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Narrative review

The multifaceted nature of lack of access to antibiotics: types of shortage and specific causes, consequences, and solutions

Enrico Baraldi [1,*], Christine Årdal [2], Emil Aho [3], Gabriel-Adrian Popescu [4], Tsegaye Melaku [5]

[1] Department of Business Studies, Uppsala University, Uppsala, Sweden
[2] Norwegian Institute of Public Health, Antibiotic Resistance and Infection Prevention, Oslo, Norway
[3] Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden
[4] Department of Infectious Diseases, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[5] School of Pharmacy, Institute of Health, Jimma University, Oromia, Ethiopia

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ABSTRACT

Background: Maintaining access to a broad range of old and new antibiotics is increasingly difficult due to supply, market, and demand issues. Next to immediate negative consequences for individual patients and healthcare systems, antibiotic unavailability can accelerate resistance development due to unmotivated use of suboptimal broad-spectrum antibiotics.
Objectives: Although academics and policymakers agree that lack of access to antibiotics is a major public challenge, there are widely different situations of lack of access that are not always clearly identified. Therefore, this paper aims to clarify potential confusion by delving into four different types of lack of access, their specific causes, consequences, and potential solutions.
Sources: The paper builds on a narrative review of academic and policy literature about lack of access to antibiotics and potential solutions to address it.
Content: We discuss causes as well as economic and clinical consequences of four different types of antibiotic unavailability: short-term shortages, long-term shortages, deregistrations, and lack of registration. The discussion is supported by examples from Norway, Romania, and Ethiopia, three countries characterized by clearly different market sizes and ability to pay. Common causes for all types of lack access include unattractive markets, dependence on few suppliers and insufficient communication, whereas other causes are specific to one type (e.g. insufficient inventories cause short-term shortages or regulatory complexity hinders registration). Longer lack of access entails more serious clinical consequences and higher risk of resistance development, but may not correspondingly increase costs in the long-term if alternatives are identified.
Implications: It is essential to understand the type of unavailability at hand because no single solution can address all types. For instance, stockpiling addresses short-term shortages, but not long-term ones or deregistrations. However, supply chain transparency and pooled procurement are remedies that support other solutions and can cope with several types of lack of access. **Enrico Baraldi, Clin Microbiol Infect 2025;31:333**

Introduction

Over the last 75 years more than 200 antibiotic substances have been developed and marketed, 50 of which are included in the WHO's Essential Medicines List (EML) [1,2]. Maintaining access to the full breadth of antibiotics, at least those on the EML, is necessary not only to treat common infections but also for prophylaxis in other treatments like chemotherapy. Additionally, although bacteria evolve resistance mechanisms to common antibiotics, they may still be susceptible to older substances. For example, aztreonam, a 'forgotten' antibiotic [3], has been shown useful in treating multidrug-resistant infections [4,5].

Reliable access to a full arsenal of antibiotics is important not only for curing infections but also hindering resistance

* Corresponding author: Enrico Baraldi, Department of Business Studies, Uppsala University, Box 513, Uppsala, SE 751 20, Sweden..
E-mail address: enrico.baraldi@fek.uu.se (E. Baraldi).

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development caused by use of suboptimal antibiotics [6,7]. In particular, narrow-spectrum antibiotics targeting selected pathogens should be preferred, but when they are unavailable, broad-spectrum alternatives are often prescribed [8].

The causes of lack of access to antibiotics are multifaceted [9–12] and specific to particular kinds of antibiotics. For instance, narrow-spectrum and paediatric formulation antibiotics have smaller markets less economically attractive for market authorization holders (MAHs) to supply [13]. Causes and consequences of lack of access also differ by the duration of the lack of availability. For example, shortages may vary in length, but the unavailability is expected to be eventually resolved; as opposed to market withdrawals or substances not registered in a market, making an antibiotic permanently unavailable. Shortages [9,13,14] are typically caused by more or less protracted supply chain problems [15–17], whereas deregistered medicines [3,18–20] are the result of insufficient revenues [21–23]. Therefore, it is important to distinguish between these situations and this article aims to clarify potential confusion when discussing lack of access.

