Global Fund to Fight AIDS, Tuberculosis and Malaria to improve its performance with use of the resource planning software EPICOR. Quantification and forecasting were improved by the switch from paper-based to digital data collection *(73)*. Further improvements in forecasting and supply planning were introduced between 2016 and 2021 under the US Global Health Supply Chain Technical Assistance Program *(74)*, with establishment of an electronic logistics management information system. The system links health facilities, MSD and the Ministry of Health and is used to monitor stocks, order replenishments and detect stock-outs. The initiative has resulted in a notable decrease in the frequency of stock-outs *(74)*.

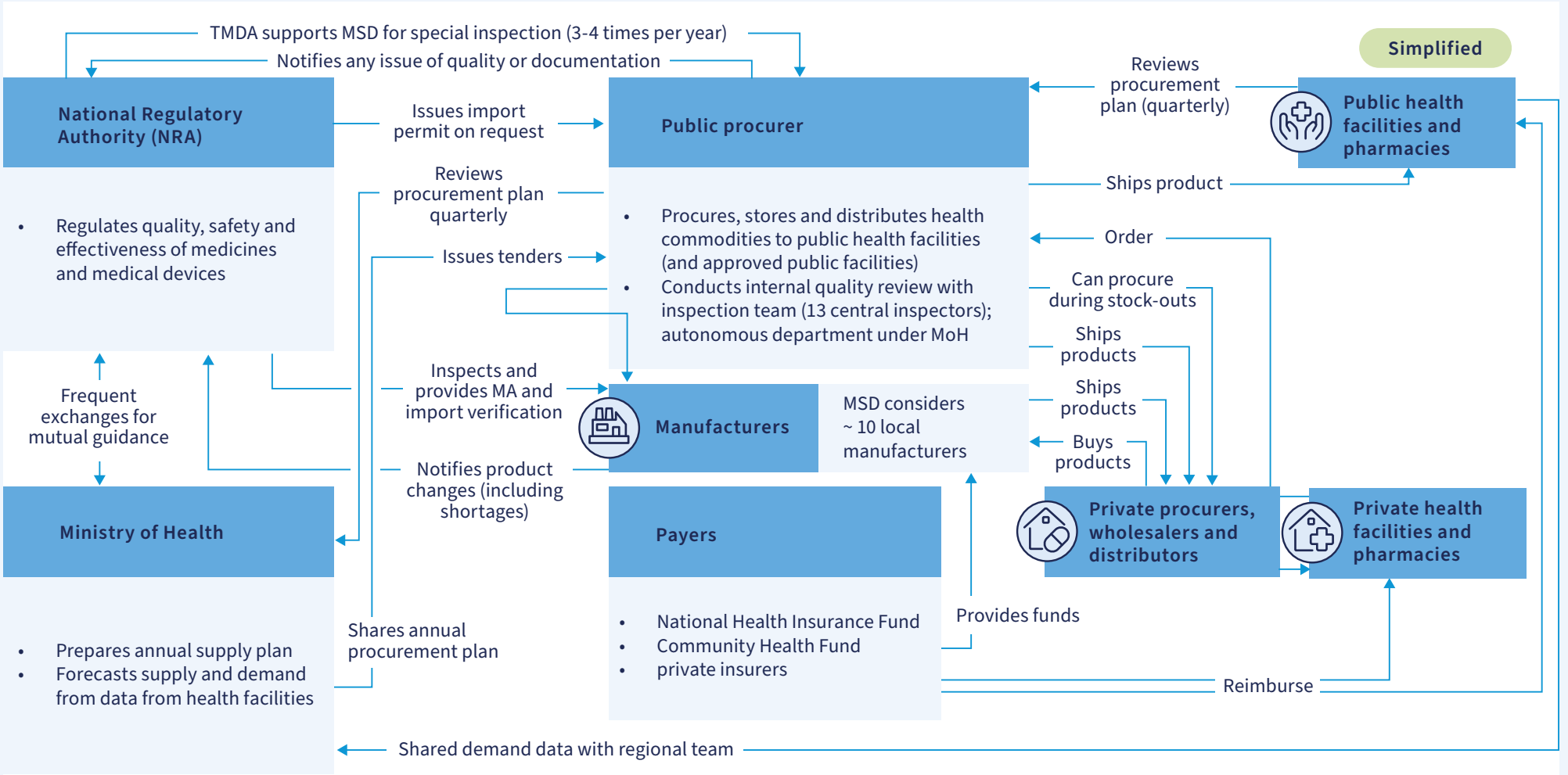
Other measures reported by experts at MSD include strengthening sourcing. For example, MSD introduced requirements for buffer stocks, specifying that stock must cover a minimum of 5 months' and a maximum of 9 months' demand. MSD has a policy of awarding at least three suppliers for each molecule to ensure back-up supplies in shortages. To encourage local sourcing, local manufacturers are allowed to charge prices up to 15% higher than those of international sources. MSD is planning several multi-year contracts for antibiotics once effective forecasting and supply planning are in place. According to an interview with an MSD expert, these two measures, diversification of the supplier base and introduction of multi-year contracts, have the greatest impact for addressing stock-outs and shortages.

The NRA also enhances flexibility in cases of acute shortages. Thus, in emergencies, the NRA can authorize importation from manufacturing sites approved by SRA/WHO listed authorities (WLA), or selected NRAs in other EAC countries. The NRA can also use accelerated approval procedures for substitutes during emergencies. A supply chain expert interviewed for this analysis observed increasing reluctance to use such waivers for registration, as they could compromise quality by bypassing the NRA's usual procedures. It is recommended that, instead of waivers, flexibility be incorporated into the NRA's policy framework by clearly defining situations in which waivers can be used and appropriate risk mitigation measures.

Collaboration is being institutionalized, with several initiatives for regional harmonization. The EAC Medicines Regulatory Harmonization programme, launched in 2012, is a regional programme within the African Medicine Regulatory Harmonization initiative for standardizing regulation of medicines, vaccines and medical devices *(75)*. Registration is simplified by joint assessments and registration, while each NRA is responsible for initial screening, validation and overall coordination *(76)*. In addition, a policy for increasing local production of antibiotics in the EAC has been endorsed *(77)*. The MSD conducts quarterly reviews of its supply plan with the NRA, health facilities and other partners to improve the plan and anticipate potential shortages.

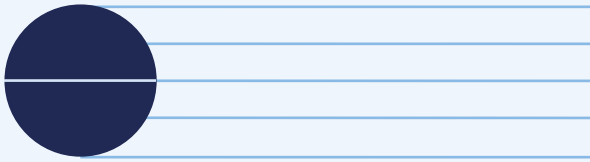
The NRA is also strengthening its regulatory core functions. For instance, it is part of an EU-funded project, Building Resilient Research Ethics, Diagnostics and Medicines, to strengthen its regulatory frameworks, research ethics and clinical trial oversight *(78)*.

United Republic of Tanzania



United Republic of Tanzania | Key learnings

- Different drivers of shortages require different measures: While NRAs can react rapidly to acute shortages (e.g. by granting regulatory flexibility), entities in the national supply chain are often better positioned to address local shortages and stock-outs by increasing supply and optimizing sourcing.
- The characteristics of a health system determine changes that can be made: The United Republic of Tanzania has one dominant organization for various steps in procurement and distribution. Therefore, system-wide changes could be made with less dependence on central coordination. This would be more difficult in a decentralized health system with several bodies responsible for procurement and distribution, as in Nigeria.
- Mitigation of the risk of shortages may be in the mandate of the procurer: As MSD is required to maintain a minimum number of suppliers for essential medicines and to keep a buffer stock, it is indirectly mandated to diversify risks and anticipate shortages.



United States of America

Context

National regulatory authority: US FDA

Classification: SRA, WHO-listed authority

About:

- among the world's largest, best-funded NRAs, with a budget in 2023 of > US$ 8 billion *(83)* and over 15 000 employees *(79)*;
- mandated by Executive Order 13588 (2011) *(80)* and the CARES Act (2020) to monitor drug supplies *(81)*

Health system:

- dominated by the private sector, with decentralized procurement;
- largest pharmaceutical market, with strong bargaining power, such as on regulatory aspects, with manufacturers *(82)*.

Shortage situation: Since the start of the COVID-19 pandemic, the USA has experienced shortages in various drug classes, including antibiotics such as amoxicillin, rifapentine, azithromycin, doxycycline, tobramycin and bicillin *(4,5,83)*.

The US FDA has introduced various measures to address drug shortages, such as enhancing regulatory flexibility for approval of drugs and manufacturing sites. A supply chain expert interviewed for this analysis observed increasing reluctance to use registration waivers because of the risk of compromising quality by bypassing NRA procedures. It is recommended instead to include flexibility in defining situations in which they can be used, and appropriate measures to mitigate risk. In its annual report to Congress, the FDA reported that, in 2022, regulatory flexibility measures were used in 87 instances affecting 76 products *(8,84,85)*.

Temporary flexibility includes release of medically necessary products of questionable quality; however, to mitigate any risks, FDA requires certain measures, such as supplying products with a filter to remove particulate matter, extra testing before release of the product, third-party oversight of production to ensure quality, and providing special instructions to health-care professionals and patients.

