World Health Organization

SIXTY-NINTH WORLD HEALTH ASSEMBLY **A69/42**
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Addressing the global shortages of medicines, and the safety and accessibility of children's medication

Report by the Secretariat

1. The Executive Board at its 138th session considered an earlier version of this report[1] and a draft resolution.[2] The Board noted the report and agreed to further consultations on the draft resolution during the intersessional period with a view to finalizing the draft for submission to the Sixty-ninth World Health Assembly.

2. Reports on shortages and stock outs of essential medicines have been increasing in recent years. This has become a global problem, with documented supply failures of antibiotics, anaesthetics, chemotherapy medicines and many others. It has been described in high-, middle- and low-income countries and is related to manufacturing problems, as well as supply chain and health-care financing challenges.

3. Shortages of essential medicines are being documented in most parts of the world with increasing frequency. Many shortages have been linked to products that are older, off-patent or difficult to formulate and that have a tightly-defined shelf life and few manufacturers (or a sole manufacturer).[3] Sterile injectable products are particularly at risk. The reasons for shortages have been investigated in many studies and in several countries and include the following: a limited number of manufacturers for the finished product or the active pharmaceutical ingredient; poor visibility of demand; overly aggressive price reduction practices in procurement; fragmented and low volume markets; and business decisions. For example, the expense of responding to regulatory requirements for a generic product in multiple countries may be prohibitive, with the result that manufacturers may decide to cease production.

4. Interruptions in manufacturing are exacerbated when market challenges combine with weak supply systems. This occurs principally when: data from supply chains to substantiate actual demand are not readily available and are of poor quality; practices for managing procurement and the supply chain are inadequate, and this problem may be accentuated by tender contracts that are poorly timed, that lack sufficient definition of quality requirements and that are focused on obtaining the lowest prices. The unwillingness or inability of manufacturers to respond in these conditions can contribute to shortages. Benzathine penicillin, for example, has been in chronic short supply for several years.

[1] Document EB138/41.

[2] See the summary records of the Executive Board at its 138th session: eleventh meeting and twelfth meeting, section 2 (document EB138/2016/REC/2).

[3] Gehrett BK. A prescription for drug shortages. Journal of the American Medical Association 2012;307:153–154. doi:10.1001/jama.2011.2000.

Although this antibiotic is only recommended for a limited number of indications, these include congenital syphilis and rheumatic heart disease, the treatment of which is dependent on the product. The main problems in this case include a limited number of manufacturers that can consistently produce at required quality levels, very poor forecasting of the demand and a relatively low price.[1]

5. Medicines for children are also subject to shortages. Many regulatory authorities have limited capacity to undertake appropriate regulation to ensure good-quality products for children, clinical trials are not always done in paediatric populations, and there are problems with the capacity to diagnose uncommon diseases in children. Examples are endocrine disorders in children, which can be treated very effectively – when they are recognized – with a small group of essential medicines that are mostly off-patent but seem to be in short supply globally.

CONSEQUENCES OF SHORTAGES

6. Negative impacts of shortages are inability to fulfil prescriptions and to deliver needed medicines, as well as poor quality prescribing and poor use of medicines. The results are poor health outcomes, which have been documented, for example, in relation to mortality in children owing to lack of cancer treatment and to inappropriate use of antibiotics when first-line regimens are not available. Inappropriate use of second- and third-line regimens can contribute to drug resistance and limit treatment options. In addition, such regimens often have a higher cost. The global burden of undertreatment and failure to treat is not known; however, the problem of shortages, given their increasing trend, combined with poor use of medicines will become increasingly complex to resolve. Where shortages have been experienced, there have been reports of spurious/falsely-labelled/falsified/counterfeit medical products entering the supply chain, with risks for the health of patients.

7. High-income, middle-income and low-income countries all may have different reasons for shortages in relation to supply chains, but payment systems for products can cause problems in all settings. Changes in payment structures or systems that provide perverse incentives to use expensive products may also lead to shortages of low-priced alternative treatments. Rigid, lengthy or inadequate tender processes may also contribute to the problem and, although there may be strategies to limit the risk of supply shortages and/or failure through sole tenders (for instance, penalties for failure to supply), research is needed on how effective these have been in reducing shortages in different settings.