In particular, we examine the various types of antibiotic unavailability, their causes and consequences, and potential solutions. We view access in terms of national availability, defined as medicines found generally in stock at hospitals or pharmacies [24]. We accordingly do not focus explicitly on the other access features of affordability and presence 'within 1 hour's walk of the population' [25], and use interchangeably the two terms 'access' (patient centric) and 'availability' (healthcare facility centric) in this paper. We consider four types of unavailability: short-term shortages, long-term shortages, deregistration, and lack of registration; and explore examples in three countries characterized by different market size and ability to pay: Norway (a high-income country [HIC]), Romania (until 2021 an upper-middle-income country), and Ethiopia (currently a low-income country).

A short-term shortage is the inability of an MAH to adequately supply a medicine for a period of 3 months or less. We selected this timeframe because two-thirds of shortages are resolved within 3 months [12]. A long-term shortage is one lasting longer than 3 months. A deregistration occurs when a marketed medicine is withdrawn from a jurisdiction. Finally, lack of registration means that no MAH has pursued marketing the antibiotic in a jurisdiction. The next section delves into the causes and consequences of each of these four types of unavailability, followed by an analysis of their differences and similarities. We conclude by discussing policies to address the various types of unavailability.

Four types of lack of access: causes, consequences, and examples

Short-term shortages

Short-term shortages, those less than 3 months, are generally caused by: supply problems including production accidents or quality issues [12,26], raw material scarcity and disruptions due to natural disasters and geopolitical conflicts [12,15], aggravated by vulnerable supply chains with one single MAH or upstream nodes [27,28]; limited demand forecast ability of suppliers [29,30] and of local healthcare facilities, especially in low- and middle-income countries (LMICs) [9,16,17]; insufficient communication and transparency in supply chains [11,31,32]; unexpected demand surges and uncertain sales due to lack of volume commitments [12]; 'race-to-bottom' procurement requiring cost cuts and preventing supply upgrades [11,26] and expensive inventories [12,26].

These shortages can have both clinical and economic consequences. Clinical effects include adverse events, delayed care, and the use of less effective treatments [8,33–35], as well as negative health outcomes, such as deteriorations in clinical status visible in some cohort studies [36]. Economic consequences include increased healthcare professionals' workload and drug costs [8,34,37–39].

For example, in Norway, narrow-spectrum phenoxymethylpenicillin paediatric syrup, supplied by two MAHs, has recurrent short-term shortages causing physicians to switch to broader-spectrum alternatives, most recently during winter 2022–2023 [40]. In Romania, nitrofurantoin is the first-line treatment for cystitis, with a three-fold increased use in the 2011–2019 period [41]. However, several short-term shortages in 2020–2022 reduced its consumption below 2011 levels, while increasing the use of oral cephalosporins and quinolones, with the negative effect of resistance pressures and more frequent *Clostridioides difficile* infections [42]. Romania's low national prices contribute to shortages because local distributors re-export antibiotics to European countries with higher prices. In Ethiopia, amoxicillin dispersible tablets, prioritized and included in the national EML, were out of stock for an average of 34 days in health centres and 28 days in hospitals in 2018 [43]. Such shortages are often caused by supply-demand mismatches linked to miscommunication between pharmacies and clinicians [44], as well as over-the-counter sales of antibiotics at partial doses without prescriptions [45], driven by economic interests and inadequate knowledge [46]. Other governance-related causes of shortages are procurement challenges after changes in Ethiopian EMLs or purchases by the central public supply agency and regional governments without a thorough review of supply chains.

Long-term shortages

Long-term shortages are driven by the same causes as short-term shortages when they persist over time and by further 'hidden' upstream issues in supply chains, such as dependence on single active pharmaceutical ingredient (API) sources, especially if concentrated in offshored countries [16,30,32,47], and old products with difficult-to-transfer production files [31]. Additional causes are extreme price competition leaving a single MAH on the market [11,17], disadvantageous ordering requests imposed on LMICs for very low-priced products [17], and their weak procurement systems [9,17]; hoarding by competing users [26] and cascading effects of shortages from a country to another [31].

Long-term shortages have initially the same consequences as short-term shortages [8,33–35], but negative effects may level off over time as physicians and pharmacists learn how to handle actual stockouts, e.g. by using alternative drugs [36]. However, longer shortages of antibiotics have far-reaching consequences beyond the individual patient, namely triggering resistance from increased use of suboptimal broad-spectrum antibiotics [8,9,33]. Costs for additional visits to physicians typically increase [34], but long-term shortages may not entail increased drug costs if healthcare providers can find alternatives with similar costs [30].