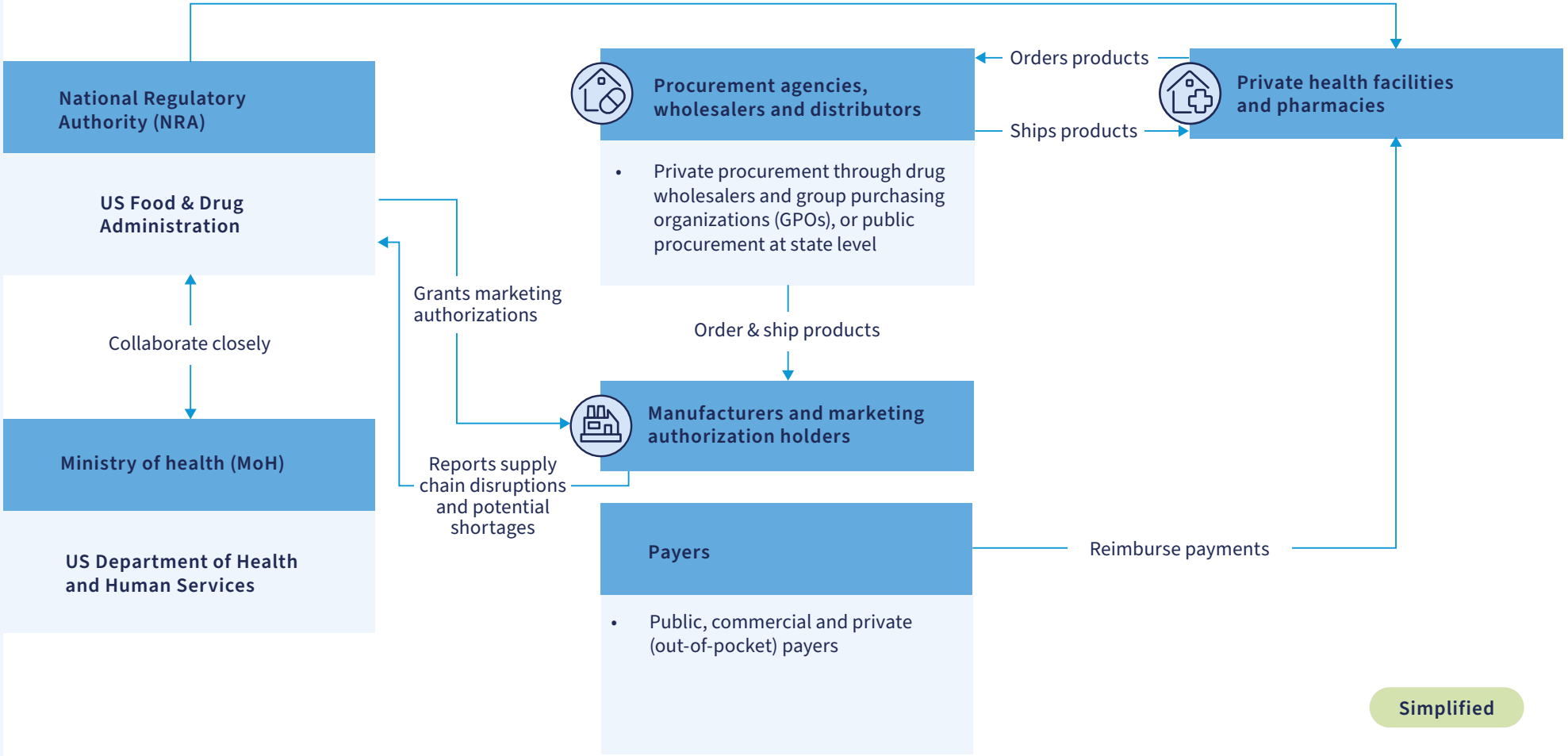
In some cases, to prevent a shortage, the FDA has allowed continued distribution of a drug of unknown quality on condition of a simultaneous review of a supplementary product. The FDA also uses temporary regulatory flexibility with respect to new sources of medically necessary drugs when all alternative approaches have been exhausted. The FDA also exercises temporary flexibility by extending the expiry date of products to meet demand *(85)*.

Further measures include strengthening sourcing. The Department of Health and Human Services has established a consortium with the private sector to increase domestic production of critical medicines *(84)*. For example, in August 2021, USAntibiotics announced repatriation of the production of amoxicillin from China *(86)*.

Other measures are to increase transparency. Manufacturers are required to report temporary or permanent interruptions in production to the FDA, and a list of shortages is published by the Center for Drug Evaluation and Research. The mobile app "DrugShortages" of the FDA and the American Society of Health System Pharmacists provides public information on shortages.

Several measures have been initiated to institutionalize collaboration. In July 2018, FDA established the Agency Drug Shortages Task Force to identify the causes of drug shortages and propose potential long-term solutions. Members of the Task Force include officials from several federal agencies, including the FDA, the Department of Health and Human Services, the Centers for Medicare and Medicaid Services, the Office of the Assistant Secretary for Preparedness and Response, the Department of Veterans Affairs and the Department of Defense. The Task Force also held sessions with stakeholders from academia, medical organizations, pharmacies, hospitals, drug manufacturers, trade associations, group purchasing organizations, distributors and payers *(85)*.

United States of America



Summary of measures	
Enhance flexibility for acute shortages	• temporary flexibility with respect to the raw material source or manufacturing site • temporary extension of expiry date, if safe • temporary flexibility for batch releases • fast track of approvals of alternative products in an acute shortage
Strengthen sourcing	• work with manufacturers to increase the supply of identified products
Increase visibility	• registries for manufacturers to report upcoming shortages (early warning system) • establishment of forecasting system: match expected demand and supply to identify potential shortages • public catalogue of national shortages (in some cases, with suggestions for alternatives) • provision of guidance to health-care professionals and the public
Institutionalize collaboration	• country-specific risk management plan for addressing shortages • dialogue • working groups

Key learnings

In a fragmented health system dominated by the private sector, central coordination is essential. In the absence of a central procurement agency in the USA, the NRA is the central coordinating body, with an official mandate to monitor the drug supply.

Information on supply and demand is essential. Establishment of a central database of shortages and their locations allows alignment of stakeholders and sharing of information.

Market power, whether in a large economy or due to pooled procurement, determines a country's influence on manufacturers. Because of its strong bargaining power, the USA can demand concessions from manufacturers, such as data reporting. Such concessions might be difficult to obtain in smaller countries but could be achieved through pooled procurement.

4. Measures for addressing shortages of antibiotics in LMIC

Below, a set of measures is provided for consideration by LMIC. First, the measures described above are assessed for their anticipated impact and the work required for their implementation. Then, the requirements for successful implementation are discussed.

4.1 Assessment of measures by impact and ease of implementation

Fig. 12 shows the assessment of the set of identified measures according to anticipated impact and ease of implementation.

Anticipated impact

The criteria for prioritizing measures according to their anticipated impact were:

- impact size: extent to which a measure addresses shortages of sub-groups of medicines (e.g. applicable only in hospitals) or larger groups (e.g. all antibiotics or even all essential medicines);
- direct and indirect impact: impact on shortages of supplies of antibiotics. For instance, identifying an alternative treatment is considered to have a more direct impact than a less direct measure such as publishing a catalogue of shortages.
- short- and long-term impacts: Long-term measures that prevent shortages, such as regional harmonization of regulatory requirements, were ranked higher than temporary, short-term solutions such as flexibility in labelling or package size, which are designed for emergencies.
- essential for other measures: For example, national tracking and tracing are considered crucial for transparency in supply and demand and are ranked relatively high for the work involved.

Ease of implementation

Each mitigation measure has specific prerequisites or an impact on other parameters, which influence the effort required for implementation. The following dimensions were considered:

