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## Short Communication

Forgotten antibiotics: a follow-up inventory study in Europe, the USA, Canada and Australia <sup>☆</sup>Céline Pulcini <sup>a,\*</sup>, Simone Mohrs <sup>b</sup>, Bojana Beovic <sup>c</sup>, Inge Gyssens <sup>d,e</sup>, Ursula Theuretzbacher <sup>f</sup>, Otto Cars <sup>b</sup> on behalf of the ESCMID Study Group for Antibiotic Policies (ESGAP), ReAct Working Group on Old Antibiotics <sup>1</sup><sup>a</sup> Service des maladies infectieuses et tropicales, Université de Lorraine Faculté de médecine, Centre hospitalier régional universitaire (CHRU) de Nancy, Nancy, France<sup>b</sup> ReAct—Action on Antibiotic Resistance, Department of Medical Sciences, Uppsala University, Uppsala, Sweden<sup>c</sup> University Medical Centre Ljubljana, Ljubljana, Slovenia<sup>d</sup> Department of Medicine, Radboud University Nijmegen Medical Centre, and Department of Medical Microbiology and Infectious Diseases, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands<sup>e</sup> Hasselt University, Hasselt, Belgium<sup>f</sup> Center for Anti-Infective Agents, Vienna, Austria

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## ABSTRACT

The objective of this study was to update a 2011 survey, conducted on behalf of the ESCMID Study Group for Antibiotic Policies (ESGAP), studying the availability of old but clinically useful antibiotics in North America, Europe and Australia. This follow-up survey was performed in 2015 in 40 countries among specialists from the pharmaceutical, infectious diseases and microbiology sectors in North America, Europe and Australia in order to assess the availability through usual marketing processes of 36 systemic antibiotics (addition of 3 antibiotics compared with the 2011 survey) selected for their ability to treat infections caused by resistant bacteria and their unique value for specific criteria. The questionnaire was sent by e-mail to national contacts belonging to ESGAP and ReAct networks. In all, 39 of the 40 countries participated in this survey. The number of available antibiotics differed considerably from one drug to another as well as from one country to another (e.g. 7 antibiotics available in Estonia, 24 in France). Overall, 25/36 selected antibiotics were marketed in 20/39 countries or less. From 2011 to 2015 (data available for both periods in 37 countries for 33 antibiotics), the number of available selected antibiotics increased in 13 countries and decreased in 17. In conclusion, despite the ongoing bacterial resistance crisis, the situation regarding the availability of 'forgotten antibiotics' has worsened since 2011. Urgent measures are needed to ensure better availability of these antibiotics on a global scale as a conservation measure to ensure sustainable and responsible use of antibiotics.

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## 1. Introduction

Bacterial resistance has become an international priority, clearly identified as a global threat to humanity and modern medicine [1]. Innovation, access to existing and new antibiotics, and responsible use must all be pursued simultaneously [2,3].

In 2011, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Antibiotic Policies (ESGAP) performed a study which showed that 22 of 33 old but potentially useful antibiotics were marketed in fewer than 20 of the 38 included countries in Europe, the USA, Canada and Australia; economic motives were the major cause for absence of marketing of these antibiotics [4]. This follow-up study, conducted in collaboration with the international network Action on Antibiotic Resistance (ReAct), provides an update of the 2011 data regarding market

availability of these selected antibiotics in Europe, the USA, Canada and Australia.

## 2. Materials and methods

### 2.1. Selection of potentially useful antibiotics for assessing market availability

We started from the list used in the 2011 survey and applied the same inclusion criteria. Systemic antibiotics were selected for their potential value against current resistant bacteria and/or for their unique value for specific criteria, as detailed previously [4]. We added three antibiotics to the 2011 survey list: ticarcillin/clavulanic acid (for its value in infections due to *Stenotrophomonas maltophilia*); ampicillin/sulbactam (for its value in infections due to *Acinetobacter baumannii*); and polymyxin B.

### 2.2. Survey on the availability of the 36 selected antibiotics in Europe, the USA, Canada and Australia

A total of 40 countries were invited to participate in the survey (Appendix A) compared with 38 in the 2011 survey. A national contact was approached by e-mail in September 2015 to report on the availability of the selected antibiotics in their country; these contacts belonged to personal networks of the authors and/or were members of ESGAP and/or ReAct, and they were asked to specify the source of information they used (mostly national drug agencies).

