Meeting Report

Antibiotic Shortages: Magnitude, Causes and Possible Solutions

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Norwegian Directorate of Health, Oslo, Norway

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World Health Organization

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Introduction

The main aim of the meeting, held on 10-11 December 2018 in Oslo, was to enable stakeholders to discuss antibiotic shortages and availability including the magnitude of supply instability, causes, and possible actions to create predictable supply. The meeting sought to address the following questions:

- What are the causes for lack of availability and shortages of antibiotics?
- What are the consequences of antibiotic shortages and supply instability, and what actions are governments currently undertaking to improve availability?
- What are potential short- and long-term solutions?
- How can different stakeholders support the process to mitigate future shortages in antibiotics?

While availability to quality-assured antibiotics is a global challenge, this meeting focused on the specific market failure of predictable supply of older existing antibiotics that have been in shortage over the last years or have low prices and/or modest sales, with the intent to identify potential solutions.

Key issues addressed included: antibiotic demand forecasting; manufacturing; procurement practices; pricing of generic antibiotics; linked and delinked financial reimbursement models; pooled procurement models; regulatory challenges and opportunities; the benefits and disadvantages of local production; and, to some extent, the economic and societal impact of shortages.

The meeting was organized and hosted by the World Health Organization (WHO), the Norwegian Directorate of Health, and the Norwegian Institute of Public Health. The overall project was financed by a grant from the Swedish International Development Cooperation Agency (SIDA) through ReAct – Action on Antibiotic Resistance. Attendees included representatives from Member States, non-governmental organizations, individual experts and generic producers of antibiotics. The meeting was divided into two days with the first day focusing on the problem of shortages and unstable availability and the second day on potential solutions.

Summary of the proceedings

The meeting was opened by Bent Høie, the Norwegian Minister of Health and Care Services; Bjørn Guldvog, Director General of the Norwegian Directorate of Health; Otto Cars, founder of ReAct and member of the Interagency Coordination Group on Antimicrobial Resistance; and Peter Beyer, Senior Advisor at the World Health Organization, Department of Essential Medicines & Health Products.

In their opening statements, speakers emphasized that antibiotics should be considered a global common good, since they have shared and beneficial value to all people. Antibiotic shortages thus constitute a major societal threat. Existing antibiotics often in shortage, like narrow spectrum penicillins, are commonly used in countries with lower rates of antibiotic resistance, such as the Scandinavian countries, although they can be used effectively in countries with high resistance rates, e.g. in small children where respiratory tract infections are common. However, these antibiotics are often not used due to lack of knowledge about their area of use, uncertainty about their efficacy when resistance is high, or a lack of availability/supply. They are also not always

included in national/international treatment guidelines which are often based on which antibiotics are available in the country, rather than the best antibiotic to treat the infections and with the least impact on the development of antibiotic resistance. Since development of resistance to an antibiotic is accelerated with increased use, the continued use of older existing antibiotics allows newer antibiotics to be preserved, such as broad-spectrum antibiotics.

The meeting focused on the antibiotic market in Meeting report: Antibiotic shortages - magnitude, causes and possible solutions the European Region and several antibiotics that were identified by WHO to be frequently in shortage due to lack of supply. The meeting focused on market dynamics to assess the root causes of shortages, including transparency of the supply chain and prices, which are also part of the WHO Fair Pricing Initiative. The objectives of the project were to provide market insights on 10 antibiotics in eight countries, namely identifying manufacturers, sources of active pharmaceutical ingredient (API), price levels and market size/consumption to analyse the situation of the problem and identify possible solutions. The key questions were:

- Do we need more data and, if yes, how do we generate it?
- What are the main obstacles and how can we overcome them?
- What are the most promising solutions?
- What is the best strategy to procure antibiotics?
- What can WHO do? (A guide for antibiotic procurement? An annual market survey? Provide more data? Explore specific solutions? etc.)
- Do we need European demand forecasts? (Regular market surveys on prices, volumes and production capacities?)
- How can shortages of antibiotics be elevated to the political agenda?

What causes lack of availability and shortages of antibiotics?

During the meeting's second session, stakeholders from different countries presented an overview of their experiences with shortages and the steps they had taken to address them. The experiences of several European countries indicate that shortage of antimicrobial agents is common, and the frequency of shortages seems to be increasing, despite Europe's position as the second largest regional manufacturing center of antibiotics. The following reasons were highlighted by the presenters:

- The ***main reason*** for vulnerable supply of older antibiotics is that the market has low returns and/or limited size, and few actors in the production and supply chain (see illustration below).