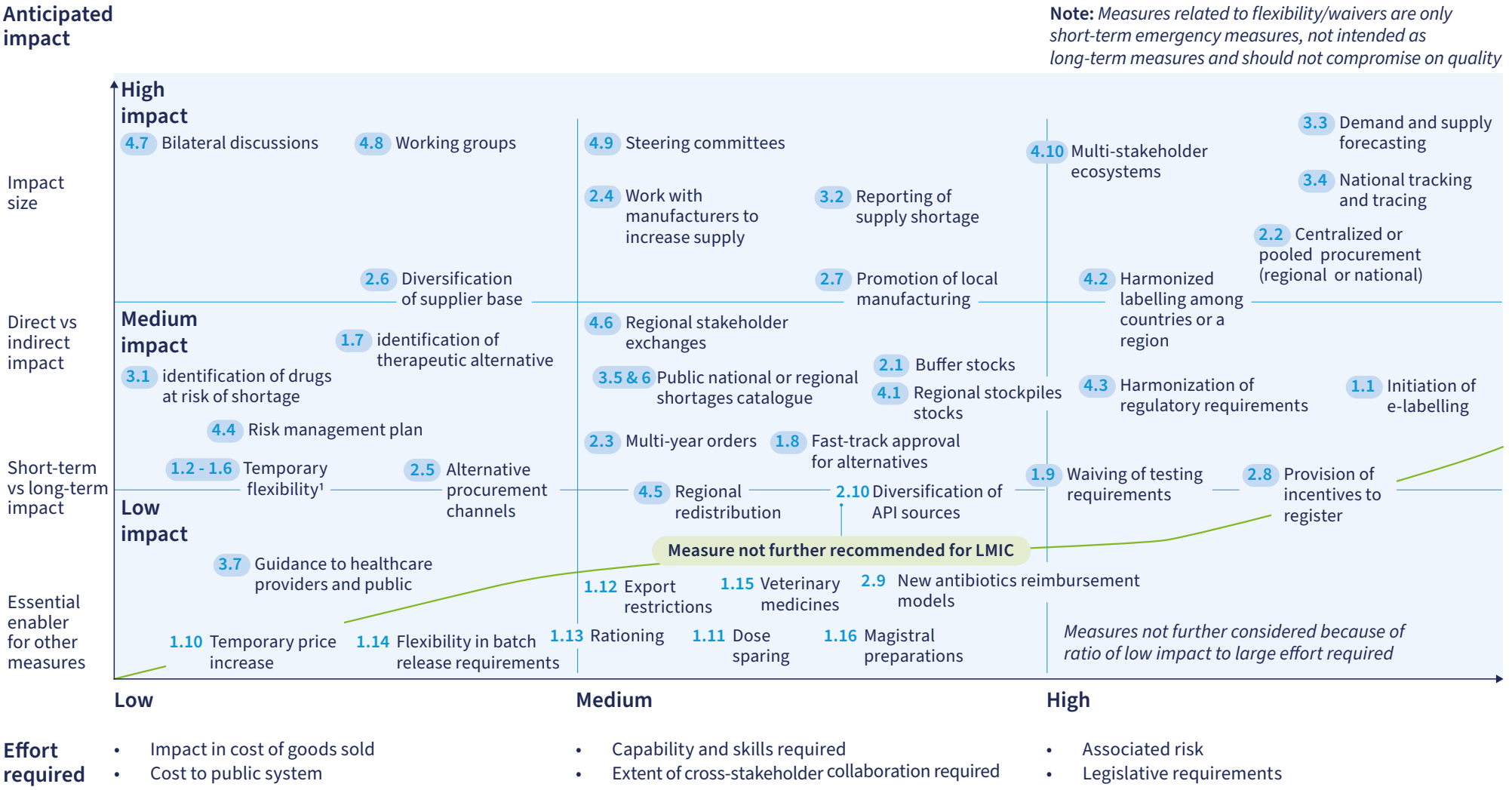
- Impact on cost: This dimension includes how the measure influences the manufacturer's cost of goods sold), potentially increasing the cost of drugs. For instance, requiring manufacturers to report shortages will incur additional cost, thus increasing their operational expenses.
- Cost to public systems: The cost to national governments of implementing a measure. Establishment of a comprehensive monitoring infrastructure or building stockpiles require substantial investment by a country.
- Legislative requirements differentiate measures. Some, such as cross-sectoral exchanges on shortages, do not require legislation and are thus less intensive. Others may require legislative changes, such as allowing imports from other markets, and longer-term changes, such as e-labelling and diversified procurement of antibiotics.
- Capabilities and skills required: Some measures, such as establishment of a forecasting system, will require additional capabilities that will have to be developed, or responsibility might be temporarily shifted to a stakeholder with the necessary capabilities (e.g. a procurement organization).
- Cross-stakeholder collaboration, such as measures that necessitate working with manufacturers to increase supply are ranked higher in terms of work required.
- Associated risk: Some of the measures described will impact shortages in two ways, such as fostering local manufacture by accepting higher prices. While such interventions will increase the overall secured supply, in the short term it could mean that a country can purchase only smaller quantities if its health budget is fixed.

Deprioritized measures that are not recommended

Measures with a low ratio of impact to effort were not considered further. These include introducing flexibility in quality standards, export restrictions, dose sparing, rationing, use of veterinary medicines for humans and use of magistral preparations.

Export restrictions in particular are not recommended, as they can lead to hoarding, which may worsen global shortages.

Fig. 12. Measures assessed for anticipated impact and ease of implementation



[1]1.2 Allow import of non-registered product if approved by the SRA/WHO listed authorities (WLA), WHO PQ or a reliant NRA; 1.3 Temporary permit to import products destined for other markets; 1.4 Temporary extension of expiry date, if safe; 1.5 Temporary flexibility in package size; 1.6 Temporary flexibility in source of raw material or manufacturing site

4.2 Matching measures to the country context

The countries addressed in this report, LMIC, are highly diverse. Each has unique governmental, regulatory and policy conditions and contexts. A "one size fits all" solution is therefore not feasible. The requirements of low-income countries such as the Democratic Republic of the Congo, Ethiopia or Nepal therefore differ from those of lower–middle-income countries such as Kenya and Viet Nam and upper–middle-income countries such as Malaysia and South Africa.

The measures identified also differ widely in the requirements for implementation. While some require primarily political will or additional resources in the NRA or ministry of health, others require solid legislative change, bargaining power with manufacturers, local manufacture or advanced digital infrastructure.

A set of measures is therefore proposed for consideration, grouped according to complexity. Countries might be more inclined to adopt measures of basic complexity that can be implemented without any significant regulatory or structural change. Measures of medium complexity require regulatory changes, investment and/or complex political decisions. High-complexity measures require structural changes in the medicines supply chain or complex data. Countries might also choose tools from each level, as local systems might be at different stages, such as having pooled procurement but less investment available for regional collaboration.

The characteristics of a country's health system and of its regulatory environment also determine the appropriateness of specific measures.

- NRA mandate: The capacity and mandate of the NRA (e.g. maturity level and whether it has a mandate to address drug shortages) will determine the extent to which a country's NRA can adopt specific measures.
- Market size and geographical location: Well-connected countries with large populations and/or a high gross domestic product are more attractive for manufacturers than small landlocked countries. These characteristics determine a country's bargaining power with manufacturers and hence to implement measures such as a requirement for reporting shortages.
- Local manufacturing facilities: The presence of local manufacture is a prerequisite for initiatives such as local manufacturing requirements.
- Price-setting capacity or policy: Pricing policies and the possibility of adjusting prices are essential for strategies such as temporary price increases to encourage manufacturers.
- Fragmentation and proportions of public and private institutions in health care and procurement systems: Countries with a dominant public health system and procurement of most medicines by a single public institution are better positioned to implement some measures, such as supplier diversification and track-and-trace systems, than countries with a fragmented ecosystem.
- Supply chain structure: A central point of entry, such as a large port, through which most drugs enter a country facilitates monitoring of drug supplies.

4.3 Measures to be considered by countries

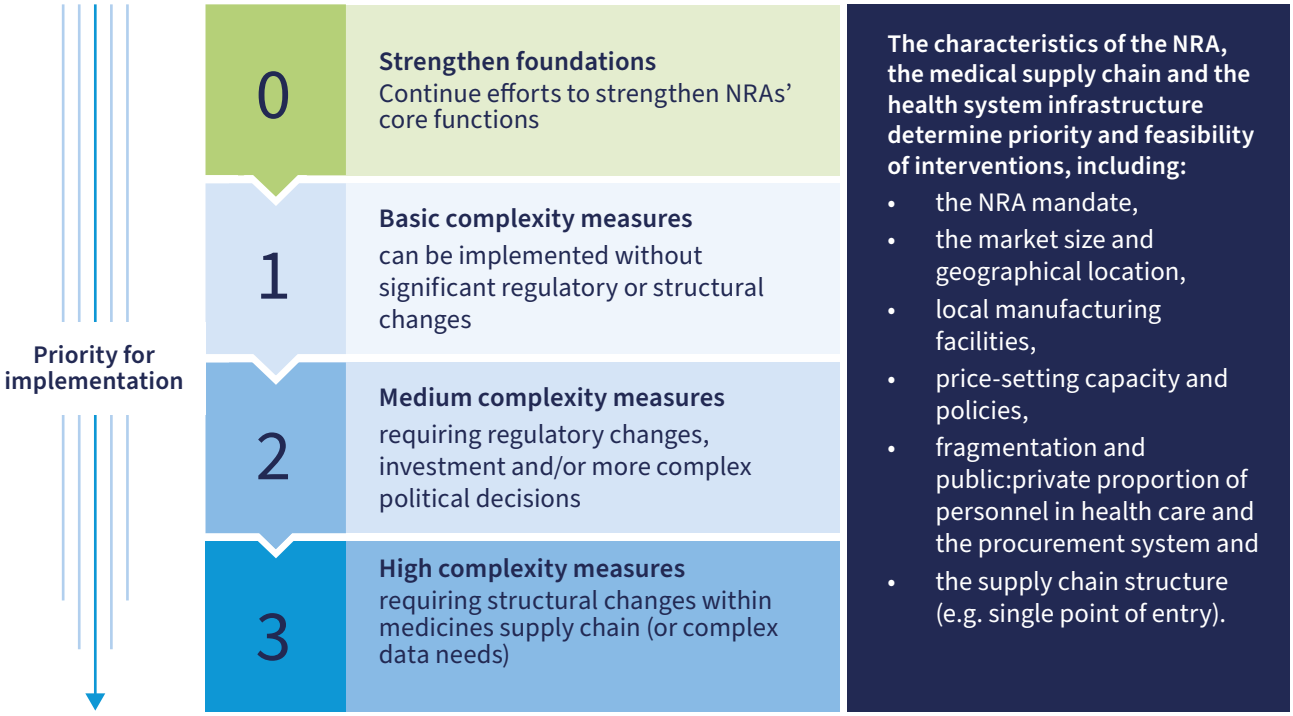
Fig. 13 illustrates the logic of dependence on country context for the effectiveness and feasibility of measures. The full set of measures for consideration is shown in Fig. 14.

Importantly, this toolbox should be read as a set of options for consideration, rather than a prescriptive recommendation. The measures are interchangeable. Thus, countries can select those that are most appropriate to their country context. Furthermore, a country may select a mix of tools to address a range of problems, as shortages may have various causes.

Four categories of measures were developed based on complexity of implementation.

