

## ENSURING ACCESS TO OLD ANTIBIOTICS

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### ***On behalf of the following non-profit non-governmental organizations:***

1. ESCMID Study Group for Antibiotic Policies (**ESGAP**); <https://www.escmid.org/index.php?id=140>
2. World Alliance Against Antibiotic Resistance (**WAAAR**); <http://www.ac2bmr.fr/index.php/en/>
3. **ReAct** – Action on Antibiotic Resistance; <https://www.reactgroup.org>
4. **ISC** [International Society of Chemotherapy] **Antimicrobial Stewardship Working Group**; <http://www.ischemo.org/working-groups/isc-wg-antimicrobial-stewardship>
5. British Society for Antimicrobial Chemotherapy (**BSAC**); <http://www.bsac.org.uk>
6. Société de Pathologie Infectieuse de Langue Française (**SPILF**, French Infectious Diseases society); <http://www.infectiologie.com>

**1. The EML (Essential Medicines List) contains only old antibiotics, available as generics.**

**2. These EML antibiotics are not marketed in all countries.**

This issue was raised in the O'Neill report (page 50).<sup>1</sup> The absence of some antibiotics from the market may have a serious impact on antibiotic prescribing. The physicians are forced to use less optimal, mostly broad-spectrum antibiotics instead; alternatives are often less effective and can have more side effects. For example, in the treatment of sore throat, amoxicillin is used instead of penicillin. Fluoroquinolones, which belong to the critically important antibiotics, are used instead of nitrofurantoin, fosfomycin or pivmecillinam for the treatment of uncomplicated cystitis, and co-amoxiclav or cephalosporins for the treatment of skin and soft tissue infections in children instead of appropriate oral formulations of antistaphylococcal penicillins. Some older antibiotics such as tetracyclines and temocillin may be used as alternatives for the treatment of resistant bacteria. The limited choice of antibiotics prevents prudent use of antibiotics, which is one of the key strategies to fight antimicrobial resistance.

In the light of the recognition of antimicrobial resistance as a major public health problem, and the efforts to improve antimicrobial prescribing worldwide (antimicrobial stewardship), the availability of antibiotics including old and new molecules is increasingly important.

In 2011, the ESCMID Study Group for Antibiotic Policies (ESGAP) performed a study which showed that 22 out of 33 old but potentially useful antibiotics were marketed in fewer than 20 of the included 38 countries in Europe, US, Canada and Australia; economic motives were the major cause for absence of marketing of these antibiotics.<sup>2</sup>

ESGAP and the international network Action on Antibiotic Resistance (ReAct) updated in 2015 this 2011 survey regarding market availability of these selected