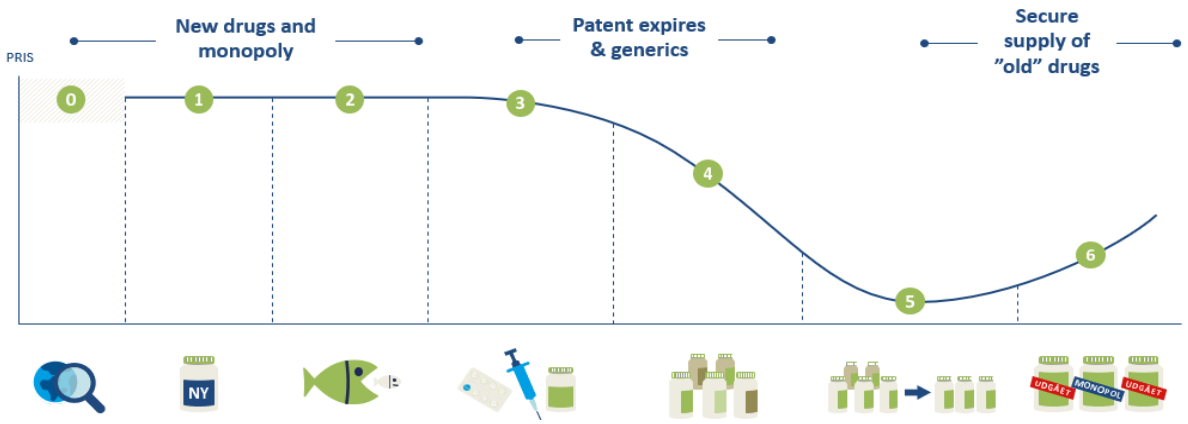

Illustration by courtesy of Amgros

y: Price for product. **x**: **0**: R&D of new products. **1**: New product introduced. **2**: Monopoly situation. **3**: Increasing competition. **4**: Generics/ biosimilars. **5**: => Critical supply. **6**: Critical supply, monopoly.

- The ***secondary reasons*** involve multiple issues:
  - **Manufacturing issues:** Much of the antibiotic production has, over the years, been moved to countries with lower production costs, e.g. India and China. To generate a profit, producers of active pharmaceutical ingredients (API) must produce large batches. Due to the modest market demand but also quality issues related to production and production facilities, many finished product antibiotics are dependent on a few API manufacturers (that may be in close proximity of each other). Consequently, production is vulnerable to shortages if accidents occur, facilities are shut down due to quality or other issues or stop production of APIs for antibiotics.
  - **Regulatory issues:** Regulatory compliance costs are significant for low margin antibiotics (fees for changes in the dossier, upgrade of production sites, quality demands). Older existing, injectable antibiotics Are most vulnerable to shortages as they have higher quality standards for sterility and complex production processes translating into higher production costs, but still with low expected return on investment (ref update of ANNEX 1).
  - **Economic issues:**
    - *Procurement models:* Purchasers often award tenders to one company offering the lowest price. This is not sustainable since margins on generics are already low and will over time lead to even fewer bidders. Lower and lower price => low revenues => low profit.
    - *Commercial withdrawals from the market* due to low demand and/ or low price.
  - **Supply issues**: e.g. increased or reduced demand, low quality
  - **Other:** e.g. lack of political commitment and engagement from relevant stakeholders

Manufacturing and production business models

As to be expected, different business models have been adopted by antibiotic manufacturers; from organizations where all production is outsourced to fully integrated manufacturers producing all components including raw materials (e.g. API), and variations in between (see illustration below).