- Measures to strengthen the core of the NRA, with emphasis on enhancing assurance of quality, safety and efficacy in medical products through robust market authorization, which includes accelerated approval pathways in various scenarios and ensuring that a variety of products is registered. Additionally, the quality of products on the market must be monitored, with mechanisms for enforcing sanctions if standards are not met to prevent circulation of substandard or falsified products.
- Measures of basic complexity can be implemented with fewer regulatory or structural changes. They involve adjustments to systems, such as importing non-registered products approved by an SRA/WHO listed authorities (WLA), offering flexibility in packaging and raw material sources, and adopting alternative procurement methods. They also include measures for communication and planning, plans for risk management, fostering cross-sectoral collaboration and providing guidance to health-care professionals.
- Measures of medium complexity require some regulatory modifications and investment and potentially more complex multi-stakeholder decision-making. Such measures are designed for improving the availability of supplies and ensuring their quality. They include initiatives such as ensuring buffer stocks, working with manufacturers and making multi-year orders based on a forecasting system. Others promote local manufacture and collaboration, such as regional redistribution mechanisms.
- Highly complex measures require significant systemic changes, significant investment or complex data. The aim of the strategies is to ensure a robust supply chain, including pooled procurement and harmonizing regulatory requirements across regions, such as with e-labelling. Advanced measures, such as forecasting demand and supply and establishing national tracking systems, ensure long-term resilience to shortages.

Fig. 13. The effectiveness and feasibility of measures depend on the country context



Source: : WHO (31)

Fig. 14. Measures can be implemented in a stepwise approach, starting with basic complexity ones and moving to more structural ones

0 **Strengthen foundations** Continue efforts to strengthen NRAs' core functions
0.1 Acceleration of general registration
0.2 Strengthening of quality assurance and enforcement of control

	1 **Basic complexity measures** can be implemented without significant regulatory or structural changes	**2** **Medium complexity measures** requiring regulatory changes, investment and/or more complex political decisions	**3** **High complexity measures** requiring structural changes within medicines supply chain (or complex data needs)
Enhance flexibility for acute shortages	**1.2** Allowing import of a non-registered product if approved by SRA, WHO PQ or reliant NRA **1.5** Temporary flexibility in pack size **1.6** Temporary flexibility in raw material source and/or manufacturing site **1.7** Identification of alternatives for shortage -prone antibiotics in advance	**1.3** Temporary permit to import products destined **1.4** Temporary extension of expiry date, if safe **1.8** Fast-track of approvals (emergency) for substitute products **1.9** Temporary waiving of testing requirements	**1.1** National buffer stock
Strengthen sourcing	**2.5** Temporary permit to switch to alternative procurement channels such as private distributors	**2.4** Work with manufacturers to increase supply of identified products **2.6** Requirements for diversification of suppliers **2.7** Requirement to purchase, including locally manufactured products	**2.1** Pooled procurement **2.2** Pooled procurement **2.3** Requirements for diversification of suppliers
Increase visibility	**3.1** Identification of essential drugs particularly prone to shortages (EML sub-category) **3.7** Provision of guidance to health-care providers and the public	**3.2** Registries for manufacturers to report upcoming shortages (early warning system) **3.5 & 3.6** Public national/regional shortages catalogue	**3.3** Establishment of forecasting system: match expected demand and supply to identify potential shortages **3.4** National tracking and tracing system to create visibility of demand
Institutionalize collaboration	**4.4** National risk management plan on addressing shortages **4.7** Bilateral discussions	**4.5** Regional redistribution mechanism to exchange products **4.6** Use of regional fora and bodies to strengthen shortage collaboration **4.8** Working groups	**4.1** Regional stockpiles **4.2** Harmonized labelling among countries or in a region **4.3** Regional harmonization of regulatory requirements (including CMC) **4.9** Steering committees **4.10** Multi-stakeholder ecosystems

5. Implementation considerations and conclusion

AMR is a significant global health threat, and acceleration of AMR is intricately linked to shortages of quality-assured antibiotics, indicating that urgent concerted action is required. In LMIC, the urgency of addressing antibiotic shortages has been recognized in only a few countries, and only a few participants recognized it as a major issue. Several types of shortages are observed, from global shortages due to fragile global supply chains to local shortages due to weak national medical supply chains. Shortages are often less visible in LMIC, as they are often masked by frequent stock-outs and circulation of antibiotics of unknown quality. There is a significant lack of data on the supply of and demand for these drugs in LMIC, and the distribution of poor-quality products persists due to insufficient enforcement.

The problem of antibiotic shortages in LMIC is expected to intensify. NRAs in HIC have adopted various measures to prevent them, including flexibility and pathways to strengthen sourcing and allowing flexibility to increase short- and long-term supplies, encouraging manufacturers to increase registration and production, fostering supplier diversity, enhancing visibility through registries of shortages and demand and supply, and improving preparedness for acute shortages through institutionalized stakeholder collaboration. Although some of these measures are also used in LMIC, many are not, and a step change is necessary. Regional collaboration can improve the situation. For example, the EAC Medicines Regulatory Harmonization programme accelerates progress through South–South cooperation, showing that change is achievable, Regional infrastructure can be used to track demand and supply, for pooled procurement and for guidance on universal measures, such as studies on safe expiry dates.

Given the wide variation in country contexts, there is no universal solution. The analysis began with the measures used by NRAs; however, it was recognized that measures should be contextualized, given the different remits of institutions in different contexts. The feasibility of measures is determined by a number of factors in a health system and in the country's legislation. A toolbox of measures categorized into three areas is proposed: core measures for immediate implementation, medium-term initiatives for increased preparedness and deep structural changes for long-term impact. The measures could be adopted in a stepwise manner, starting with simpler initiatives and moving progressively towards more comprehensive structural changes that require concerted action. The basis is continued strengthening of the core capabilities of NRAs.

The difference between HIC and LMIC in implementing measures should be addressed. In the context of ongoing antibiotic shortages, it is important that LMIC continue and extend their commitments, which will require national, regional and global collaboration. A comprehensive strategy is essential, which should address not only current shortages but should strengthen resilience against future crises. By facilitating strategic partnerships, knowledge exchange and equitable resource distribution, the disparity between HIC and LMIC can be bridged to ensure uniform access to essential medicines and increase global health security.

Endeavours to mitigate antibiotic shortages go beyond the immediate objective of securing drug availability to catalysing broader improvements in global health. Effective measures against antibiotic shortages will reinforce other global health priorities, including management of general drug shortages, strengthening regulatory systems, encouraging local pharmaceutical manufacture, eliminating falsified medicines and strengthening supply chains and health systems.

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Annexes

Annex 1. Organizations that participated in expert interviews

Type of organization	Region	Organization
National regulatory authority	Africa	Tanzanian Medicines and Medical Devices Authority
	Africa	Rwanda Food and Drugs Authority
	Africa	Ghana Food and Drug Authority
	Africa	Burkina Faso Agence Nationale de Règlementation Pharmaceutique
	Africa	Pharmacy and Poisons Board Kenya
	Africa	Ministère de la Santé du Sénégal
	Africa	South African Health Products Regulatory Authority
	Asia	Malaysia National PharmaceuticalRegulatory Agency
	Asia	Philippines Food and Drug Administration
	Americas	United States Food and Drug Administration
	Europe	European Medicines Agency
Ministry of health	Africa	Kenya Ministry of Health
	Africa	South African National Department of Health
Regional or global health authority	Africa	Africa Centres for Disease Control and Prevention
	Africa	New Partnership for Africa's Development
	Africa	East African Community
	International	WHO RSS
	International	African Vaccine Regulatory Forum
Research institute	International	Center of Global Development
	International	Management Sciences for Health
Non-governmental organizations	Americas	US Pharmacopeia
	International	Bill & Melinda Gates Foundation
Private sector	International	International Federation of Pharmaceutical Manufacturers and Associations
	International	Menarini
	International	Merck & Co.
	Africa	Maisha Meds
Procurement organizations	Africa	United Republic of Tanzania - Medical Store Department
	Africa	United Republic of Tanzania – Aga Khan Hospital
	Africa	Mission for Essential Drugs and Supplies

Annex 2. Types of shortages and identified measures

Table A2.1 Types of shortages and identified measures

Global shortages		National level shortages in LMIC			Subnational or institutional shortages (stock-outs)		
R&D challenges	**Global supply chain challenges**	**Lack of registration**	**Affordability issues**	**Lack of demand planning capacity**	**Lack of visibility of national stock**	**Lack of visibility of products of unknown quality**	**HCP preference**
2.9 New antibiotics reimbursement models (e.g. subscription model in HIC)	2.1 National buffer stock (manufacturers, pharmacies)	1.1 Initiation of e-labelling	2.2 Centralized or pooled procurement (regional or national)	1.1 Initiation of e-labelling	1.1 National buffer stock (manufacturers/ pharmacies	1.1 Initiation of e-labelling	2.7 Requirement to purchase/ or include locally manufactured products
2.8 Incentives for manufacturers to register shortage-prone products (market exclusivity)	4.1 Regional stockpiles	4.2 Harmonized labelling among countries or a region	2.3 Multi-year orders	2.4 Work with manufacturers to increase supply of identified products	1.2 Allowing import of non-registered product if approved by SRA, WHO PQ or reliant NRA	3.4 National tracking and tracing system to create visibility of demand	4.6 Use of regional fora and bodies to strengthen collaboration on shortages
1.8 Fast-track of approvals (emergency) for substitute products	1.1 Initiation of e-labelling	2.9 New antibiotics reimbursement models (e.g. subscription model in HIC)	5.1 New antibiotics reimbursement models (e.g. subscription model in HICs)	1.2 Allowing import of non-registered product if approved by SRA, WHO PQ or reliant NRA	1.3 Temporary permit to import products destined for other markets	4.5 Cross-sectoral stakeholder network and communication channels to act rapidly during emergencies (NRA, manufacturers, MoH, procurement agency, trade agency, regional players)	