COUNTRY APPROACHES TO LIMIT SHORTAGES

8. Several strategies have been tried to avert or reduce shortages. Multiple reporting systems exist within specialized programmes or at national level − in particular in high-income countries. For example, manufacturers in European Union Member States are obliged to inform the health authorities in advance of anticipated shortages. A combination of notification systems as well as systematic regulatory and financing and reimbursement responses may help at a health system level. These systems would need to be combined with efforts to ensure that medicines are used according to treatment guidelines. In particular, it is important to ensure that inappropriate substitute products are

[1] Wyber R, Taubert K, Marko S, Kaplan EL. Benzathine penicillin G for the management of RHD: concerns about quality and access, and opportunities for intervention and improvement. Global Heart 2013:8;227–234 DOI: http://dx.doi.org/10.1016/j.gheart.2013.08.011 (accessed 2 March 2016).

not used simply because they are easier or more commercially attractive to supply. It is not clear yet whether mandatory or voluntary notification works best or who should do the notifying; nor is there certainty that these processes can be applied in countries with weak regulation and information systems.

9. Additional approaches to managing acute shortages, preventing future shortages and reducing the impact of shortages on the provision of care to patients include: the use of online information systems to facilitate direct reporting to health authorities of information on shortages; coordination between producers; and, in some situations, such as emergencies, the use of exceptional procedures for the granting of market authorizations. Also, some countries have promoted initiatives to encourage the production and registration of generic versions of medicines in short supply.

10. Mechanisms for combining and sharing notifications about medicines at risk of shortage could be investigated and explored. The supply of pharmaceuticals is a multinational business. Therefore, a system for global monitoring is needed in order to promote early detection of shortages and to encourage countries, the international community and other relevant stakeholders to cooperate in developing a joint rapid response.

11. Pricing interventions can also be used to reduce shortages. In the Australian context, manufacturers can request a higher price for products with limited markets.[1] It has been suggested that in the context of the United States of America, where prices of oncology products decreased following the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, that setting minimum prices for some products in order to encourage continuity of supply would improve supply of oncology products.

12. It is important to develop proactive strategies with actions to be taken to identify and maintain the supply of medicines that are essential for health care and that are vulnerable to shortages in supply. The usual market approach to medicines supply through encouraging generic manufacturers to produce the medicines of interest has shown enormous benefits in lowering prices and increasing affordability. Too low prices, however, may drive manufacturers out of the market, and higher prices of alternative newer products may result in them being preferentially supplied, with a decline in market for vital but cheaper medicines. Limiting competition can also result in problems with supply of essential medicines, including shortages.

NEW STRATEGIES TO MITIGATE THE RISK OF SHORTAGES

13. At the global level, a set of essential medicines could be identified for which shortages have been reported or there exists a risk of shortages, and an international agreement about ensuring continuity of manufacturing and supply could be investigated. For example, without methotrexate successful treatment of many oncological and immunological conditions is severely jeopardized – yet this product has been reported as in short supply repeatedly. Questions that a general international agreement would have to resolve include: What is the core problem? What incentives are appropriate to create and maintain stability in the global market? Could a multiyear global advance purchase commitment be worked out? Would an agreed global minimum price that is commercially attractive help to keep a medicine on the market? How would such a price be set?

[1] See Australian Government Department of Health, The Pharmaceuticals Benefit Scheme, http://www.pbs.gov.au/info/industry/pricing/pbs-items/fact-sheet-requesting-a-change-to-an-existing-price (accessed 2 March 2016).

MEDICINES FOR CHILDREN

14. The adoption by the Health Assembly in 2007 of resolution WHA60.20 on better medicines for children led the Secretariat to introduce a programme of work on that subject. Its results have included creation of the WHO Model List of Essential Medicines for Children (most recently updated in April 2015), the setting of global standards for formulations of medicines for children, identification of clinical trials in children through the WHO International Clinical Trials Registry Platform, publication of information about prices of selected medicines for children, and identification of missing products, such as fixed-dose combination medicines containing the appropriate dose of the components for tuberculosis in children.

15. The shortage of treatments of tuberculosis for children was successfully addressed by WHO and its partners. After a change in tuberculosis treatment guidelines in 2010, the pharmaceutical industry was reluctant to invest in redeveloping medicines to treat children with tuberculosis, citing the cost of new trials for regulatory submissions and the fact that the market was small and poorly understood as barriers to investing. UNITAID's STEP TB Project invested in trials to reduce risk and engaged with manufacturers to ensure regulatory submissions. The Project also worked with countries with high burdens of tuberculosis and major procurers to improve the ability to quantify the actual demand and need.

