Commentary

Ensuring universal access to old antibiotics: a critical but neglected priority

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Despite most guidelines recommending old antibiotics that are still effective, mostly available as generics, these antibiotics are not universally marketed or available. This lack of availability may have a serious impact on antibiotic prescribing. Physicians may be forced to use less optimal, often broad-spectrum antibiotics instead. Such alternatives may also be less effective, may have more adverse effects, and may drive the selection of resistance. For example, in the treatment of sore throat, amoxicillin is used instead of penicillin. Fluoroquinolones are used instead of nitrofurantoin, fosfomycin or pivmecillinam for the treatment of cystitis, and co-amoxiclav or i.v. fosfomycin are valuable alternatives for the treatment of some resistant bacteria. The limited access to these old antibiotics is a threat to antibiotic stewardship.

In 2011, the ESCMID Study Group for Antimicrobial stewardship (ESGAP) showed that 22 out of 33 old but potentially useful antibiotics were marketed in fewer than 20 of the 38 included countries in Europe, USA, Canada, and Australia; economic motives were the major reason for not marketing these antibiotics [1]. ESGAP and the international network ReAct (Action on Antibiotic Resistance) updated this survey in 2015 [2]. The situation was worse than in 2011, with even fewer antibiotics available in the included countries. Again the economic situation was the main reason reported for not marketing these antibiotics, including high registration costs and small market size (limited volume sales and low prices), leading to a perceived lack of return on investment for pharmaceutical companies. Other reasons were lack of demand (low use by clinicians and absence of recommendation of these drugs in national/international guidelines), and lack of awareness or low prioritization of the problem by health authorities. There are no published data on this topic in low- and middle-income countries (LMICs), but anecdotal reports suggest that the situation could even be worse.

Besides this absence of marketing, there are also repeated and prolonged shortages of supply for these antibiotics worldwide in different settings. Quadri et al. showed that 148 antibiotics were in short supply between 2001 and 2013 in the USA, with 22% of drugs experiencing multiple shortage periods [3]. They also showed a concerning rise in reported shortages since 2007, with an increase
of 0.35 additional antibiotics experiencing shortage every month. Antibiotics used against multidrug-resistant bacteria (such as carbapenems and colistin) were affected by these shortages and extended periods of no supply. A 2011 US physician survey also showed that more than half of the respondents reporting a shortage declared that patient outcomes were negatively affected as the alternative drugs were less effective, more toxic, or more costly [4]. In many LMICs, lack of antibiotic supply in hospitals may be due to budget constraints and/or bureaucracy, impeding purchasing from the central or hospital administration, despite the availability of drugs in the market. Less is known about antibiotic shortages in Europe [5]. In the above-mentioned 2015 survey [2], several participants spontaneously reported severe problems in availability of some antibiotics due to shortages (for example, for i.v. flucloloxacin, i.v. fosfomycin, ticarcillin–clavulanic acid), even though the documentation of shortages was not an objective of the study. A European survey conducted among more than 600 hospital pharmacists from 36 countries reported that antimicrobials were the most affected therapeutics [6]. Causes for these shortages are multiple and complex, including failures in manufacturing processes, scarcity of raw materials, concentration of manufacturing in emerging economies, pressure on profit margins, and sometimes dependence on a single producer [7]. No studies have been conducted to assess the exact consequences of antibiotic shortages on patients’ outcomes, but national agencies reported that some patients experienced negative outcomes because of a less effective or more toxic alternative. Beyond the impact on patients, shortages may undermine people’s confidence in the public health system and in national and supranational organizations’ abilities to provide adequate healthcare and supply systems. Despite this being a clear global concern and a worldwide threat to national action plans to combat antimicrobial resistance, no co-ordinated response has yet been taken. A first step would be to set up standardized monitoring systems to estimate the scale of the problem; this could be incorporated into the World Health Organization (WHO) planned surveillance programmes of antimicrobial use, and also linked to ongoing work at WHO on shortages [8]. A next step would be to facilitate the dialogue between providers, national agencies and international organizations to find sustainable ways to address both availability and pricing. Existing procurement mechanisms such as the EU Joint procurement agreement to facilitate medical countermeasures and the Global Drug Facility could be used as a template [9,10]. A European four-year project led by Co-operation in Science and Technology (COST, http://www.cost.eu/COST_Actions/ca/CA15105) will focus on promotion, manufacturing, procurement disruption, clinical management of shortages, and the impact on patient outcomes to propose a European solution. Whereas the project covers all medicines, antimicrobials have been identified as a key priority.

