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Short Communication

Forgotten antibiotics: a follow-up inventory study in Europe, the USA, Canada and Australia [☆]

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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 fosfomycin 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. fosfomycin, 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 fosfomycin, 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 fosfomycin).

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-

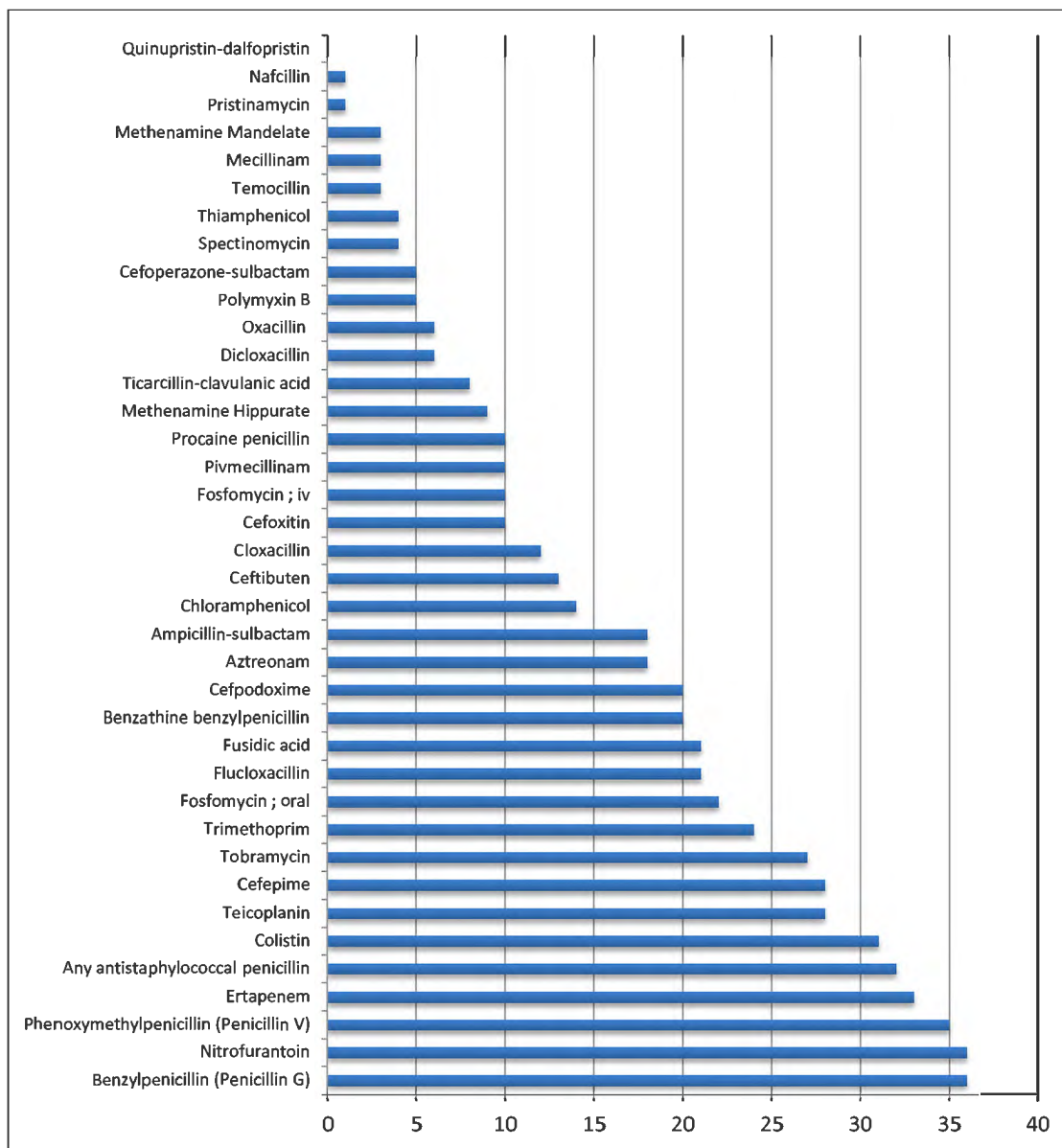


Fig. 1. Availability of 36 selected antibiotics in 39 countries (Europe, the USA, Canada and Australia), displayed by antibiotic. Only the antibiotics available via usual marketing processes are presented.