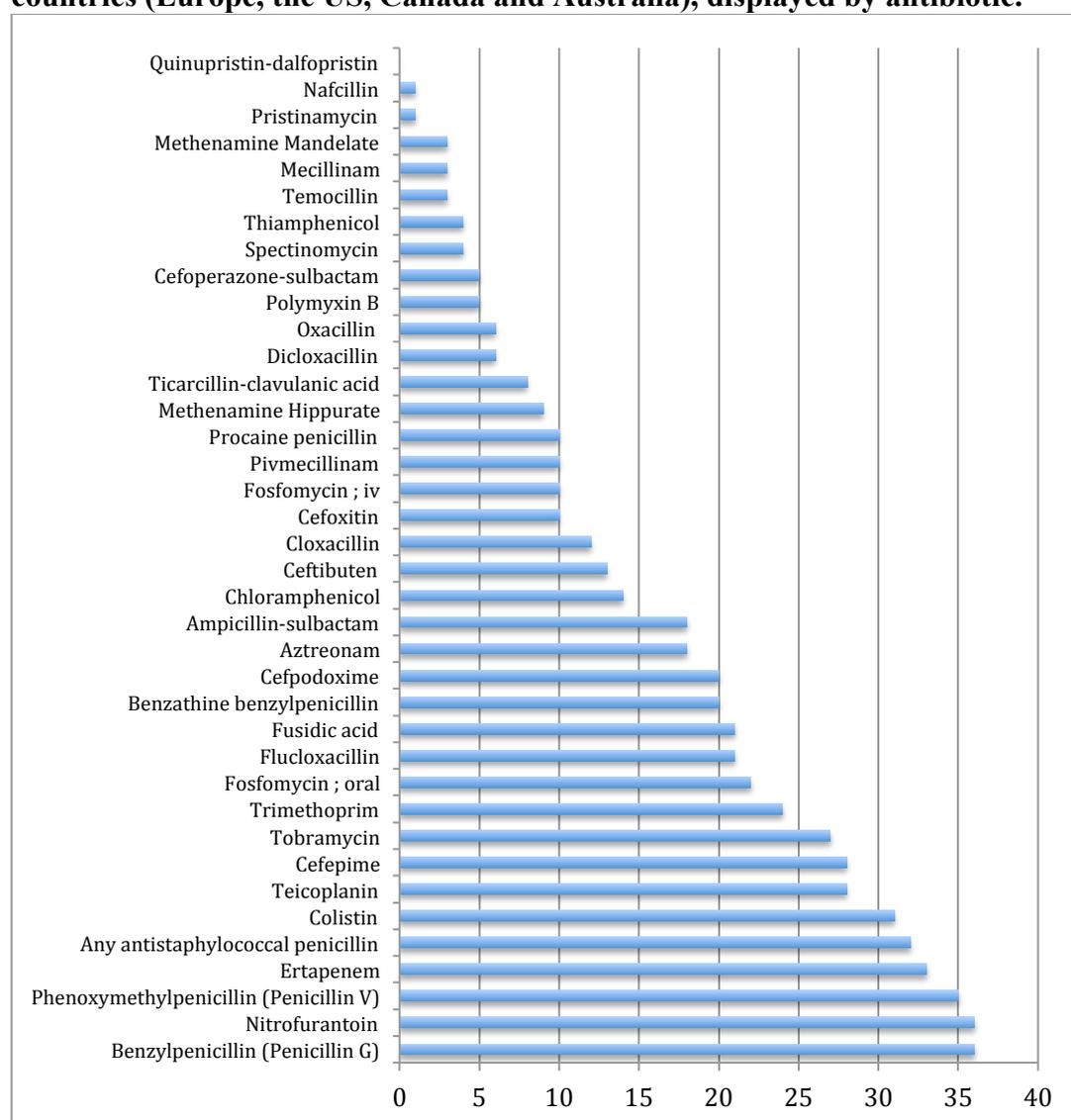
<sup>1</sup> Review on Antimicrobial Resistance - Tackling Drug-Resistant Infections Globally: final report and recommendations – 2016 (<https://amr-review.org/Publications>)

<sup>2</sup> Pulcini C, Bush K, Craig WA, Fridodt-Moller N, Grayson ML, et al. (2012) Forgotten antibiotics: an inventory in Europe, the United States, Canada, and Australia. Clin Infect Dis 54: 268-274.

antibiotics in Europe, the US, Canada and Australia (Figure below).<sup>3</sup> The situation was worse than in 2011, with even fewer antibiotics available in the included countries. Economic motives were also the major cause reported for absence of marketing of these antibiotics: barriers to new availability of antibiotics that had not previously been registered in a country included high registration costs, combined with small market size and volume sales, low prices, leading to a perceived lack of return on investment for pharmaceutical companies. Some contacts also mentioned lack of demand and low use by clinicians as well as absence of recommendation of these drugs in national/international guidelines. Finally, lack of awareness or low priority of the problem by health authorities were also stated.

There are no published data on this topic in low-middle income countries, but informal contacts with colleagues suggest that the situation is similar.

**Figure - Availability (via usual marketing processes) of 36 selected antibiotics in 39 countries (Europe, the US, Canada and Australia), displayed by antibiotic.**



<sup>3</sup> Pulcini C, Mohrs S, Beovic B, Gyssens IC, Theuretzbacher U, Cars O (2017) Forgotten antibiotics: a follow-up inventory study in Europe, US, Canada and Australia. *Int J Antimicrob Agents* 49(1):98-101.

