

## Reviving old antibiotics

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In the face of increasing antimicrobial resistance and the paucity of new antimicrobial agents it has become clear that new antimicrobial strategies are urgently needed. One of these is to revisit old antibiotics to ensure that they are used correctly and to their full potential, as well as to determine whether one or several of them can help alleviate the pressure on more recent agents. Strategies are urgently needed to ‘re-develop’ these drugs using modern standards, integrating new knowledge into regulatory frameworks and communicating the knowledge from the research bench to the bedside. Without a systematic approach to re-developing these old drugs and rigorously testing them according to today’s standards, there is a significant risk of doing harm to patients and further increasing multidrug resistance. This paper describes factors to be considered and outlines steps and actions needed to re-develop old antibiotics so that they can be used effectively for the treatment of infections.

### Introduction

As bacterial resistance to antibiotics increases, physicians more often need to use old antibiotics that may still be active against some of the existing MDR or XDR pathogens.<sup>1,2</sup> These early, now resurgent, antibiotics were developed during the 1950s–70s but some of them fell out of favour, mainly due to the availability of newer antibiotics with better tolerability, improved activity or more convenient administration routes (Table 1). These old antibiotics were never developed using a structured process for drug assessment and regulatory approval. Current standards and the requirements for clinical testing have evolved over time. As a consequence, revived old antibiotics are being prescribed using the limited knowledge generated 50–70 years ago. This practice may carry significant risks for patient outcomes, adverse events and the emergence of resistance. The lack of up-to-date evidence with these drugs underscores the importance of ‘re-developing’ these drugs in academic and clinical settings based on a concerted global strategy (Figure 1).

### Which old antibiotics need to be re-developed?

Currently and into the near future, there are few or no treatment alternatives for MDR or XDR bacterial strains causing the infections listed below.<sup>3</sup>

#### (i) Community-acquired infections caused by ESBL-producing Enterobacteriaceae

Enterobacteriaceae that produce ESBLs are resistant to aminopenicillins and cephalosporins, and are frequently co-resistant to fluoroquinolones, aminoglycosides and other antibiotics.<sup>4</sup> The two main enterobacterial species harbouring ESBLs with their associated co-resistances, namely *Escherichia coli* and *Klebsiella pneumoniae*, are recognized as important causes of community-acquired urinary tract infections (UTIs). Old antibiotics that are increasingly used as revived oral treatment options for UTIs are fosfomicin trometamol,<sup>5</sup> nitrofurantoin<sup>6</sup> and mecillinam.<sup>7</sup>

#### (ii) Hospital-acquired infections caused by ESBL-producing Enterobacteriaceae

The increasing prevalence of ESBL-producing Enterobacteriaceae with co-resistance to other antibacterial drug classes has triggered the empirical use of carbapenems and has led to increasing selection pressure and carbapenem resistance.<sup>8</sup> Carbapenem-sparing agents are needed in hospitals; old drugs such as fosfomicin (intravenous) and temocillin to treat ESBL-producing bacteria are increasingly used where available.<sup>9,10</sup>

**(iii) Severe hospital-acquired infections caused by carbapenem-resistant Gram-negative bacilli**

These bacteria are usually XDR and only susceptible to polymyxins (colistin, polymyxin B) or sometimes tigecycline, fosfomycin and/or some aminoglycosides.<sup>11</sup> Polymyxins have had a substantial resurgence as a last-line treatment over the last decade. A set of key objectives was developed in 2013 to explore the factors

**Table 1.** First description of selected revived antibiotics

Antibiotic	Year of first publication
Colistin <sup>29</sup>	1947
Chloramphenicol <sup>30</sup>	1947
Nitrofurantoin <sup>31</sup>	1954
Minocycline <sup>32</sup>	1966
Fosfomycin trometamol <sup>33</sup>	1969
Mecillinam <sup>34</sup>	1975
Temocillin <sup>35</sup>	1981

affecting the safe and effective use of polymyxins, to identify gaps in knowledge and to set priorities for future research.<sup>12</sup>

Although the resistance problem is a global challenge, the solutions may vary in different regions of the world. Reviving old antibiotics as a quick solution to the thin antibiotic discovery and development pipeline requires agreement on the most promising candidates for further action. Old antibiotics are useful to avoid potential use of newer, costly antibiotics, which should be reserved for the future. A process for prioritizing the most relevant and important candidates for re-development is required that accounts for their availability internationally, the resistance landscape and the characteristics of the drug in a global and geographically diverse context.