For example, in Norway, there was a long-term shortage of erythromycin (both tablets and syrup) in 2023–2024, despite having two European MAHs. When lacking erythromycin, physicians are advised to prescribe broader-spectrum alternatives like azithromycin for *Mycoplasma pneumoniae* [48]. In Romania, cefazolin, a first-generation cephalosporin is probably the most important antibiotic for perioperative prophylaxis. Because of two major shortages in 2013–2015 and 2017–2019, its consumption went down almost to nothing during the 2013–2019 period, whereas the use of suboptimal antibiotics, especially cefuroxime and ceftriaxone, increased respectively by 89% and 34% between 2012 and 2019 [41]. The medical consequences were estimated in increased resistance to second- and third-generation cephalosporins [42]. After these long-term shortages, cefazolin's consumption rapidly increased well beyond its original pre-shortage levels, whereas the consumption of cefuroxime and ceftriaxone decreased

in 2019–2023 by 33% and 9%, respectively [41], that is, less than their increase in 2012–2019. Ethiopia has faced historical shortages of several antibiotics, both for hospital and community use. Cefazolin was unavailable for several years in Ethiopian hospitals [44], despite inclusion in the national Standard Treatment Guidelines (STGs) and EML [49,50]. This historic shortage is aggravated by a misalignment between STGs and EML, so that, even when available on the market, cefazolin does not match the required usage at Ethiopian healthcare facilities [51]. Among community drugs, all formulations of phenoxymethylpenicillin are routinely unavailable over longer periods. Ethiopia was also among the 95 countries afflicted in 2014–2017 by long-term shortages of benzathine penicillin, a crucial antibiotic for preventing and treating syphilis and rheumatic heart disease [52].

Deregistrations

The withdrawal of an antibiotic usually is a consequence of 'race-to-bottom' purchasing practices that reduce profitability [11,17,47], 'winner-takes-it-all' tendering [12], small market sizes (below Euro 90 000 yearly sales according to a Swedish study [13]), old products with difficult to upgrade or change manufacturing sites [31], and prioritization of new antibiotics with higher margins [9]. In terms of impact, deregistration corresponds to a shortage becoming permanent. Hence, many consequences match those of longer-term shortages [8,33–35,37,38], with a potential additional consequence of modifying treatment guidelines to adapt to the permanent absence of a substance.

In Norway, the only paediatric phenoxymethylpenicillin tablet (165 mg) was withdrawn in 2021. As phenoxymethylpenicillin has a bitter taste, it is beneficial to have low-dose paediatric tablets that can either be swallowed whole or crushed into food to disguise the taste. However, this deregistration, combined with shortages of the paediatric syrup (see above), resulted in physicians prescribing broader-spectrum alternatives. In Romania, the other first-line treatment for cystitis fosfomycin-trometamol was deregistered by its main foreign supplier, who had more than 99% of sales in 2022, a share that could not be covered by a local supplier. The negative consequence was a rebound in use of oral cephalosporins and of quinolones [42]. In Ethiopia, erythromycin has been traditionally used for several conditions (community-acquired pneumonia, Legionnaires' disease, prevention of neonatal conjunctivitis, and chlamydia). However, the recent exclusion of erythromycin from the current EML [50] essentially limited its availability in the Ethiopian market, increasing suboptimal use of macrolides (azithromycin and clarithromycin) that are also more expensive.

Lack of registration

Antibiotics may not be registered in countries due to regulatory complexity extending times and increasing costs despite low expected sales [19], MAHs avoiding unprofitable markets [3,47,53], unclear local needs/demand, especially for drugs lacking recommendations in guidelines [3], confusion in priorities [9,54], and weak purchasing procedures in LMICs [9]. The consequence of lack of registration is that an antibiotic is unavailable across the entire country, irrespective of affordability or capillary access. The problem afflicts especially, but not exclusively, LMICs with nefarious consequences like increased mortality and potentially millions of avoidable deaths [55] and increased resistance due to repeated use of few available and less active antibiotics [56].