### **3. There are repeated and prolonged shortages of these EML antibiotics worldwide in all settings.**

U.S. physicians have been reporting shortages of antibiotics as an increasing problem over the past 20 years. Quadri *et al.* showed that 148 antibacterial drugs were on shortage between 2001 and 2013 in the USA, with 22% of drugs experiencing multiple shortage periods.<sup>4</sup> In addition, they also showed a worrisome rise on antimicrobial shortages since 2007, with an increase of 0.35 (95%CI 0.22-0.49) additional drug experiencing shortage every month. Antimicrobial used against multidrug-resistant pathogens (such as carbapenems and colistin) were concerned by these shortages. A survey conducted in 2011 among US physicians also showed that more than half of the respondents reporting a shortage declared that it negatively affected patient outcomes because the alternative drugs were less effective, more toxic or more costly.<sup>5</sup>

Less is known about antimicrobial shortages in Europe. ESGAP presented the result of a survey at the 2007 ECCMID where 71% of the respondents reported having experienced at least one shortage of antimicrobials within the last 12 months. These shortages concerned notably cefepime, meropenem, mupirocin and piperacillin/tazobactam, which are used against multidrug resistant bacteria. Besides, only 19% of the hospitals reported having been informed adequately about the upcoming shortage. In the 2015 'ESGAP/React Forgotten antibiotics survey' mentioned before,<sup>3</sup> several respondents spontaneously reported severe problems in availability due to shortages for some antibiotics (for example for iv flucloxacillin, iv fosfomycin, ticarcillin-clavulanic acid), even though shortages were 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 area.<sup>6</sup>

An international survey performed in 2011 in 56 different countries also showed that 11/56 countries (20%) did not have colistin on their market, and that another 20% (58/284) of respondents experienced shortages for this antibiotic.<sup>7</sup>

Causes for these shortages are multiple and complex, including notably flawed manufacturing processes, scarcity of raw materials, concentration of manufacturing in emerging countries, and pressure on profit margins.

No studies have been conducted to assess precisely the consequence of antimicrobial shortages on patients' outcomes, but national agencies reported that some patients experienced negative outcomes because of a less effective or more toxic alternative.

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<sup>4</sup> Quadri F, Mazer-Amirshahi M, Fox ER, Hawley KL, Pines JM, Zocchi MS, May L (2015) Antibacterial drug shortages from 2001 to 2013: implications for clinical practice. *Clin Infect Dis* 60(12):1737-42.

<sup>5</sup> Gundlapalli AV, Beekmann SE, Graham DR, Polgreen PM; Infectious Diseases Society of America's Emerging Infections Network (2013) Perspectives and concerns regarding antimicrobial agent shortages among infectious disease specialists. *Diagn Microbiol Infect Dis* 75(3):256-9.

<sup>6</sup> [www.eahp.eu/sites/default/files/shortages\\_report05online.pdf](http://www.eahp.eu/sites/default/files/shortages_report05online.pdf)

<sup>7</sup> Wertheim H, Van Nguyen K, Levy Hara GL, Gelband H, Laxminarayan R, Mouton J, Cars O (2013) Global survey of polymyxin use: A call for international guidelines. *J Glob Antimicrob Resist* 1:131-134.

Beyond the impact on patients in need of out-of-stock drugs, such shortages will undermine people's confidence in the public health system and in national and supranational organizations abilities to provide decent health care system.

While all countries are concerned by these shortages, there is no coordinated response taken hitherto currently. A first step into action could be to improve the communication between providers and national agencies in order to recognize an upcoming shortage. Some also suggested to license military pharmaceutical companies to manufacture out-of-stock drugs.<sup>8</sup> There is also a European project led by Co-operation in Science and Technology (COST, [www.cost.eu/COST\\_Actions/ca/CA15105](http://www.cost.eu/COST_Actions/ca/CA15105)) from April 2016 for 4 years on medicines shortages. It will focus on promotion, manufacturing, procurement disruption, clinical management of shortages and the impact on patient outcomes. Whilst it covers all medicines, antimicrobials have been identified as a key problem. It aims to produce a European solution.