**Knowledge gaps**

Substantial progress has been made in key areas over the last 20 years in the development of newer antibiotics. These include: bioanalytical methods for accurate quantification of antibiotics in biological fluids; better understanding of antimicrobial

- Prioritize old antibiotics that are still useful and need to be ‘re-developed’ and made more widely available
- Identify the knowledge gaps and define the necessary high-quality studies
- Form collaborative groups with extensive complementary skills to ‘re-develop’ the prioritized antibiotics
- Utilize existing initiatives and networks by coordinating the needed initiatives and merge them into concerted global action
- Raise awareness and assure public funding for these programmes
- Create an open information and data hub for existing and new information about revived antibiotics
- Organize dissemination and communication to all stakeholders
- Inform and engage regulatory agencies as well as governments, policy makers and payers to ensure the availability of good quality drugs and information to guide their use
- Generate guidelines for the rational use of each old antibiotic and integrate them into clear stewardship programmes
- Engage pharmaceutical producers to avoid the risk of shortage
- Monitor appropriate use of revived antibiotics by consumption and resistance surveillance programmes
- Integrate the ‘re-development’ of old antibiotics into the global actions to fight antibacterial resistance

**Figure 1.** Actions needed to revive useful antibiotics.

pharmacokinetics/pharmacodynamics (PK/PD), including exposure–effect and exposure–emergence of resistance relationships; and dose-finding approaches and optimizing dosing regimens, including individualization, susceptibility breakpoint setting, safety assessment and evidence-based therapy based on randomized controlled clinical trials.<sup>13</sup> These are also the most obvious knowledge gaps for revived antibiotics.

Although independent single studies may be published and contribute to our new understanding of revived drugs, many important gaps remain. As discussed in the following section, concerted action can identify knowledge gaps concerning revived antibiotics using a collaborative re-development process.

## How to re-develop revived antibiotics?

For recently approved antibiotics, the formal preclinical and clinical development processes are highly regulated and undertaken predominately by a pharmaceutical company as an investment for future returns. Re-development of old antibiotics is necessarily different as these drugs are usually long out of patent protection. Consequently, there is no financial incentive for the sometimes numerous generic companies involved in their manufacture and distribution to fund the necessary studies. Thus, public funding through agencies such as the European Commission and the US National Institutes of Health is often the only option available.<sup>14,15</sup> The general structure of re-developing an antibiotic starts with a systematic review to identify knowledge gaps and select the most important non-clinical and clinical studies. Ensuring sufficient funding (preferably for a collaborative project that integrates a wealth of expertise) is the prerequisite for any further action. It is important to undertake early communication with regulatory agencies, manufacturers and other involved players. Finally, issuing treatment guidelines based on the findings of the new studies and communicating these findings to the medical community ensures the translation of knowledge to the bedside.

The most advanced revived antibiotic is colistin, which is being re-developed in academic clinical studies supported by public funding, albeit not based on a collaborative and structured process. New methods and knowledge have superseded the original information, especially in the areas of PK/PD, analytical assays, dosing optimization (including in special patient populations), toxicity and the emergence of resistance in relation to drug exposure.<sup>16,17</sup> The efficacy of colistin versus colistin/carbapenem combination therapy is currently being tested in a well-designed randomized clinical trial in the EU-funded AIDA project (FP7 HEALTH.2011.2.3.1-1—Preserving Old Antibiotics for the Future), supported by numerous non-clinical studies. A similar multi-centre, multi-country clinical trial, funded by the NIH (<https://clinicaltrials.gov/ct2/show/NCT00235690>) is currently ongoing. Both of these studies demonstrate the value of international collaboration and pooling results in challenging clinical settings. In the AIDA project other revived antibiotics, such as nitrofurantoin, fosfomycin trometamol, oral minocycline and rifampicin, are being assessed, knowledge gaps identified and new information generated as a contribution to a public re-development process.

## Clinical study issues

Most of the original clinical studies that supported the approval or early clinical use of old antibiotics do not satisfy our current

demand for high-quality clinical trials and evidence. These early studies were often small, not randomized and had poor microbiology follow-up, and were therefore open to a range of biases and data misinterpretation. Additionally, patient populations relevant to modern needs were usually not included and knowledge about appropriate dosing regimens was in its infancy. Contemporary observational studies examining old antibiotics are plagued by unavoidable selection bias. Randomized controlled clinical studies in relevant patient populations using modern designs to improve efficiency are needed to provide relevant information for improved usage of revived antibiotics. Trials should target specific pathogens, especially resistant bacteria, or a group of indications relevant to the antibiotic being assessed.

Although conducting high-quality clinical studies with limited funding is challenging, there are advantages, such as the availability of clinical expertise with access to relevant patient populations and the application of clinical endpoints that are not driven by marketing considerations or approval requirements. However, there are common problems of investigator-initiated randomized controlled trials in academic settings, such as single-centre studies with a small number of patients, incomplete data collection, prolonged study duration, slow recruitment over time and premature study termination. To face the problem of underpowered studies, coordination of study protocols will allow comparability with respect to the interventions (dosing and schedule), outcome assessment, microbiological analysis, pooling of results and outcomes. It is important to use available resources in the most efficient way to avoid conducting many low-quality trials with limited patient numbers instead of one or two multicentre high-quality randomized controlled trials.