Finally, many paediatric formulations of old antibiotics have very limited availability. Ensuring access to paediatric-friendly formulations of antibiotics creates particular challenges. For antibiotics that have good oral bioavailability, suspensions are known to offer superiority in terms of absorption compared with crushing adult tablets or mixing the contents of capsules with food [11]. But suspensions have many problems and increasingly dispersible tablets are being used, although these are not always marketed where tablets or capsules are readily available (cloxacillin, oxacillin), requiring hospital pharmacies to produce their own on site. Dispersible tablets offer advantages over liquid preparations with regard to shelf life, transport and storage costs, especially in LMICs where refrigeration may not be readily available and minimization of cost is paramount to affordable access. The recent development of mini-tablets (2–4 mm in diameter) which have demonstrated good acceptance in trials of children aged from 6 months to 6 years shows promise [12]. For antibiotics administered parenterally, vial sizes of powders for suspension may not be appropriately sized for administration of neonatal doses, especially extremely pre-term infants who require repeated and prolonged courses of antibiotics. For example, fosfomycin powder for oral suspension is produced in doses inappropriate for paediatric patients (3 g sachets, EU) and tobramycin for i.v. administration is produced in 80 mg vials where the recommended neonatal dose is 4–5 mg/kg. Child-friendly formulations for some old antibiotics have been withdrawn from the market (e.g. pristinamycin syrup in France). Moreover, paediatric pharmacokinetic data for old antibiotics are generally limited, creating further challenges with appropriate dosing in paediatric patients. Economic incentives tied to pre-defined Target Product Profiles are needed together with academic collaborations such as the European Paediatric Formulation Initiative and non-profit product development partnerships such as GARDP (Global Antibiotic Research & Development Partnership) to encourage production of paediatric antimicrobial formulations.

In conclusion, one might question the value of the considerable global investments currently underway in research and development for new antibiotics without simultaneously making powerful efforts to make better use of our existing ones. International agencies and organizations such as WHO and the European Commission could consider taking the lead in developing a strategy for ensuring the sustainable production, registration, and availability of old antibiotics that may help address growing problems of drug resistance as well as addressing the serious shortage or complete lack of other antibiotics (see recommended actions, Box 1). This may require designing proposals that would facilitate their registration across countries, a greater presence of national governments in decisions and production, transferring technology to other manufacturers, or providing appropriate and targeted economic incentives to encourage their development and commercial availability. Significantly improved global access to key older antibiotics, in particular the old antibiotics that have been in clinical use for several decades, will remain a major challenge.

**Box 1**

**Suggested next steps for action**

1. Define (through the WHO Essential Medicines List and/or an ad-hoc WHO working group) the set of ‘key access’ antibiotics for which there should be universal access.
2. Access here could be defined as: ‘An adult or child are able to receive when clinically required the appropriate antibiotic for their clinical infection syndrome at an appropriate dose, duration, formulation, quality and price.’
3. Monitor the current global availability of these key access antibiotics. This includes both use—through the WHO Surveillance on Antimicrobial Use programme—and supply through a survey of global generic antibiotic producers of these key access antibiotics, including the formulations and cost. Monitor shortages through a common centralized mechanism.
4. Conduct an antibiotic access gap analysis between clinical need and appropriate medicine availability. This needs to include an assessment of this variation by region and age.
5. Re-evaluate the pharmacokinetic/pharmacodynamic targets for these out-of-patent antibiotics in the context of the global variation in rates of resistance.
6. Consider the potential roles and feasibility of a Global Antibiotic Access and Conservation Fund, initially with the objective of implementing the five actions mentioned above.
antibiotics in their optimal formulation, quality and cost could result from a co-ordinated set of actions that several countries and WHO might be willing to support or engage in.

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**References**