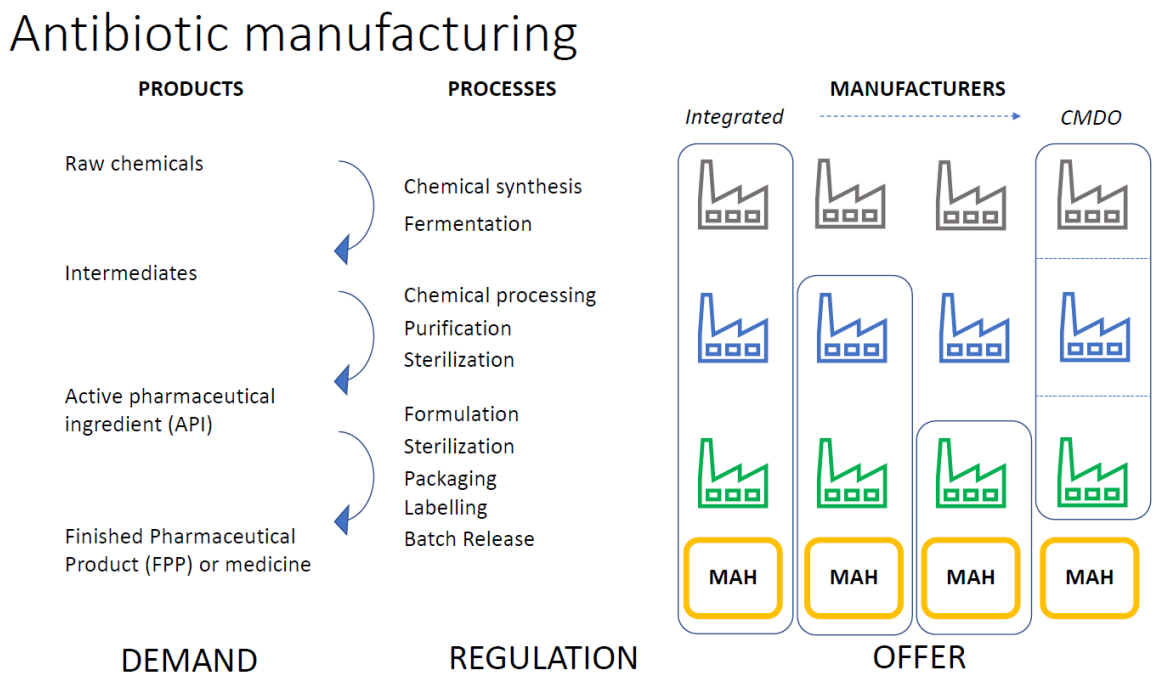

Illustration by Francisco Blanco

Whereas previously most finished antibiotic manufacturers were dependent upon API produced in Europe, it is now mainly being produced in China and India. There is little transparency regarding the production of the various ingredients of an antibiotic. This is considered confidential and proprietary information only available to regional and national regulatory agencies where marketing authorization has been sought by the finished product producer. This lack of transparency makes it difficult to perform a true risk assessment to determine areas of greatest vulnerability. The information is only revealed multi-nationally when a major supply disruption occurs. For example, in 2017 the world's supply of piperacillin/tazobactam was interrupted due to a fire at the sole API supplier. Data available on 10 select antibiotics (Amoxicillin-clavulanic acid, Benzathine penicillin, Piperacillin-tazobactam, Cefepime, Imipenem + cilastatin, Meropenem, Gentamicin, Sulfamethoxazole + trimethoprim and Fosfomycin) suggest that two API producers are involved in over 50% of the market authorizations (MAs) and that API sources in Asia are linked to 52% of MAs and European sources linked to 47% of them.

Regulation and market authorization

Regulatory challenges applicable to antibiotics:

Many generic antibiotics are old products that entered the markets decades ago when there were different standards for clinical trials and regulatory documentation. Collecting the evidence to meet current standards would be expensive and unrealistic for a company to finance given the profit margins. Therefore, countries are highly dependent upon companies that have historically held national marketing authorization. With few market authorization holders for certain products, the loss of one of these companies may translate into shortages of the company's portfolio. To prevent shortages, countries have in some instances added additional requirements:

- Marketing authorization holders (MAHs) must inform drug authorities in case of expected shortage or withdrawal of MA,
- MAHs must bear the cost of imports in case of a shortage,

- MAHs must design and implement redundancy plans, and
- MAHs are held to maximum total payouts with payment "clawbacks" at the end of financial year.

Some of these requirements may make the market even more unattractive if non-compliance leads to financial penalties that are not proportionate to the revenues generated. Countries have rarely developed their own redundancy plans so there is marginal understanding of which antibiotics may have increased demand due to shortages. There is a risk that one shortage may create cascading shortages as unexpectedly high demand on substitute antibiotics depletes the global stocks. This raises equity concerns when remaining stock are sold to countries willing and able to pay higher prices.

Even though the global demand of many older existing antibiotics could be significantly larger based upon the therapeutic need, the market remains fragmented. Despite the availability of international antibiotic prescribing guidelines containing these important antibiotics, there is a lack of standardization with different antibiotics or doses being recommended in different countries, even in countries with similar resistance profiles. Similarly, the classification of diseases may differ.