Table A2.1 (continued) Types of shortages and identified measures

Global shortages		National level shortages in LMIC			Subnational or institutional shortages (stock-outs)		
R&D challenges	**Global supply chain challenges**	**Lack of registration**	**Affordability issues**	**Lack of demand planning capacity**	**Lack of visibility of national stock**	**Lack of visibility of products of unknown quality**	**HCP preference**
2.6 Requirements for diversification of suppliers	4.2 Harmonized labelling among countries or a region	1.8 Fast-track of approvals (emergency) for substitute products	2.7 Requirement to purchase or include locally manufactured products	1.3 Temporary permit to import products destined for other markets	1.4 Temporary extension of expiry date, if safe	4.7 Use of regional fora and bodies to strengthen collaboration on shortage	
2.10 Requirements for diversification of API sources	2.2 Centralized or pooled procurement (regional or national)	2.7 Requirement for purchase or inclusion of locally manufactured products	3.3 Establishment of forecasting system: match expected demand to supply to identify potential shortages	1.5 Temporary flexibility in package size	1.5 Temporary flexibility in package size		
4.3 Regional harmonization of regulatory requirements (including CMC)	2.3 Multi-year orders	2.8 Incentives for manufacturers to register shortage-prone products (market exclusivity)	3.4 National tracking and tracing system to create visibility of demand	1.6 Temporary flexibility in raw material source or manufacturing site	1.6 Temporary flexibility in raw material source or manufacturing site	3.4 National tracking and tracing system to create visibility of demand	
1.15 Authorization of use of veterinary medicines	2.4 Work with manufacturers to increase supply of identified products	4.3 Regional harmonization of regulatory requirements (including CMC)	3.5 Public national shortages catalogue (sometimes with suggestions for alternatives)	1.4 Temporary extension of expiry date, if safe	1.8 Fast-track of approvals (emergency) for substitute products	3.5 Public national shortages catalogue (sometimes with suggestions for alternatives)	
1.16 Authorization of use of magistral preparations	1.3 Temporary permit to import products destined for other markets	3.1 Identification of essential drugs particularly prone to shortages (EML subcategory)	3.6 Public regional shortages catalogue (sometimes with suggestions for alternatives)	1.14 Temporary flexibility for batch releases	1.10 Temporary allowance for price increases on products in shortage covered by public system	4.4 National risk management plan on addressing shortages	

Table A2.1 (continued) Types of shortages and identified measures

Global shortages		National level shortages in LMIC			Subnational or institutional shortages (stock-outs)		
R&D challenges	**Global supply chain challenges**	**Lack of registration**	**Affordability issues**	**Lack of demand planning capacity**	**Lack of visibility of national stock**	**Lack of visibility of products of unknown quality**	**HCP preference**
3.2 Registries for manufacturers to report upcoming shortages (early warning system)	1.5 Temporary flexibility in package size		4.4 National risk management plan on addressing shortages	1.10 Temporary allowance for price increases on products in shortage covered by public system	1.11 Reduced dosing or dose-sparing	4.5 Regional redistribution mechanism to exchange products	
3.3 Establishment of forecasting system: match expected demand to supply to identify potential shortages	1.6 Temporary flexibility in raw material source or manufacturing site	3.7 Provision of guidance to health-care providers and the public	4.5 Cross-sectoral stakeholder network and for rapid action during emergencies (NRA, manufacturers, MoH, procurement agency, trade agency, regional players)	2.5 Temporary permit to switch to alternative procurement channels such as private distributors	1.12 Temporary export restrictions on locally produced products	4.6 Use of regional fora and bodies to strengthen collaboration on shortages	
3.4 National tracking and tracing system to create visibility for demand	1.4 Temporary extension of expiry date, if safe	4.4 National risk management plan on addressing shortages	4.6 Regional redistribution mechanism for exchanging products	1.11 Reduced dosing or dose-sparing	1.13 Temporary rationing or prioritization of populations in need	4.7-10 Communication[a]	
3.5 Public national shortages catalogue (sometimes combined with suggestions for alternative)	1.14 Temporary flexibility for batch releases	4.5 Regional redistribution mechanism to exchange products	4.7 Use of regional fora and bodies to strengthen collaboration on shortages	1.12 Temporary export restrictions on locally produced products	1.14 Temporary flexibility for batch releases		
3.6 Public regional shortages catalogue (sometimes combined with suggestions for alternative)	1.10 Temporary allowance for price increases on products in shortage covered by public system	4.6 Use of regional fora and bodies to strengthen collaboration on shortages		1.13 Temporary rationing or prioritization of populations in need	2.4 Work with manufacturers to increase supply of identified products		

Table A2.1 (continued) Types of shortages and identified measures

Global shortages		**National level shortages in LMIC**			**Subnational or institutional shortages (stock-outs)**		
R&D challenges	**Global supply chain challenges**	**Lack of registration**	**Affordability issues**	**Lack of demand planning capacity**	**Lack of visibility of national stock**	**Lack of visibility of products of unknown quality**	**HCP preference**
	1.11 Reduced dosing or dose-sparing	4.7-10 Communication		2.7 Requirement to purchase or include locally manufactured products	2.5 Temporary permit to switch to alternative procurement channels, such as private distributors		
	1.12 Temporary export restrictions of locally produced products			3.1 Identification of essential drugs particularly prone to shortages (EML subcategory)	3.3 Establishment of forecasting system: match expected demand and supply to identify potential shortages		
	1.13 Temporary rationing or prioritization for populations in need			3.2 Registries for manufacturers to report upcoming shortages (early warning system)			
	1.7 Identification and communication of alternatives for shortage-prone antibiotics in advance						

Annex 3. Country profiles: measures by region and country

African Region

Profile: Ghana

Regulatory stakeholders

Ghana FDA is the country's NRA, responsible for the regulation of food, drugs and other health-related products. The procurement and supply chain directorate of the Ministry of Health sets procurement standards and supervises management of the Central Medical Stores, which are responsible for drug procurement in the public sector.

Ghana | Summary of measures	
Strengthen sourcing	• temporary permit for alternative procurement channels, such as private distribution • requirement to purchase or include locally manufactured products
Enhance flexibility for emergencies	• No
Increase visibility	• No
Institutionalize collaboration	• regional redistribution mechanism for exchanging products

Shortages experienced

A representative of the Ghana FDA reported that the country had experienced no major shortages of antibiotics in recent years. Stock-outs occur, however, in Government health institutions, and national shortages occur due to delays in importation. For instance, a shortage of the antiretroviral drugs abacavir and lamivudine *(1)* occurred, which was attributed in media reports to delays in delivery, the drugs being held in Ghana's harbour awaiting a tax waiver from the Ministry of Finance. Similar issues of stock-outs and shortages have been reported to be due to inefficiency in the private and public supply chains for health commodities *(2)*.

Interviewees reported additional cases of national shortages, including increased disruption of transport from Asia to Africa in late 2022, which affected the availability of raw materials and led to price mark-ups and subsequent shortages. In addition, a shortage of vaccines for polio and for diphtheria, tetanus and polio occurred in 2023.

Implemented or planned measures to address shortages

The Ghana FDA prohibits importation of selected finished pharmaceutical products to encourage local manufacture and reduce dependence on the global market. The ban affects over 40 generic drugs, including seven antibiotics, such as amoxicillin capsules (250 mg, 500 mg), co-trimoxazole suspension (40/200 mg/5 mL) and tablets (80/400 mg, 160/800 mg) and doxycycline capsules (100 mg). The country allows importation of the raw materials for local production.

During a shortage of polio vaccine in 2023, Nigeria supplied vaccines from its national stockpile.

Furthermore, when public pharmacies experience stock-outs, patients can present their prescriptions at private pharmacies to access the required medications. In these cases, national health insurance reimburses the cost.

Profile: Kenya

Regulatory stakeholders

The Pharmacy and Poisons Board (PPB) serves as the NRA in Kenya. It is responsible for regulating, inspecting and ensuring the safety and quality of pharmaceutical products. Their responsibilities include registering new products for the pharmaceutical sector. The PPB has achieved maturity level 3 according to the WHO Global Benchmarking Tool *(3)*.

The Ministry of Health shapes health policies and provides technical assistance to the 47 county governments, which are responsible for delivering local health services. It develops guidelines and policies for general and strategic health programmes such as for HIV, malaria, tuberculosis and maternal health. Products (including antibiotics) that are selected for appropriate treatment and included in one of the programmes (e.g. co-trimoxazole for HIV in children) are procured by the Kenya Medical Supplies Authority and reimbursed by the National Health Insurance Fund *(4)*.

The National Health Insurance Fund is part of Kenya's universal health coverage scheme. With private insurance companies, it financed health expenses for 88.4% of the population in 2014 *(5)*. The Medical Supplies Authority is the public medical procurement and distribution agency, with a mandate to procure, store and distribute health products and technologies. It is also responsible for forecasting and quantification of products. As the strategic national stock reserve, it cooperates with the 47 county governments *(6)*.

The State Department of Trade monitors all pharmaceutical imports. There are also numerous private wholesalers and distributors.