16. Shortages of each product (or group of similar products) will have different causes and their rectification will require specific and targeted interventions. Other products for children are also listed on the invitations for expression of interest issued by the WHO Prequalification Programme for HIV/AIDS, including hepatitis B and C, and malaria, and interventions continue with the aim of securing their availability, from manufacturing to national supply chains.

17. The Paediatric medicines Regulators Network was established to promote collaboration between regulatory authorities on the regulation of medicines for children. Some high-income countries have legislation related to medicines for children with the aim of optimizing and promoting the development of appropriate products, but similar legislation is not generally in place in low- and middle-income countries. There will be value in further developing the Network and providing more support to countries for building appropriate capacity to regulate medicines for children appropriately and encourage their research and development.

18. Prices of paediatric medicines are generally higher than equivalent products for adults. In part, this price differential may be due to higher development costs of special dosage forms for children and the need for additional clinical trials. Low volumes can also be a cause. A better understanding of research and development costs would enable a constructive dialogue on how to establish a fair and affordable price for medicines for children.

19. Understanding the costs of development of medicines is particularly important for uncommon and genetic diseases in children (variously classified as orphan and rare diseases). New and effective products for many genetic disorders are becoming available but they are generally extremely expensive. Further there is a degree of confusion between what are truly orphan or rare diseases, based on the global burden of disease, and what have been defined as orphan diseases for the purposes of regulatory authorities who can provide incentives for manufacturers to encourage their development and production. There is some evidence that these incentives are now being exploited, resulting in high prices and problems with access. Should a country choose to make these products available through health insurance schemes, the impact on their pharmaceutical budgets can be substantial.

20. Overall, the demand side of the market for many medicines may need to be more actively managed. There are limited data to guide manufacturing and procurement decisions about medicines for many diseases in children. At the same time, health care workers try to provide effective care through the use of extemporaneous preparations, which may offer short-term solutions but may also be associated with risks due to poor-quality production or ingredients not tolerated well by children. Health care workers may also have limited expectations and confidence in the availability and value of medicines for children and hence not promote their use.

TOWARD A POTENTIAL SYSTEMIC APPROACH TO PREVENT AND MANAGE SHORTAGES OF ESSENTIAL MEDICINES

21. A Technical Consultation on Preventing and Managing Global Stock Outs of Medicines, was held in WHO Geneva on 8 and 9 December 2015. The Consultation recognized that shortages and stock-outs of medicines and technologies are of concern to all countries and that there is a need for coordinated and global action on approaches to prevent and manage shortages.

22. Several options were identified for actions that may lead to a reduction of the problem of shortages, both generally and specifically for medicines for children. These options include:

(a) harmonized definitions of "stock outs" and "shortages", established standards for reporting and application of a globalized notification system and response mechanisms;

(b) proper assessment to define products at risk and sharing of validated information about products in short supply;

(c) global agreement on actions to diminish specific shortages of essential medicines at risk of shortage, including global coordination with manufacturers; development of an approach to market-shaping for medicines at risk, in collaboration with global partners;

(d) recording of best practices for regulators in responding to shortages and expansion of regulatory collaboration on essential medicines susceptible to shortages, including best practices on early detection of shortages;

(e) adequate financing and prices to allow for compliance with good manufacturing practices and ensure quality products; centralized negotiation to preserve essential medicines susceptible to shortages, including definition of minimum volume and fair price;

(f) recording of best practices in procurement and supply management, including optimal use of tendering and the use of technology to improve the availability and quality of demand data, learning from the experience of regional pooled procurement mechanisms and other major procurers;

(g) analysis and understanding of costs of research and development for medicines for uncommon diseases in children;

(h) expansion of the activities of the Paediatric Medicines Regulators Network to promote appropriate legislation, regulatory strategies and capacity, and monitoring of medicines in children;

(i) continued promotion of ethical and appropriate clinical trials in children of all age groups;

(j) collaboration with partners to ensure appropriate demand for medicines for children, including medicines for uncommon diseases.

23. Meeting the targets specified in relation to access to medicines in Sustainable Development Goal 3 (Ensure healthy lives and promote well-being for all at all ages), as well as completing the unfinished agenda of the Millennium Development Goals, will require coordinated action to address the factors described in this report. Continuing to react to stock outs and shortages on a case-by-case basis, especially those caused by market dynamics, will severely compromise the ability to achieve equitable access to essential medicines; more active approaches to shaping the market for essential medicines on a global scale will be needed.

ACTION BY THE HEALTH ASSEMBLY

24. The Health Assembly is invited to note the report.

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