The lack of standardization is rooted in the inability to apply for marketing authorization in new markets due to the lack of regulatory documentation. The lack of evidence also hampers the inclusion of older existing antibiotics in evidence-based prescribing guidelines. Guidelines and susceptibility testing are based upon nationally available antibiotics rather than the optimal antibiotic. Furthermore, susceptibility testing data are sometimes lacking on a large scale for these antibiotics. Yet there is also potentially some benefit in this diversity of prescribing in that it may also slow the development of antibiotic resistance.

What are the consequences of antibiotic shortages and supply instability*?*

Financial and societal costs

Shortages hurt all stakeholders. Patients may receive suboptimal treatment including delayed treatment, intravenous injections rather than oral forms, and greater side effects. In the worst case, preventable deaths occur. Society is placed at greater risk when broad spectrum antibiotics are substituted for the preferred narrow spectrum antibiotic. There are increased healthcare costs, not only to manage undesirable side effects but also to put systems in place to manage shortages. A few countries have begun to quantify the cost of drug shortages, demonstrating increased costs of shortages for one antibiotic to be between € 20-30 million. Industry faces reputational risk and must refocus its work force to manage the supply disruptions.

There is a strong desire from all sides for greater communication surrounding shortages. Healthcare providers want warnings of potential supply disruptions long before they occur. Yet most reports of shortages come after the shortage has started. Companies are incentivized to utilize just-in-time manufacturing systems to minimize their internal costs, meaning that they may be alerted of supply disruptions within a production cycle, which may be as short as days. They are also incentivized to rely on one API supplier since the cost of listing an additional supplier on the dossier is significant, as is the updating of the dossier by supply changes. Due to increased reporting requirements and reputational risk, companies are also incentivized to try to mitigate

any supply problems and thereby communicate shortages only when mitigation measures have failed. The combination of these factors makes it unlikely that warnings of supply shortages can be expedited.

Options for the way forward? Stakeholders discussed several potential options for the way forward, mostly addressing the management of shortages (short-term) and not the root causes (long-term). These ideas represent high-level discussion amongst experts and require further consideration, stakeholder input, and evidence review. The options listed were not endorsed by the group nor are they listed in any particular order.

Short-term options

Improve demand forecast: Governments could improve demand forecasts of essential antibiotics so that producers can adequately plan to meet demand.

Improve reserves: Governments could consider stockpiling, requiring companies to stockpile or increase buffer stocks of critically important antibiotics. This could include physical stockpiles at hospitals and community pharmacies or buffer stock requirements from wholesalers. This is already in place in different countries.

Improve early warnings: Governments could review barriers to communication from marketing authorization holders regarding potential shortages. This may include examining reporting requirements and potential penalties. These efforts would focus on removing communication barriers while maintaining accountability. Different countries have introduced mandatory reporting requirements.

Improve predictability: Governments could develop recommendations listing substitute antibiotics in case of shortages. This would give producers greater predictability about how shortages may affect the demand of substitute antibiotics. WHO could also lead this work in collaboration with Member States.

Improve political awareness: This topic would benefit from the production and dissemination of an advocacy paper containing the real costs of shortages and situation analyses of patient safety.

Improve communication: The European Medicines Agency (EMA) could notify Member States when previously-approved factories fail good manufacturing practices (GMP) inspection or withdraw from GMP review, including the products impacted. WHO could operate a shortage notification system where shortages are reported with potential predications for the spread of the shortage. European countries could commit to populating the system with their shortages.

Improve use of old antibiotics: WHO, European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and others could work with Member States to advise on potential areas where guidelines could be adjusted, and older existing antibiotics included.

Long-term options

Improve market attractiveness: Countries could explore different methods of performing susceptibility testing against all relevant known antibiotics, rather than the limited subset of antibiotics available in country. In this way, the efficacy of older antibiotics would be more apparent, potentially increasing demand. A first step would be to have EUCAST test all known relevant antibiotics to determine the clinical breakpoints and then provide recommendations on which set of antibiotics (including the older ones) to test in routine, both for clinical and epidemiological purposes (e.g. testing of fosfomycin or pivmecillinam in urine).

Changes in regulatory practices: Countries could create a regulatory pathway where the regulatory agency (or other suitable agency) can identify and register medicines, at high risk of shortage?

rather than leave it to the companies to broaden the possible supplier basis. Ideally, this could be done on a regional level through the EMA.