Shortages experienced

Some interviewees reported instances of shortages of antibiotics, such as of ceftriaxone in 2023, which was due to problems at the manufacturing site; however, shortages were generally not considered an urgent issue. Concern was raised about generics of unknown quality, which may mask any shortages of quality-assured, effective products. It was estimated that up to 30% of drugs available in Kenya are falsified. Shortages of insulin have occurred in recent years, due to a combination of global shortages and issues of access *(7)*.

Implemented or planned measures to address shortages

The PPB allows temporary flexibility to increase the short-term supply of products in shortage. For example, the PPB can allow entry of products intended for other African markets, which may have different labelling and package size requirements, e.g. during a shortage of insulin in 2022. Labelling in English nevertheless remains a requirement.

Accelerated approval of substitute products can be used to fast-track marketing authorization. The PPB can rely on inspections for general health products conducted by reference regulatory authorities such as an SRA/WHO listed authorities (WLA),, WHO PQ, the Medical Device Single Audit Programme and other recognized entities. In emergencies, such as war or threats from chemical, biological, radiological or nuclear sources, the PPB is empowered to issue approvals during acute shortages with reduced clinical trial data when no standard treatment or diagnostic is available.

To increase the transparency of demand and supply, the medical supply chain in Kenya is being increasingly digitized, such as introduction of an electronic logistics management information system. A faith-based procurement agency, the Mission for Essential Drugs and Supplies, has begun to implement a system for monitoring consumption of essential drugs. Innovative private-sector players have also begun to introduce innovative systems for digitization of the supply chain and transparency, such as the pharmacy software start-up Maisha Meds *(8)*, which provides a user-friendly, cost-effective digital inventory system, with barcode scanning technology in an app for mobile devices. The system assists pharmacies in managing sales and automatically notifies them when products are nearing stock-outs or their expiration date.

Support for local pharmaceutical manufacturing is a priority for the Kenyan Government, and, currently, 62% of drugs are procured locally, according to the Kenya Medical Supplies Authority *(9)*. The Ministry of Health offers pricing advantages of up to 15–20% for domestic products. Additionally, the PPB gives faster approval for locally manufactured products and a 50% discount for registration.

Kenya | Summary of measures	
Strengthen sourcing	• requirement to purchase and include locally manufactured products • incentives to manufacturers to register shortage-prone antibiotics (market exclusivity)
Enhance flexibility for emergencies	• allow import of non-registered products if approved by an SRA, WHO PQ or reliant NRA • temporary permit to import products destined for other markets • fast-track approvals of substitute in an acute shortage • temporary waiving of testing requirements
Increase visibility	• establishment of forecasting system to match expected demand with supply for potential shortages)
Institutionalize collaboration	• No

Profile: Senegal

Regulatory stakeholders

The Agence Sénégalaise de Réglementation Pharmaceutique (Senegal Agency for Pharmaceutical Regulation, ARP) is the main regulatory body. Other bodies in the country's health-care system and antibiotic supply chain are the Ministry of Health and Social Action, the public procurement agency and importers.

Senegal | Summary of measures	
Strengthen sourcing	• requirement for diversification of suppliers
Enhance flexibility for emergencies	• temporary permit to import products destined for other markets • temporary extension of expiry date, if safe • fast track of approvals (in an acute shortage) for substitute products
Increase visibility	• No
Institutionalize collaboration	• regional redistribution mechanism to exchange products • use of regional forums and bodies to strengthen collaboration

Shortages experienced

ARP experts interviewed for this study reported that Senegal had faced shortages in the past of third-generation cephalosporins, with a notable shortage of piperacillin-tazobactam. Episodic stock-outs were also seen of products such as phenobarbital (antiepileptic) and anti-diarrhoeals *(10)*.

No large shortages occurred, however, because of use of several sources of supply. An ARP expert was reported to have commented ‘’We obtain our supplies from Europe, but the proportion of imports is very low compared to the import of medicines via the Indian sector. Most of our products come from India and the Maghreb” *(11)*.

Implemented or planned measures to address shortages

The challenge of medicine shortages is considered increasingly urgent by the public health sector. According to informants at the ARP, the Ministry of Health and Social Action is developing a strategy to address shortages. At present, in cases of severe shortages, the ARP has increased flexibility to increase the supply of drugs. For example, during the COVID-19 pandemic, the ARP approved Sinopharm vaccines with labelling in English. Additionally, in extraordinary circumstances, the country has extended the expiration dates of certain drugs, such as HIV medications.

Interviewees reported that the public procurement agency had created a stock monitoring and alert system, which notifies agencies of low stocks. The medical procurement agency can engage in regional exchange of drugs that are in shortage through its membership in the Association Africaine des Centrales d’Achats de Médicaments Essentiels (African Association of Purchasing Centres for Essential Medicines). Diversification of sources of supply is another key measure.

The Government has an ambitious plan to increase its independence from global pharmaceutical markets, with a target of meeting 50% of national requirements for medicines through local manufacturing by 2035.

European Region

Profile: European Medicines Agency

Regulatory stakeholders

The EMA evaluates and monitors medicines used in the EU to ensure their safety, efficacy and quality. After significant shortages of medicines during the COVID-19 pandemic, EMA's mandate was extended to monitoring shortages of medicine that could result in a crisis and also to reporting shortages of critical medicines during public health emergencies and major events. The Agency collaborates with national authorities and the pharmaceutical industry to monitor, prevent and manage shortages and to safeguard public health and medicine supplies. The EMA executive group, the MSSG, monitors shortages and the supply and demand for critical medicines during crises. The MSSG can make recommendations during critical shortages and also monitors shortages that could lead to a major event and acute shortages.

The MSSG is supported by the Medicine Shortages Single Point of Contact Working Party, composed of points of contact in competent national authorities, which monitors events that could affect the supply of medicines. In a shortage that could lead to a major event or an acute shortage, the single point of contact can refer to the MSSG *(12)*.

For management of a shortage of a nationally authorized product, the Coordination Group for Mutual Recognition and Decentralized Procedures supports the EMA by improving coordination of implementation of regulatory measures and promoting initiatives to reduce barriers between Member States for faster national access and distribution, including reduction of "regulatory triggered" shortages *(13)*.

Shortages experienced

Since 2021, the European Union has had significant shortages of antibiotics, which have been attributed to increased demand during the COVID-19 pandemic, supply chain disruptions and limited manufacture. Critical antibiotics, including those for treating severe infections and resistant bacteria, have been in short supply *(12)*.

Implemented or planned measures to address shortages

In 2023, the MSSG issued a toolkit of strategies to prevent and address critical shortages rapidly and in a coordinated manner during a shortage *(14)*. The toolkit proposes various measures according to the severity and nature of the shortage. They include centralized procurement, regional stockpiles of essential medicines, and temporary regulatory flexibility, such as allowing the importation of products intended for other markets, different package sizes and safe extension of expiry dates.

The MSSG has drawn up a list of the "main therapeutic groups" of medicinal products that are necessary for emergency care, surgery and intensive care to be used to respond to an acute public health shortage or major event.

To ensure a sufficient supply of antibiotics for the autumn–winter season 2023–2024, EMA, with the Health Emergency Response Authority, has modelled possible gaps in supply and demand. Data on supply and demand were collected from manufacturers and from past sales. The MSSG recommended partnerships with MAH and manufacturers to increase production for the season.

EMA, with the heads of medicines agencies and the European Commission, has initiated a pilot project for electronic labelling of human medicines with product information in Member States *(15)* to ensure timely availability of products. The joint action Coordination and Harmonisation of the Existing Systems against Shortages of Medicines – European Network (CHESSMEN) initiative was established to "provide a harmonized response to mitigate medicines shortages and contribute to the timely availability of medicinal product" in 22 European Member States *(16)*.

EMA | Summary of measures	
Strengthen sourcing	• national buffer stocks (manufacturers and pharmacies) • regional stockpiles • centralized or pooled procurement (regional or national) • work with manufacturers to increase supply of identified products • requirement to diversify API sources • requirement to purchase and include locally manufactured products • incentives to manufacturers to register shortage-prone antibiotics (market exclusivity)
Enhance flexibility for emergencies	• e-labelling • temporary permit to import products destined for other markets • temporary flexibility in package size • temporary flexibility in raw material source or manufacturing site • temporary extension of expiry date, if safe • temporary flexibility for batch releases • reduced dosing or dose sparing • temporary rationing or prioritization of populations in need • fast track of approvals (acute shortages) for substitute products • authorization of human use of veterinary medicines • authorization of magistral preparations
Increase visibility	• identification and communication of alternatives for shortage-prone antibiotics in advance • identification of essential drugs particularly prone to shortages (Essential Medicines List subcategory) • registries for manufacturers to report upcoming shortages (early warning system) • establishment of forecasting system: match expected demand to supply to identify potential shortages • public national shortages catalogue (sometimes combined with suggestion for alternative) • public regional shortages catalogue (sometimes combined with suggestion for alternative) • provision of guidance to health-care professionals and the public
Institutionalize collaboration	• country-specific risk management plan for addressing shortages • harmonized labelling among countries in the region • regional harmonization of regulatory requirements (including for chemistry, manufacturing and controls) • regional redistribution mechanism to exchange products • use of regional forums and bodies to strengthen preparedness for shortages • dialogue • working groups • steering committees • multistakeholder ecosystem

Profile: Denmark

Regulatory stakeholders

The Danish Medicines Agency (Lægemiddelstyrelsen) is mandated to ensure the safety, efficacy and availability of drugs. In addition to regulation, its functions include prevention of drug shortages by monitoring and mitigating supply levels and facilitating solutions when shortages occur *(17)*.