In Norway, flucloxacillin is deregistered, despite physicians' request for access particularly for children's skin and wound infections. Romania, until 2024, lacked access to an important new

Table 1
Causes, consequences, and solutions for four types of lack of access

Type of lack of access	Causes	Consequences	Policy solutions
Short-term shortage (<3 mo)	Disruptions in vulnerable supply chains with single MAH/upstream nodes Limited demand forecast ability Insufficient communication and transparency Great demand and sales uncertainty 'Race-to-bottom' prices preventing production upgrades and inventories	Clinical: Adverse events Delayed care Use of less effective treatments Negative health outcomes Economic: Increased workload to healthcare professionals Increased drug expenditures	Improved communication, forecasting and supply chain transparency [9,12,28,53,58,59] Stockpiling, increased inventories [12,28,47,58,60] Good purchasing practices: Rewarding delivery precision, long-term contracts and esp. parallel sourcing [12,13,28,47,53,58]
Long-term shortage (>3 mo)	Same as above, but prolonged Upstream issues in supply chains: dependence on single API sources in offshored countries Difficult factory changes Extreme price competition leaving a single MAH Disadvantageous ordering requests and weak procurement systems in LMICs Hoarding and cascading effects across countries	Same as above initially but levelling off over time (esp. drug costs if cheaper alternatives available) Increased antimicrobial resistance from use of suboptimal antibiotics esp. broader-spectrum Higher patient and healthcare costs for additional physician appointments	Improved communication, forecasting, and supply chain transparency Good purchasing practices: Rewarding delivery precision, long-term contracts, and especially parallel sourcing Mutual recognition of marketing authorizations and common packages/leaflets [12,13,28,58] to facilitate transfer between countries Pooled procurement to enlarge market size [9,18,47,53,60] Production capacity expansion and geographic diversification [9,18,32,53,58]
Deregistration (withdrawal from a market)	Low profitability Single-winner tenders Small market sizes Old products difficult-to-transfer to better factories New antibiotics with higher margins prioritized	Same as a permanent shortage, esp. use of suboptimal antibiotics driving resistance Potential changes in treatment guidelines	New reimbursement, revenue guarantees [9,19,47,53,60] Mutual recognition of marketing authorizations to reduce regulatory costs Pooled procurement to enlarge market size Clear and coordinated priority setting [9,47,53]
Lack of registration (product never registered in country)	Regulatory complexity combined with low expected sales Avoidance of unprofitable markets Unclear local needs/demand and guidelines Confusions in priorities and weak purchasing procedures	Full unavailability in a whole country Strongly increased mortality, esp. in LMICs Increased resistance due to repeated use of handful antibiotics	New reimbursement, revenue guarantees Intercountry coordinated price increases [28,47] Pooled procurement to enlarge market size Clear and coordinated priority setting Mutual recognition of marketing authorizations to reduce regulatory costs [9]

API, active pharmaceutical ingredient; LMIC, low- and middle-income country; MAH, market authorization holder.

'reserve' antibiotic, cefiderocol, one of the very few antibiotics active against metallo-β-lactamase (MBL)-producing isolates. Local high and raising levels of resistance to carbapenems of *Klebsiella pneumoniae* in the past 10 years [57] made treatment very difficult from 2020. Yet, despite approval by the European Medicines Agency since 2020, cefiderocol became available in Romania only in 2024, a delay bringing two major consequences: loss of activity of colistin against MBL-producing *K. pneumoniae* due to its frequent use in these infections in the absence of other options [42]; cefiderocol reaching Romania with its activity against MBL-producing *K. pneumoniae* partially lost, probably due to cross-resistance induced using other cephalosporins (unpublished data from Bucharest hospitals indicate 30–40% resistance to cefiderocol). In Ethiopia, several antibiotics are not registered by any MAH, including 'access' antibiotic nitrofurantoin, the last-resort colistin and newer 'reserve' antibiotics like meropenem+vaborbactam, despite all being listed in Ethiopian EML and STGs [49,50].

