Managing Antimicrobial Resistance Through Behavior Change, March 2021

Where are our antibiotics? Three possible solutions to address antibiotic shortages and improve global antibiotic supply

Enrico Baraldi, Therese Fagerqvist, Sofia Wagrell, Ines Khadri, Carl Kronlid, Simone Callegari

Antibiotics are a cornerstone of modern medicine – and yet, access to established antibiotics is a major problem across the globe. There is sometimes a shortage of established old generic products, locally or even globally. Some antibiotics may suddenly be withdrawn from markets, if considered economically unattractive. When antibiotics become unavailable, patients are exposed to unnecessary suffering, healthcare costs surge and antibiotic resistance accelerates because suboptimal antibiotics have to be used to substitute them.

The COVID-19 epidemic has brought to the fore the key problem of drug shortages, as demand for medicines such as painkillers, anaesthetics and some classes of antibiotics peaked while supply was disrupted globally. Some countries even introduced export restrictions on active pharmaceutical ingredients (APIs) and final products.[1] However, drug and especially antibiotic shortages are not a new phenomenon – rather they have slowly been increasing over the last 10 years.[2] In modern healthcare systems, an antibiotic shortage typically causes additional costs for replacements, whereas the consequences are more extreme in low-income countries, often causing increased mortality. Assessing the costs of shortages is extremely complex, but some estimates point to costs of USD 20–30 million per antibiotic shortage.[3]

There are several reasons why shortages occur, such as a sudden surge in demand which cannot be met with timely orders, disasters or accidents, discontinued production or quality problems in production, with the latter accounting for over 60% of shortage events.[4, 2] However, there are a set of complex *root causes* at play behind these reasons for single events of antibiotic shortages; most of them concern financial and profitability issues related to the entire antibiotic field, from API supply sectors all the way to end markets.[3, 4] The general problem of low profitability for the various actors in this field can be broken down into several specific causes that in turn generate multiple effects which further aggravate the problem. Key problems include the absence of volume commitment through long-term contracts and strong fluctuations in local demand,[5] which cause both *low profit per unit and uncertainty about volumes*. On the *manufacturing side*, the rigid production systems cause problems in that they are not flexible enough to cope with the aforementioned uncertainty, because of both regulatory constraints (e.g., on moving manufacturing of established products from one plant to another) and technical constraints. Furthermore, many facilities require modernisation and upgrading in the face of stricter environmental requirements, among other things. However – when it comes to antibiotics – this can be a problematic investment, given the low profitability. Also, existing plants are usually already operating at close to full capacity and the costs for building a new plant can exceed USD 100 million.[4]

Objective of the workshop

The objective of the workshop was to discuss potential solutions and ways forward to address the root causes of antibiotic shortages. Since the problem is complex and potentially contains an endless number of issues to be discussed, the workshop was focused around the following three main themes and their potential solutions and their respective pros and cons:

1. Enhancing transparency in antibiotic supply chains.
2. Improving profitability for antibiotic suppliers.
3. Upgrading production systems.

These topics were discussed one after the other in three parallel breakout rooms, after which the discussions were summarised in a plenary session. The participants represented several different academic fields (ranging from medicine to management science), the industry, NGOs, and governmental and transnational agencies. About 30 people participated in the workshop.

© Shutterstock

Outcome of workshop discussions

The outcome of the discussions can be summarised in four main areas with suggestions for ways forward:

1. Creating incentives for the industry to keep providing antibiotics

Getting the industry to keep providing antibiotics, despite low sales volumes and low profitability, is key to preserving a continuous supply in the future. The discussion settled on two focus areas to be addressed:
a) Enhancing the predictability in production.
b) Creating financial incentives for producing antibiotics.

An enhanced predictability could be achieved through changes in procurement and contracting systems. If procured volumes were predetermined for a specific period of time, the planning of production would be easier for the suppliers. Today, a supplying company can win a procurement contract to deliver a specific antibiotic, often without any guaranteed volumes, but with a requirement to supply a given volume if needed. The predicted sales are based on estimates from previous periods, but volumes can never be guaranteed. A complementary solution would be to extend the contract periods, which could also aid in enhancing predictability for companies and make it easier to plan production and thus reduce uncertainty. Another central precondition to enhanced predictability is transparency: more available information about the actual needs in the healthcare system would help producers plan and estimate production more accurately and better meet fluctuations in demand and handle single events causing stockouts.
Financial incentives were identified as one core aspect to ensure that specific antibiotics stay on the markets and to prevent stockouts. The workshop concluded that there is a call for new economic mechanisms that can cater for the specific requirements that underlie antibiotics, considering that their availability is conditioned by a 'reversed market logic': antibiotic use has to be kept as low as possible, at the same time as healthcare requires a broad arsenal of dosage forms and a large variety of different types of antibiotics, which are necessary to curb the escalating situation of antibiotic resistance. Hence, supplying companies need to provide a broad array of antibiotic products to be used (sold) as little as possible, implying that the market function is 'out of play' and other mechanisms have to be implemented to ensure the availability of antibiotics. A suggestion is to give the supplying companies an annual fixed compensation for providing a critical and low-volume antibiotic to a specific market.