Denmark | Summary of measures	
Strengthen sourcing	• national buffer stock (manufacturers and pharmacies)
Enhance flexibility for emergencies	• temporary permit to import products destined for other markets • temporary flexibility in package size • temporary extension of expiry date, if safe
Increase visibility	• registries for manufacturers to report upcoming shortages (early warning system) • public national catalogue of shortages (sometimes combined with suggested alternatives) • public regional catalogue of shortages (sometimes combined with suggested alternatives)
Institutionalize collaboration	• use of regional forums and bodies to strengthen preparedness for shortages • dialogue • working groups

Shortages experienced

As in most European countries, Denmark is experiencing severe shortages of medicines, including antibiotics, which have attracted significant public attention, especially since the post-pandemic surge in infections. For instance, a newspaper article in October 2023 reported calls to allow pharmacies to dispense penicillin in alternative dosages, which is currently not allowed without the approval of a health-care provider *(18)*.

Implemented or planned measures to address shortages

During the COVID-19 pandemic, the Danish Medicines Agency collaborated with national pharmaceutical wholesalers to establish a strategic stockpile of essential drugs for acute use, including antibiotics, insulin and asthma medicine. The Agency also introduced a permit for compassionate use to give health-care professionals access to non-market medicines for critical care as part of flexibility in addressing drug shortages.

The Agency maintains a publicly available national shortage list, enabling effective communication with MAHs responsible for reporting shortages. The National Council for the Security of Supply of Medicines also assesses the medicine supply and finds solutions, representing a collaborative approach to the management of shortages. The Agency has mandated MAHs to give advance notification of any shortages or of cessation of product marketing. The Agency also grants exemptions from standard regulatory requirements for labelling, deadlines and package leaflets under specific circumstances and may grant extension of the shelf-life of products. Through the principle of mutual recognition, it approves the storage period of ≥ 6 weeks approved in Sweden, with the additional condition of proof of the robustness of the product *(19)*.

To strengthen collaboration and preparedness, the National Council for the Security of Supply of Medicines was established to ensure an overview of medicines supply, including pharmaceutical companies, pharmacy organizations, health-care providers, patient associations, other Government agencies and professional associations.

Profile: Germany

Key regulatory stakeholders

Germany's NRA is the BfArM, which is responsible for the safety of medicinal products, narcotics and medical devices *(20)* and also for monitoring the drug supply and publishing a list of shortages.

The Federal Ministry of Health establishes the legislative framework for manufacture, clinical trials, marketing authorization, distribution and monitoring of medicinal products and medical devices to ensure that they fulfil the requirements for quality, effectiveness and safety *(21)*.

Shortages experienced

Like most other European countries, Germany is experiencing severe shortages of medicines, including antibiotics, which have attracted significant public attention, especially since the post-pandemic surge in infections. For instance, in the winter of 2022–2023, Germany experienced shortages of penicillin and of paediatric drugs *(22)*.

Implemented or planned measures to address shortages

In response to recurring drug shortages, such as those in the winter of 2022–2023, the Parliament passed the Act to Combat Supply Shortages and Improve the Supply of Medicines in July 2023.

The legislation, drafted by the Ministry of Health, introduces measures to anticipate and mitigate shortages of essential medicines. It includes measures to be implemented by BfArM and by manufacturers, pharmacies, hospitals, wholesalers and statutory health insurers. It introduces measures for temporary flexibility to use alternative products during shortages. Pharmacies can thus prescribe medications with the same API but different packaging or strength if the medication is not available from two pharmaceutical wholesalers within a reasonable time. Health insurers and manufacturers have been granted the flexibility of adjusting the prices of paediatric medicines, discontinuing fixed amounts and rebate contracts and increasing prices by up to 50% of the last fixed amount.

The legislation includes strengthening sourcing. Manufacturers and MAH must adhere to mandatory stockpiling of rebated drugs for a 6-month supply, and pharmaceutical wholesalers must maintain a supply of paediatric medicines for at least 4 weeks. Statutory health insurance funds must prioritize antibiotics with APIs produced in Europe. They can increase prices for reserve antibiotics to encourage manufacturers to invest in research and development.

The BfArM identifies potential or current shortages and monitors the market of off-patent medicines, including essential antibiotics for which the APIs are in critical shortage. The BfArM is also mandated to publish shortages of essential paediatric medicines after consultation with the advisory council under the German Medicine Act Section 52b (3b).

BfArM is a member of the EMA MSSG and the CHESSMEN initiative.

Germany | Summary of measures

Strengthen sourcing	• national buffer stock (manufacturers and pharmacies) • new model for reimbursement of antibiotics (e.g. subscription) • requirement for diversification of sources
Enhance flexibility for emergencies	• temporary flexibility for package size • temporary allowance for price increases for products in shortage covered by the public system
Increase visibility	• identification of essential drugs prone to shortages (Essential Medicines List subcategory) • registries for manufacturers to report upcoming shortages (early warning system) • establishment of forecasting system to match expected demand with supply to identify potential shortages • public catalogue of national shortages (sometimes combined with suggestions for alternatives)
Institutionalize collaboration	• dialogue • working groups • steering committees

[a] Participants: BfArM, associations (e.g. health-care professionals, manufacturers, pharmacists, wholesalers, hospitals, insurance funds, patients), public authorities (Ministry of Health, research institutes)

[b] Essential list developed by representatives of the advisory committee, certain departments and paediatric associations

Act to Combat Supply Shortages and Improve the Supply of Medicines (Parliament passed law in July 2023 to strengthen the measures to prevent and mitigate shortages

Federal Ministry of Health (MoH)	**Draft created**
Parliament	**Law passed**
NRA (BfArM)	**Required to implement measures defined by law**
Other stakeholders *(manufactures pharmacies, hospitals, wholesalers, national health insurers)*	**Required to implement measures defined by law**
Advisory Council for Delivery and Supply Shortages *(within BfArM)*[b]	**Monitors and evaluates supply**

Measures for temporary flexibility in emergencies

Pharmacies	Prescription of different medication with same API, different package size, different API strength, when medication cannot be supplied by two wholesalers within a reasonable time (AMG § 52b para. [2])
Health insurers, manufacturers	Pricing flexibility (stopped fixed amounts and rebate contracts for paediatric medicines, and raise their dispensing prices by up to 50% of the most recent applicable fixed amount)
Statutory health insurance funds, manufacturers	Pricing increase for reserve antibiotics to incentivize R&D

Measures to strengthen sourcing

Pharmacies and hospitals	Mandatory stockpiling of medications classified by MoH as in threatened shortage or due to supply-relevant market concentration
Manufacturers and market authorization holders	Mandatory stockpiling of rebated drugs for a 6-month supply
Pharmaceutical wholesalers	Mandatory stockpiling to maintain a supply of paediatric medicines for at least 4 weeks
Statutory health insurance funds, manufacturers	Requirement to prefer antibiotics with APIs produced in Europe in public procurement

Measures to increase visibility

NRA	Publication of essential paediatric medicines list after consulting advisory council (under German Medicine Act (AMG) Section 52b (3b))[a] Early warning system established, including a public database giving an overview of current or potential shortages (more access rights to NRA to obtain information from hospitals and pharmacies)
NRA, manufacturer or market authorization holder	Self-report of (potential) supply shortages, especially for essential APIs, via PharmNet.Bund database, transfer of supplies data on medicinal products every 2 months, potential follow-up for hearings by NRA

Profile: Sweden

Key regulatory stakeholders

The Swedish Medical Products Agency (Läkemedelsverket) ensures the availability and safety of medications in Sweden and manages drug shortages. The Swedish Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket) assesses the comparability of package sizes for substitute drugs.

Sweden | Summary of measures	
Strengthen sourcing	• new antibiotic reimbursement models (e.g. subscription model)
Enhance flexibility for emergencies	• temporary permit to import products destined for other markets • temporary flexibility in package size
Increase visibility	• advance identification and communication of alternatives for shortage-prone antibiotics • registries for manufacturers to report upcoming shortages (early warning system) • public catalogue of national shortages (sometimes combined with suggestions for alternatives) • public catalogue of regional shortages (sometimes combined with suggestions for alternatives)
Institutionalize collaboration	• use of regional forums and bodies to strengthen preparedness for shortages

Shortages experienced

Like most European countries, Sweden has recently had shortages of antibiotics and paediatric formulations. Because of relatively restrictive prescription procedures, however, some antibiotics are in low demand, and some products are not available on the Swedish market due to low perceived market potential. To overcome this problem, Sweden has introduced a reimbursement subscription model *(23)*.

Implemented or planned measures to address shortages

Sweden's innovative reimbursement subscription model for off-patent antibiotics represents a significant shift in the procurement of antibiotics, which encourages manufacturers to provide a continuous supply. In addition, the Agency has published a list of upcoming and current shortages, integrated into the EMA list.

By granting temporary exemptions, Sweden's NRA allows the sale of approved medicinal products in non-standard packaging when no suitable alternatives are available on market. MAHs are required by the Medicinal Products Act to notify the MPA promptly of potential drug shortages to manage shortages. Importers and distributors that are not MAHs are also encouraged to report shortages, as they have a significant impact on the market and health-care provision. When an MAH intends to stop marketing a medicinal product, dual notification is required: to the MPA and to the Swedish eHealth Agency.