covery and development of antibiotics, yet few of these projects address how to ensure that existing antibiotics are available to clinicians worldwide. The problem of access to old antibiotics (due to marketing or shortages issues) is not clearly stated in the European Commission or the World Health Organization (WHO) action plans; much more emphasis is placed on innovation and development of new antibiotics. This topic has only been mentioned very recently in the UK Review on Antimicrobial Resistance final report [7] and in the European Council conclusions on the next steps under a One Health approach to combat antimicrobial resistance [8]. Availability and sustainability of existing resources are quite neglected compared with innovation.

How could access to existing antibiotics for all who need them worldwide be improved? Joint procurement procedures, addressing both availability and prices, are in place in many regions of the world but have not yet been used for common acquisition of old antibiotics. Although legal frameworks exist (for instance the Joint Procurement Agreement of the European Union for cross-border

medical countermeasures) [9], awareness among policymakers remains low. Old antibiotics are off-patent drugs and are regulated in Europe by national regulatory authorities. Joint procurement procedures require regulatory action in cases where old antibiotics have not been registered or the approval has been retracted. In the USA, recent extreme price hikes of old drugs show the need for political action and transatlantic agreements. Again, regulatory authorities play an important role if old antibiotics that are not approved in a specific country are involved. A joint procurement agreement would predictably increase the production volume and incentivise manufacturers; this approach could be particularly valuable for increasing availability in the many European countries that have small population sizes. A tender procedure should always consider selecting more than one manufacturer to avoid the risk of drug shortages due to manufacturing issues.

All policy and regulatory actions need to be based on increased awareness of the usefulness of certain old drugs to relieve selection pressure and to serve as last-line treatment for