Comparing causes and consequences of lack of access

Table 1 [9,12,13,18,19,28,32,47,53,58–60] summarizes the causes and consequences of the four types of unavailability, and introduces the various solutions proposed in policy and academic reports matching each type and its respective causes. Several causes are common for all types, e.g. low profitability, unattractive markets, dependence on few suppliers, insufficient communication, and unclear needs/priorities, whereas other causes are specific to a particular lack of access, e.g. vulnerable-to-disruptions supply chains and lack of inventories cause short-term shortages as opposed to upstream problems like geographic concentration and difficulties in changing factories or cascading effects among countries, which cause long-term shortages, or regulatory complexity that hinders registration. There are also some country-specific causes, e.g. over-the-counter partial-dose sales, miscommunication clinician/pharmacies, changed EMLs without supply reviews, and misalignment between EMLs and STGs (Ethiopia); much lower prices than other European countries incentivizing parallel export (Romania)s; or a small market size (Norway), despite strong ability to pay.

The clinical and economic consequences vary between the four types of unavailability, but do not simply become longer when moving from short-term shortages to the other three types: resistance also increases due to protracted use of suboptimal, especially broad-spectrum antibiotics. Interestingly, drug costs may not increase over long-term shortages and withdrawals because healthcare systems may adapt by finding inexpensive alternatives or even change treatment guidelines. Country-specific consequences are also visible: use of suboptimal paediatric formulations in Norway or reduced activity when new products such as cefiderocol eventually are registered in Romania.

No single solution is capable to solve all four types of lack of access, but some may benefit multiple types, such as pooled procurement or mutual recognition of marketing authorizations. Some solutions fit well only one type of unavailability but not others, e.g. stockpiling—a solution considered by the European Commission [27,58]—can address short-term shortages but unlikely long-term shortages and certainly not withdrawals or lack of registration.

Conclusions

Because no single solution can solve all types of unavailability, there is a need for dedicated policies targeting each type. However, some policies support others and work across the types. In particular, transparency is key for both short- and long-term shortages [9,12,28,53,58,59] and a precondition for other solutions to work: for instance, building supply resilience via multiple MAHs is ineffectual if they are all dependent upon the same API producer [12,13,28,47,53,57]. Supply chain transparency is essential to identify products with sole suppliers or geographic concentrations at API level and then design tailored interventions to strengthen access.

Pooled procurement between countries [9,18,47,53,60] is a solution that can address several types of unavailability (long-term shortages, withdrawals, and missing registrations) by expanding the size of markets and making them more attractive to suppliers. This is the core idea behind initiatives like GARDP's SECURE [18,60] and the UN's Global Drug Facility [9,52] to improve access in LMICs, building on the successes of pooled procurement initiatives like the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and the Gavi Alliance. However, this demand-side intervention alone may also have negative consequences, such as favouring largest suppliers and putting smaller ones out of business, thereby increasing industry concentration [53]; and needs accordingly to be combined with supply-side interventions to create a resilient global system able to supply both HICs and LMICs, without dependence on single countries, but rather with a geographically heterogeneous supply [9,18,32,53,57].

The advantages of global pooled procurement initiatives also need to be balanced with local variations in needs (epidemiology, resistance, etc.), suggesting again that multiple policies are needed against lack of access, depending also on the specific type of antibiotic. Countries require reliable access to the full arsenal of antibiotics, but some of them will be used very rarely, making production and distribution for a single country extremely challenging and unprofitable. For the smallest markets, like paediatric tuberculosis antibiotics, a global pooled procurement and distribution solution like the Global Drug Facility may be necessary. In HICs, where antibiotic markets are shrinking because of stewardship practices and declining birth rates, maintaining access to paediatric formulations is challenging, especially for narrow-spectrum antibiotics: relevant solutions here can be the revenue guarantees already tested in the UK and Sweden [10,47], which pay for guaranteed access rather than unit sales.

This paper provides an initial conceptual framing of various types of lack of access, but further research should delve more systematically into their specific consequences, including actual calculations of their costs for patients and society and comparing these with the investments in various policy interventions. Future studies may also perform more fine-grained analyses of unavailability based on WHO's AWaRe (Access, Watch, Reserve) categorization, specific countries, and patient groups.

Author contributions

E.B. drafted the paper, its conceptual framing and final discussion, supported by C.Å. E.A. contributed elements on costs and consequences of shortages. C.Å., G.-A.P., and T.M. provided details about shortages respectively in Norway, Romania, and Ethiopia. All coauthors provided edits and comments to the manuscript during its development and subsequent revisions based on peer-reviewers comments.

Transparency declaration

Potential conflict of interest

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