Nordic health cooperation on pharmaceutical supply shortages to combat AMR is a regional approach to the management of shortages

Western Pacific Region

Profile: Philippines

Regulatory stakeholders

The Philippines FDA is responsible for ensuring the safety, efficacy and quality of health products. Drug shortages are not in its mandate but are addressed by the Pharmaceutical Division of the Department of Health.

Philippines | Summary of measures	
Strengthen sourcing	• Work with manufacturers to increase supplies of identified products • fast-track approvals for substitute products in acute shortages
Enhance flexibility for emergencies	• e-labelling • allow importation of non-registered products if approved by SRA, WHO PQ or reliant NRA • temporary permit to import products destined for other markets
Increase visibility	• No
Institutionalize collaboration	• No

Shortages experienced

The Philippines have experienced increased drug shortages, particularly of vaccines and of essential medicines for public hospitals. An assessment in a public hospital in 2022 found that antibiotics, chemotherapy and COVID-19 medications were most often in shortage or stock-out *(24)*. Other reported shortages at the height of the COVID-19 pandemic in 2019 were of paracetamol and analgesics, including Biogesic, Neozep, Rexidol, Decolgen, Bioflu, Alaxan and Tuseran *(25)*.

Implemented or planned measures to address shortages

The FDA has planned several measures for labelling on products in drug shortages. Special permits can be issued for importation of products approved by neighbouring countries, and exemption from generic labelling is permitted for some products (in English as a minimum requirement). FDA representatives also reported initial use of e-labelling of drugs during the COVID-19 pandemic, although technological challenges remain.

In 2020, the Philippines FDA adopted a collaborative procedure for accelerated registration of WHO-PQ pharmaceutical products and vaccines to reduce approval times in acute shortages *(25)*.

Currently, there are 60–70 local drug producers. Coordination with the pharmaceutical division of the Department of Health is particularly relevant during shortages; however, no systematic mechanism for regular exchange with manufacturers is in place.

To strengthen preparedness and collaboration, the pharmaceutical division holds regular meetings with MAHs, health-care professionals and disease-specific associations.

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Annex 4. Assessment of the impact of measures

Table A4.1. Assessment of the impact of measures

		Anticipated impact						Effort Required						
Number	Measure	Frequency (n=19)	Short or long term	Direct or indirect	Essential enabler	Impact size	Total impact (max 13)	Impact on cost of goods sold	Cost to public system	Capability and skills required	Legislative requirements	Associated risk	Degree of cross-stakeholder collaboration	Total effort required (max 20)
1.1	Initiation of e-labelling	1	3	1	0	4	8	2	3	3	3	2	3	16
1.2	Allowing import of non-registered product if approved by SRA, WHO PQ or reliant NRA	5	1	3	0	1	5	0	0	0	3	2	0	5
1.3	Temporary permit to import products destined for other markets	10	0	3	0	1	5	0	0	0	3	2	0	5
1.4	Temporary extension of expiry date, if safe	4	4	3	0	1	5	0	0	1	3	2	0	6
1.5	Temporary flexibility in package size	5	1	3	0	1	5	0	0	0	3	2	0	5
1.6	Temporary flexibility in raw material source or manufacturing site	2	3	3	0	1	5	0	0	0	3	2	0	5
1.7	Identification of alternatives for shortage-prone antibiotics in advance	3	0	1	3	2	8	0	0	1	3	2	1	7
1.8	Fast-track of approvals (emergency) for substitute products	10	1	3	0	3	8	2	1	2	3	2	1	11

Table A4.1 (continued). Assessment of the impact of measures

		Anticipated impact						Effort Required						
Number	Measure	Frequency (n=19)	Short or long term	Direct or indirect	Essential enabler	Impact size	Total impact (max 13)	Impact on cost of goods sold	Cost to public system	Capability and skills required	Legislative requirements	Associated risk	Degree of cross-stakeholder collaboration	Total effort required (max 20)
1.9	Temporary waiving of testing requirements	2	1	3	0	2	6	2	2	2	3	3	2	15
1.10	Temporary allowance for price increases for products in shortage covered by public system	3	3	2	0	1	4	1	0	0	2	1	1	5
1.11	Reduced dosing or dose-sparing	2	0	2	0	1	4	2	0	1	3	3	1	10
1.12	Temporary export restrictions on locally produced products	1	1	2	0	1	4	3	0	0	3	3	1	10
1.13	Temporary rationing or prioritization of populations in need	1	1	2	0	1	4	2	0	1	3	2	1	9
1.14	Temporary flexibility for batch releases	3	3	2	0	1	4	2	0	1	3	2	1	7
1.15	Authorization of use of veterinary medicines	1	0	2	0	1	4	2	0	1	3	3	1	8
1.16	Authorization of use of magistral preparations	4	1	2	0	1	4	2	0	1	3	3	1	10
2.1	National buffer stock (manufacturers/pharmacies)	9	1	3	0	3	8	1	2	1	3	2	2	11
2.2	Centralized or pooled procurement (regional or national)	4	3	2	0	4	9	1	3	3	5	2	3	17
2.3	Multi-year orders	2	0	2	0	3	7	1	0	2	5	2	1	11
2.4	Work with manufacturers to increase supply of identified products	4	1	3	0	2	6	2	1	0	5	1	3	12

Table A4.1 (continued). Assessment of the impact of measures

		Anticipated impact						Effort Required						
Number	Measure	Frequency (n=19)	Short or long term	Direct or indirect	Essential enabler	Impact size	Total impact (max 13)	Impact on cost of goods sold	Cost to public system	Capability and skills required	Legislative requirements	Associated risk	Degree of cross-stakeholder collaboration	Total effort required (max 20)
2.5	Temporary permit to switch to alternative procurement channels e.g., private distributors	5	1	3	0	2	6	2	0	0	2	1	1	6
2.6	Requirements for diversification of suppliers	3	3	3	0	4	9	2	0	0	3	0	1	6
2.7	Requirement to purchase and include locally manufactured products	7	0	2	0	4	9	3	1	0	3	2	1	10
2.8	Incentives to manufacturers to register shortage-prone products (market exclusivity)	2	1	1	0	2	6	3	2	2	5	2	2	16
2.9	New antibiotics reimbursement models (e.g. subscription model in HIC)	2	2	1	0	2	6	2	2	1	3	1	2	11
2.10	Requirements for diversification of API sources	2	1	3	0	4	9	3	0	2	3	1	1	10
3.1	Identification of essential drugs particularly prone to shortages (EML sub-category)	4	3	1	3	3	9	0	0	1	3	1	0	5
3.2	Registries for manufacturers to report upcoming shortages (early warning system)	9	2	3	3	3	11	2	1	1	3	1	2	10
3.3	Establishment of forecasting system: match expected demand with supply to identify potential shortages	4	2	2	3	4	12	3	3	3	3	2	3	17

Table A4.1 (continued). Assessment of the impact of measures

		Anticipated impact						Effort Required						
Number	Measure	Frequency (n=19)	Short or long term	Direct or indirect	Essential enabler	Impact size	Total impact (max 13)	Impact on cost of goods sold	Cost to public system	Capability and skills required	Legislative requirements	Associated risk	Degree of cross-stakeholder collaboration	Total effort required (max 20)
3.4	National tracking and tracing system to create visibility of demand	0	3	1	3	4	11	3	3	3	3	2	3	17
3.5	Public national shortages catalogue (sometime combined with suggestion for alternative)	8	0	1	3	4	9	1	2	1	3	1	2	10
3.6	Public regional shortages catalogue (sometime combined with suggestion for alternative)	3	3	1	3	4	9	1	2	1	3	1	2	10
3.7	Provision of guidance to health-care providers and the public	5	1	3	0	1	5	0	0	1	3	1	1	6
4.1	Regional stockpiles	1	3	3	0	3	8	1	3	1	3	2	2	12
4.2	Harmonized labelling among countries or a region	3	0	1	2	4	11	1	3	3	3	2	3	15
4.3	Regional harmonization of regulatory requirements	2	2	1	1	4	9	1	3	3	3	2	3	15
4.4	National risk management plan for addressing shortages	3	1	2	1	4	9	2	0	1	0	1	3	7
4.5	Regional redistribution mechanism for exchanging products	4	1	3	0	1	5	1	1	1	3	1	3	10
4.6	Use of regional fora and bodies to strengthen collaboration on shortages	5	3	1	2	4	10	2	0	0	2	1	3	8

Table A4.1 (continued). Assessment of the impact of measures

		Anticipated impact						Effort Required						
Number	Measure	Frequency (n=19)	Short or long term	Direct or indirect	Essential enabler	Impact size	Total impact (max 13)	Impact on cost of goods sold	Cost to public system	Capability and skills required	Legislative requirements	Associated risk	Degree of cross-stakeholder collaboration	Total effort required (max 20)
4.7	Bilateral discussions	10	3	3	0	5	11	1	0	0	0	1	2	4
4.8	Working groups	9	3	3	0	5	11	0	1	1	1	1	2	6
4.9	Steering committees	3	3	3	0	5	11	1	1	1	2	1	3	9
4.10	Multi-stakeholder ecosystems	1	3	3	0	5	11	2	1	2	5	1	4	15

The scale for the impact in all dimensions is 0–3, where 3 is the highest impact. “Impact size” and “legislative requirements” have the most weight in the overall scoring because of adjustment of their scales. Thus, the scale for “impact size” is from 0 to 4, 4 representing the maximum impact; and the scale for “legislative requirements” is from 0 to 5, 5 indicating the greatest significance.

Global Coordination and Partnership (GCP)

World Health Organization
20 Avenue Appia
1211 Geneva 27
Switzerland

www.who.int

9789240100695