Ensure that generic antibiotics remain a healthy business: Increasing pricing pressure or lack of volume will likely lead to additional manufacturers leaving the generic antibiotic market and focus on more profitable areas. Several new financial models to maintain availability of critical antibiotics have been detailed by the DRIVE-AB project and commissioned reports for the British and Swedish governments. These models include delinked reimbursement models, e.g., models where payments are either partially or fully linked to unit sales. Sweden is considering a pilot to test a de-linkage model. Its experiences, even at these early stages, give insight into the complexity of these models, including the challenge of paying nationally when medicines are generally reimbursed locally; the legal ramifications such as if a model could be interpreted as unauthorized state aid; aligning the selection process with national, mandatory tendering processes. Other financial models could be to provide a top-up payment for each unit sold where the additional payment comes with conditions for stable supply and environmental assurances or to provide a fixed fair price for essential antibiotics at national level which cannot be discounted, e.g. in tenders at hospital level.

Ensure healthy competition and procurement practices: Some tendering practices may unintentionally harm competition, such as awarding the full tender to the applicant that meets the requirements with the lowest price ("the winner takes it all" tender). It would be beneficial to split up tender allocations to multiple suppliers as well as utilize other characteristics as the determining factor, including guarantees for long term availability of quality products. This is easier to implement in countries with centralized procurement. In countries where health insurances and hospitals are procuring the antibiotics, more guidance and training on sustainable procurement practices for antibiotics should be developed and rolled out. Different factors (like historical performance of uninterrupted supply and diversity of API vendors and other factors such an environmental performance) could be included, vetted, and tested.

Facilitate registration of old antibiotics: For a small number of essential, existing antibiotics, it may be valuable to publicly finance the generation of the necessary regulatory documentation so that regulatory files can meet EMA standards thereby allowing manufacturers to supply other European markets. Supporting a geographic diversity of suppliers should be accounted for in the selection process as well as commitments to supply both large and small markets. Other measures could include the ability to accept multilingual packages (or electronic leaflets), or packages with pre-cut blisters (containing all necessary information e.g. name and dose of the antibiotic) adapted to unit dispensing.

Stimulate generic manufacturing: Many innovative medical treatments and procedures are dependent upon the availability of effective prophylactic antibiotics. A potentially controversial requirement could be that for all new approvals of medicines dependent upon a prophylactic antibiotic (e.g., a new oncology medicine) that the marketing authorization holder must also ensure that the "companion" antibiotic is also available in the country.

Mandate vendor transparency: It needs to be easier to perform risk assessments on the vendor supply of critically important antibiotics. These cannot be effectively performed with the current level of transparency. Member States could assess making the entire supply chain of vendors public information. Based on this information, the political aim should be to ensure that there are at least three, geographically diverse API vendors per medicine.

Ensure supply: European countries could decide that the uninterrupted supply of critically important antibiotics is so important that they must be produced locally, potentially by a publicly-financed entity. Yet to avoid geographic risks, the entity would need to be spread across several countries. This would require significant political commitment and investment. Procurement mechanisms would need to be harmonized.

Summary

This multi-stakeholder discussion was a first step towards identifying an actionable agenda towards securing a stable supply of essential, older existing antibiotics. The consequences of antibiotic shortages and supply instability are significant, especially for the patient and the healthcare system. It appears that few countries have yet quantified these consequences, although one analysis indicates a cost of one antibiotic shortage to be between € 20-30 million.

Governments are taking many different actions to improve availability, but in some cases may be exacerbating the problem by increasing the pressure on the few remaining suppliers by implementing penalties on manufacturers and awarding tenders mainly on price rather than other criteria such as supply stability. A few countries are exploring innovative model initiatives. More initiatives need to focus on creating a sustainable and predictable market which includes reviewing current procurement practices. It appears that little work has been done to increase pooled procurement and delinked rewards. It is too early to judge the success of these initiatives in increasing the demand of older existing antibiotics, which when prescribed appropriately may reduce selection pressure from other antibiotics. WHO can play an important role here in guiding countries to switch their consumption to these antibiotics in some instances.

There are many potential options for the way forward aimed at both alleviating shortages (short-term) and remedying the root causes (long-term) but focusing on the primary aim of improving predictability and ensuring competition. These ideas represent high-level discussion amongst experts and require further consideration, stakeholder input, and evidence review.

Yet, to convince governments of the importance of testing some of these options, an advocacy paper containing the real costs (societal and financial) of shortages and situation analyses of patient safety is needed. This should be an immediate priority, utilizing the dissemination of this report to discuss testing other potential solutions. Additionally, there are several high-level meetings occurring in 2019 where the topic of antibiotic shortages should be included on the agenda.

Meeting on Antibiotic Shortages:

Magnitude, Causes and Possible Solutions

10-11 December 2018, Oslo, Norway

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