## Regulatory and funding issues

Regulatory agencies must play an active role in the process of reviving old antibiotics. In Europe the revived drugs have been approved nationally, resulting in a high variability of approved Summary of Product Characteristics (SmPC).<sup>18</sup> Since 1995, the EMA has coordinated the evaluation of centrally authorized products and national referrals to ensure consistency across the EU. Although regulatory pathways that allow the EMA to harmonize and update the SmPCs of old antibiotics across the EU are available, the capacity of the EU regulatory network is limited and recommended updates to the SmPC are rare.<sup>19</sup> In the USA, the FDA only permits updating of safety information. There is clearly a need for harmonization of procedures with the main regulatory agencies worldwide.<sup>20</sup>

## Responsible use of revived antibiotics

Widespread antibiotic resistance follows the mismanagement of antibiotics. If the use of revived antibiotics is indiscriminate or involves inappropriate dosing regimens, there will be growing resistance that will rapidly impede their efficacy. Colistin is a worrying example, having rapidly induced polymyxin resistance in centres using it, leading to XDR and pan-resistant Gram-negative bacteria.<sup>21–23</sup> Stewardship programmes supported by stringent infection control measures are imperative to prevent the loss of this resource. For last-resort antibiotics such as colistin, a simple strategy that restricts prescribing to certain qualified prescribers could

facilitate appropriate use. Infection control measures, such as isolating or cohorting patients who receive colistin, may limit the spread of XDR bacteria.

### Access, not excess

Access to high-quality antibiotics is not a given in many parts of the world. In low-resource countries, access to some of these antibiotics or even future new agents is often not affordable. Access cannot be taken for granted in high-income countries either, as not all of the revived old drugs are universally approved and available.<sup>24,25</sup> Scandinavian physicians have successfully used pivmecillinam for uncomplicated UTIs since the 1970s, but in most countries pivmecillinam is not available. A similar situation applies to fosfomycin iv, which is approved in Germany, Austria, France and Spain and a small number of Asian countries, and to temocillin, which is approved in only four European countries (Belgium, Luxembourg, UK and France).

Ways of providing ready but controlled access based on local needs are required. National regulatory agencies and government bodies are called upon to address this issue on a national basis. Options include forming an international organization or using an existing one to coordinate the distribution of old antibiotics centrally. UNICEF could serve as an example of such an organization.

Even if an old antibiotic is approved in a country, it does not guarantee access. Frequent drug shortages may lead to the use of more expensive and broad-spectrum or less efficacious substitute agents. These substitutes may further accelerate the emergence and selection of antibiotic resistance. The problem has been recognized and the European Council has called upon the Member States and the European Commission to examine how to keep effective antibiotics on the market.<sup>26</sup>

### Sharing and communicating new knowledge on old drugs

Not all clinical studies on revived antibiotics are published. Open access to raw and unpublished data from old and new studies could contribute to the evidence base around the re-development process. A publicly funded, web-based, open-access repository of updated evidence on the use of antibiotics is needed to reduce the time required for information gathering. Open access information may speed up knowledge sharing. Local databases and processes, such as the Evidence summaries: unlicensed and off-label medicines (ESUOMs) funded by the UK's National Institute for Health and Care Excellence (NICE), could serve as model systems. Obvious challenges of an open data access portal are curating the data, making them user-friendly and securing funding. Such efforts require unprecedented collaborative (global) alliances at all levels of society.

As antibiotic resistance is moving rapidly, new models for rapid knowledge dissemination to healthcare professionals, academics, governments, funders, authorities, the pharmaceutical industry and the public are required. All these stakeholders are needed to build support and gain consensus on the need for rapid action to explore the benefits of using revived antibiotics to tackle antibiotic resistance as well as to engage in a coordinated effort to disseminate information and communicate with all interested parties.<sup>27,28</sup>

### Conclusions

Revived old antibiotics have useful activity against otherwise MDR bacteria. These antibiotics were not developed with the tools and knowledge applied to modern agents. Vital gaps in the knowledge needed to use these drugs appropriately require new solutions to address the problems listed in this article. Strategies are urgently needed to re-develop these drugs using modern standards, integrating new knowledge into regulatory frameworks and communicating the knowledge from the research bench to the bedside. Without a systematic strategy to re-develop these old drugs and rigorously test them according to today's standards, we risk doing harm to patients or further increasing multidrug resistance. All stakeholders, from healthcare specialists, patients, payers and manufacturers to regulatory agencies and policy makers, need to be involved in creating a roadmap for taking old antibiotics forward and putting them to work again, safely and effectively. The challenge now is to find much-needed resources—time, finances and people—to fast-track the task of optimizing the use of these potentially life-saving drugs and make them available to everyone in need.

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