#### **4. Paediatric formulations of EML antibiotics have limited availability.**

Ensuring access to paediatric-friendly formulations of antimicrobials creates particular challenges. For antibiotics that have good oral bioavailability, suspensions are known to offer superiority in terms of absorption compared with crushing tablets or mixing the contents of capsules with food.<sup>9</sup> Suspensions or dispersible tablets 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 regards to shelf life, transport and storage costs, particularly in low/middle income countries where refrigeration may not be readily available and minimisation of cost is paramount to affordable access. Furthermore, liquid formulations need to be administered in the appropriate volumes to ensure adequate treatment and consideration of the ability to tolerate fluid volume in smaller children is needed. The recent development of mini-tablets (2-4mm in diameter) which have demonstrated good acceptance in trials of children aged 6 months - 6 years shows promise.<sup>10</sup>

For antimicrobials administered parenterally, vial sizes of powders for suspension may not be appropriately sized for administration of neonatal doses, particularly extremely pre-term infants who require repeated and prolonged courses of antibiotics. Many EML antibiotics are produced in vial sizes where a prescription for a 1.5kg infant would comprise less than one-tenth of the total contents of the vial, increasing the risk of serious overdose. For example, fosfomycin powder for oral suspension is produced in doses inappropriate for paediatric patients (3g sachets, EU) and tobramycin for IV administration is produced in 80g vials where the recommended neonatal dose is 4-5mg/kg.

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<sup>8</sup> Casassus B (2015) Europe urged to take action on drug shortages. *Lancet* 385(9975):1279-80.

<sup>9</sup> Notterman DA, Nardi M, Saslow JG (1986) Effect of dose formulation on isoniazid absorption in two young children *Pediatrics* 77:850-2.

<sup>10</sup> Klingmann V, Seitz A, Meissner T, Breitkreutz J, Moeltner A, Bosse HM (2015) Acceptability of Uncoated Mini-Tablets in Neonates--A Randomized Controlled Trial. *J Pediatr* 167:893-896.

Paediatric-friendly formulations for some EML antibiotics have been withdrawn from the market (case reports describe pristinamycin syrup in circulation in France in 1981).<sup>11</sup>

**Table – EML antibiotics and examples of barriers to paediatric use (EU and US)<sup>12,13</sup>**

Withdrawn from market	No paediatric oral formulation	Vial or sachet inappropriately sized for neonatal/paediatric dosing
Pristinamycin (EU) Cloxacillin (US)	Cloxacillin (EU, US) Oxacillin (EU, US) Methenamine Hippurate (US)	Cefepime (US) Tobramycin (US) Fosfomycin PO (EU, US)

Paediatric pharmacokinetic data for EML antibiotics are generally limited, creating further challenges with appropriate dosing of these antimicrobials in paediatric patients. Economic incentives are needed together with academic collaborations such as the European Paediatric Formulation Initiative to encourage commercial production of paediatric antimicrobial formulations.

## 5. Our request

***WHO and Member States should develop a strategy for ensuring the sustainable production and registration of old antibiotics that may help address growing problems of drug resistance and of other antibiotics that face serious shortage or stockouts. This may require designing approaches to facilitate their registration across countries, transferring technology to other manufacturers, or providing appropriate economic incentives to encourage their development and commercial availability.***

<sup>11</sup> Beauvais P, Filipe G, Berniere J, et al. (1981) Oral pristinamycin therapy for bone and joint infections in children. A report of 50 cases. Arch Fr Pediatr 38 :489-93.

<sup>12</sup> Homepage for the Food and Drug Administration ([www.fda.gov](http://www.fda.gov))

<sup>13</sup> Head of Medicines Agency ([www.hma.eu](http://www.hma.eu))