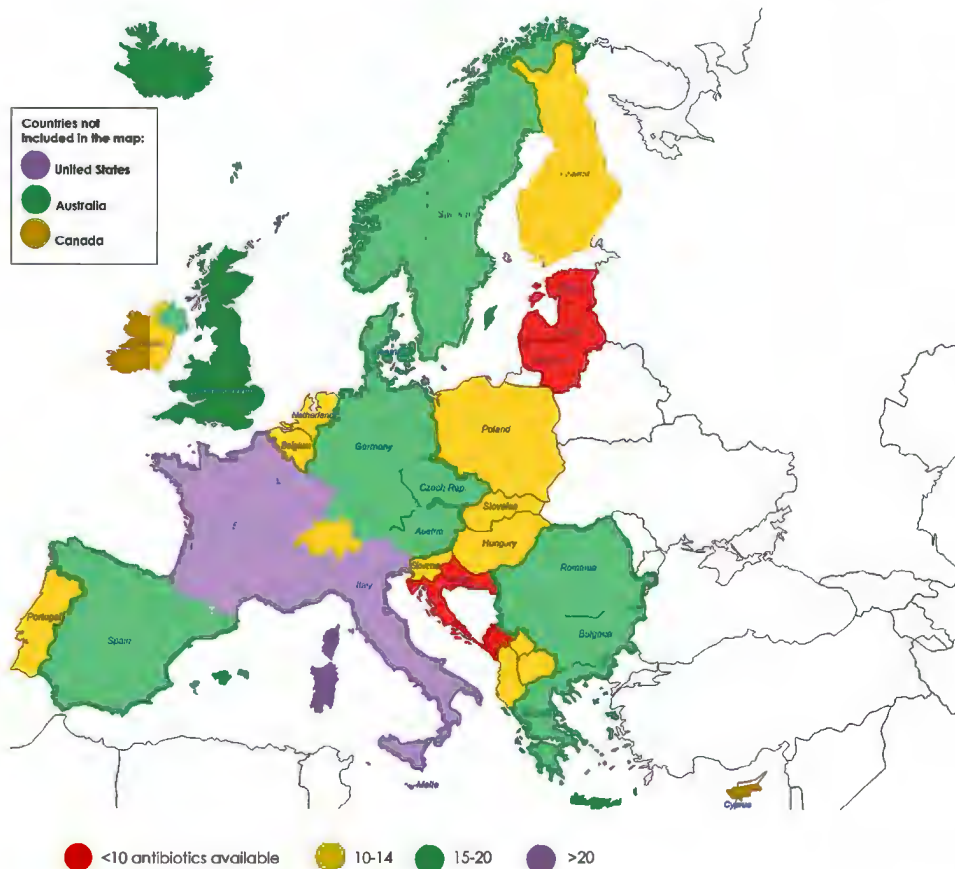


Fig. 2. Availability of 36 selected antibiotics in 39 countries (Europe, the USA, Canada and Australia), displayed by country.

multidrug-resistant pathogens. Long periods of shortages may change formularies and guidelines that result in less demand from the medical community, resulting in a vicious circle of diminishing usage of valuable old drugs. Increasing knowledge of these drugs in undergraduate and postgraduate educational programmes is also critical.

In conclusion, existing and useful antibiotics are less and less available to clinicians in Europe, the USA, Canada and Australia, and the situation has worsened since our last survey in 2011. International measures are urgently needed, and access and responsible use should be as much a priority as innovation in the public debate.

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2016.09.029.

References

- [1] World Health Organization. Global action plan on antimicrobial resistance. WHO; 2015. Available from: http://www.who.int/topics/antimicrobial_resistance/en/. [Accessed 1 August 2016].
- [2] Ardal C, Outtersson K, Hoffman SJ, Ghafur A, Sharland M, Ranganathan N, et al. International cooperation to improve access to and sustain effectiveness of antimicrobials. *Lancet* 2016;387:296–307.
- [3] Hoffman SJ, Outtersson K, Rottingen JA, Cars O, Clift C, Rizvi Z, et al. An international legal framework to address antimicrobial resistance. *Bull World Health Organ* 2015;93:66.
- [4] Pulcini C, Bush K, Craig WA, Frimodt-Møller N, Grayson ML, Mouton JW, et al. Forgotten antibiotics: an inventory in Europe, the United States, Canada, and Australia. *Clin Infect Dis* 2012;54:268–74.
- [5] Cassir N, Rolain JM, Brouqui P. A new strategy to fight antimicrobial resistance: the revival of old antibiotics. *Front Microbiol* 2014;5:551.
- [6] Muller AE, Theuretzbacher U, Mouton JW. Use of old antibiotics now and in the future from a pharmacokinetic/pharmacodynamic perspective. *Clin Microbiol Infect* 2015;21:881–5.
- [7] Review on Antimicrobial Resistance. Tackling drug-resistant infections globally: final reports and recommendations. Review on Antimicrobial Resistance; 2016. Available from: http://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf. [Accessed 1 August 2016].
- [8] Council of the European Union. Council conclusions on the next steps under a One Health approach to combat antimicrobial resistance. Council of the European Union; 2016. Available from: <http://www.consilium.europa.eu/en/press/press-releases/2016/06/17-epsco-conclusions-antimicrobial-resistance/>. [Accessed 1 August 2016].
- [9] European Commission. Explanatory note on the Joint Procurement Mechanism. Luxembourg: European Commission; 2015. Available from: http://ec.europa.eu/health/preparedness_response/docs/jpa_explanatory_en.pdf. [Accessed 1 August 2016].