2. Creating awareness of the problem in its full complexity

Antibiotic shortage is a societal problem. It is interconnected to existing structures in healthcare, procurement systems, massive negative consequences in the treatment of patients, environmental issues, global trade and production structures. Since it has both economic and medical consequences, antibiotic shortage is in essence a political issue, where policymakers have the utmost power to act and make necessary changes happen. Activities not only have to be pushed in the 'right direction', but also coordinated, since they are overlapping and interdependent.
Thus far, the problem has often been addressed from each single actor's perspective, but these perspectives are seldom coordinated or put together to unveil the larger picture and the totality of the consequences. It seems that the research community and other involved actors have failed to clearly communicate the impending severity of the problem of antibiotic shortages and what we are facing. The consequences of today's lax attitude have to be clearly communicated to policymakers, *in their full complexity*, so as to ensure that the right kinds of actions are taken. One way to do this would be to create more precise and comprehensive financial calculations of the total societal costs caused by antibiotic shortages, include how they aggravate the larger crisis of antibiotic resistance.

3. Transparency

Transparency was identified as key to solving many of the problems surrounding antibiotic shortages. Transparency is often mentioned in relation to supply chains that are hard to map due to sub-suppliers being spread across the globe and often being unknown, even if they are few in number. One central aspect that was discussed during this workshop was that we also need more *transparency on the demand side*. Today, countries do not cooperate or pool their demands for antibiotics, even for products, formulations or strengths that are rare or used at a small scale. One suggestion identified during this workshop was to pool demand for narrow-spectrum antibiotics that are sold in low volume and are at risk of being withdrawn from one or several markets. Such measures of cooperation could also be beneficial for the industry, since they could enhance predictability in demand.

4. Collaboration

The perhaps most central ingredient in addressing the availability of antibiotics is collaboration. It was concluded that collaboration has to take place at multiple levels and among a range of actors. It is first and foremost a matter of creating purposeful platforms where collaboration between different types of stakeholders can take place, so as to pave the way for joint actions that embrace a multi-actor perspective. These actors include academia, industry, healthcare providers and authorities. Second, there is a need for countries to collaborate, for example by pooling their demand for low-volume antibiotics, so as to ensure they are still provided, despite low profitability. To solve an escalating problem, in the face of high complexity and – not least – interdependencies on a global scale, countries will need to work together and *in the same direction*.

At the same time, the structure of the problem of antibiotic shortages varies between countries, since they are subject to different regulatory contexts and healthcare systems. Therefore, it was suggested that each country should perform a root cause analysis similar to that performed in Sweden by the collaboration platform PLATINEA, so as to fully understand the structure of the underlying problems in that specific context. Such analyses would also make it easier to coordinate activities over country borders.

References

1. Chatterjee P., (2020). Indian pharma threatened by COVID-19 shutdowns in China. *The Lancet*; 395(10225): 675.

2. OECD (2020). *Shortage of medicines in OECD countries*, Directorate for Employment, Labour and Social Affairs. Health Committee.

3. WHO (2019). *Meeting Report Antibiotic Shortages: Magnitude, Causes and Possible Solutions*. Norwegian Directorateof Health, Oslo, Norway 10-11 December 2018. Available at: https://apps.who.int/iris/bitstream/handle/10665/311288/WHO-MVP-EMP-IAU-2019.02-eng.pdf?ua=1

4. US FDA (2019), *Drug shortages: root causes and potential solutions*.

5. Cogan D, Karrar K, & Iyer J., (2018). Shortages, stockouts and scarcity: the issues facing the security of antibiotic supply and the role for pharmaceutical companies. Access to Medicine Foundation.

Acknowledgements

This brief is one in a series of eight policy briefs produced as an outcome of the digital 2021 Uppsala Health Summit "Managing Antimicrobial Resistance Through Behavior Change." Uppsala Health Summit is an international arena for dialogue, exploring possibilities and implementation challenges associated with advancement in medicine and public health. You can find the entire series of briefs and more information about Uppsala Health Summit at www.uppsalahealthsummit.se.

Organisers: Enrico Baraldi, Uppsala University; Therese Fagerqvist, Uppsala University; Sofia Wagrell, Uppsala University. Rapporteurs at the workshop: Ines Khadri, Uppsala University; Carl Kronlid, Uppsala University; Simone Callegari, Uppsala University.

Corresponding author: Sofia Wagrell, Uppsala University, sofia.wagrell@sts.uu.se

Uppsala HEALTH SUMMIT

Sponsors

Partners