Availability was defined as an antibiotic being easily obtainable through usual marketing processes in the country; antibiotics that had to be imported were considered not available. Collected data were entered into a Microsoft Excel® (Microsoft Corp., Redmond, WA) spreadsheet. We looked for an association between the number of available antibiotics in each country (below the median or not) and the country's population size (Student's *t*-test); we conducted this analysis with and without the USA since its population size was disproportionately larger than the other countries.

The reasons for absence of marketing of the antibiotics were also explored; finally, the national contacts were asked about any actions that had been undertaken in their country to bring these 'forgotten' antibiotics back to the market as well as about the problems encountered.

## 3. Results

### 3.1. Main results

In all, 39 of the 40 invited countries participated in this survey. The number of available antibiotics differed considerably from one drug to another (Fig. 1) and also from one country to another (e.g. 7 antibiotics available in Estonia, 24 in France) (Fig. 2; Appendix B). Of the 36 selected antibiotics, 25 were marketed in 20 or fewer countries (Fig. 1). Detailed data are available in Appendix C, and the sources of information provided by national contacts are listed in Appendix D. Some contacts drew attention to the problem of paediatric formulations of certain drugs gradually disappearing from the market.

Countries with less than 15 antibiotics available had significantly lower population sizes than countries with 15 or more antibiotics available (8 million vs. 26 million inhabitants without the USA,  $P = 0.007$ ; and 8 million vs. 43 million inhabitants including the USA,  $P = 0.037$ ).

### 3.2. Comparison with the 2011 survey results

From 2011 to 2015 (data available for both periods in 37 countries for 33 antibiotics), the number of available selected antibiotics

increased in 13 countries and decreased in 17 (Appendix C). The situation varied from one antibiotic to another, with cefpodoxime and fosfomicin increasing in availability and benzathine benzylpenicillin and quinupristin/dalfopristin disappearing from the market in several of the selected countries.

### 3.3. Reasons for absence of market availability of these antibiotics

Economic motives were 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 and 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 was also stated.

Several contacts spontaneously reported severe problems in availability due to shortages for some of these antibiotics [e.g. for intravenous (i.v.) flucloxacillin, i.v. fosfomicin, ticarcillin/clavulanic acid], even though shortages were not an objective of our survey.

### 3.4. Actions undertaken to tackle this problem and challenges encountered

Most countries have designed ways to import some of these antibiotics; however, the import schemes are often cumbersome and antibiotics might not be reimbursed in certain countries, as previously reported in detail in our 2011 survey [4].

In some countries, lobbying from academia and professional societies directed at national health authorities has been successful. As an example, temocillin is now marketed in France following a request from the French Infectious Diseases Society to the National Drug Agency. Advocating the availability of old antibiotics by governments and agencies might also encourage small pharmaceutical businesses to attempt to register products of interest; one example is oral fosfomicin, which is currently being investigated by a generic pharmaceutical company in Australia.

## 4. Discussion

Overall, the situation regarding the availability of old antibiotics has not improved in Europe, the USA, Canada and Australia, with even fewer antibiotics available now compared with 2011 [4]. The underlying reasons seem mainly economic in addition to lack of awareness and priority among health authorities. Several national contacts also reported severe and sustained shortages of old antibiotics in their countries, compromising patients' access to treatment. Furthermore, the efforts of antimicrobial stewardship are impeded by the lack of availability of narrow-spectrum antibiotics (such as penicillins and antistaphylococcal penicillins) as well as fluoroquinolone-sparing drugs for urinary tract infections (such as nitrofurantoin and oral fosfomicin).

Old antibiotics have been increasingly studied by scientists in the last few years, with rising numbers of clinical studies evaluating their efficacy for the treatment of multidrug-resistant bacterial infections, and pharmacokinetic/pharmacodynamic studies reassessing their optimal dosing [5,6]. This topic is largely discussed during international scientific meetings. Even though knowledge gaps still exist, scientific studies are planned and will close major gaps in the near future. The renewed interest of the medical community for old antibiotics contrasts with a lack of clear awareness, interest and priority from most health authorities, both nationally and internationally. Today many researchers and policymakers are studying potential new economic models for revitalising the dis-

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