Development of new antibiotics: taking off finally?

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Summary

Since 2010, awareness of the global threat caused by antimicrobial resistance (AMR) has risen considerably and multiple policy and research initiatives have been implemented. Research and development (R&D) of much-needed new antibiotics active against multiresistant pathogens is a key component of all programmes aiming at fighting AMR, but it has been lagging behind owing to scientific, regulatory and economic challenges. Although a few new antibiotics might be available in Switzerland in the next 5 years, these new agents are not based on new mechanisms of action and are not necessarily active against resistant pathogens for which there is the highest unmet medical need, i.e. multiresistant Gram-negative bacteria. Of the three new antibiotics with pending authorisation in Switzerland for systemic treatment of severe infections, oritavancin and tedizolid target Gram-positive pathogens, while only ceftolozane+tazobactam partially covers multiresistant Gram-negative pathogens. Among six antibiotics currently in phase III of clinical development, delafloxacin and solithromycin will also be useful mostly for Gram-positive infections. Importantly, the four other compounds are active against multiresistant Gram-negative pathogens: ceftazidime+avibactam, meropenem+RPX7009, eravacycline and plazomicin. The three last compounds are also active against carbapenem-resistant Enterobacteriaceae (CRE). A few compounds active against such pathogens are currently in earlier clinical development, but their number may decrease, considering the risk of failure over the course of clinical development.

At last, through public and political awareness of pathogens with high public health impact and unmet medical need, development of innovative economic incentives and updated regulatory guidance, R&D of new antibiotics is slowly taking off again.

Key words: antimicrobial resistance; multidrug resistant; anti-infective agents; research and development; pipeline; qualified infectious disease product; regulatory; unmet medical need; Switzerland

Introduction

Although antimicrobial resistance (AMR) existed well before humans started to use antibiotics to treat infections, the menace of a post-antibiotic era threatening modern day medicine is closer to reality than ever before [1, 2]. Based on modelling studies, the impact of AMR was recently quantified as potentially causing the death of 300 million people during the next 35 years and having so much impact as to decrease the world gross domestic product by...
2–3.5% compared with what it should be by 2050 [3, 4].

Although these crude predictions are based on large uncertainty and may overestimate the future health-economic impact of AMR [5], experts and policy makers agree that AMR should be considered a serious public health threat. Both common and rare pathogens found in hospitals and in the community have seen their resistance rates increase dramatically in recent decades. As reported by the World Health Organization (WHO), more than 50% of Escherichia coli, Klebsiella pneumoniae and Staphylococcus aureus are reported as resistant to commonly used antibiotics in many parts of the world [6]. Several levels of acquired resistance to antibacterial agents have been defined. Multidrug resistant (MDR) pathogens are resistant to at least one antibiotic in three or more antibiotic classes, extensively drug resistant (XDR) pathogens are resistant to at least one antibiotic in all but one or two antibiotic classes and pan-drug resistant (PDR) pathogens are resistant to all antibiotics in all clinically relevant antibiotic classes [7]. The causes of such a rise in resistance are multiple, from natural evolution to antibiotics overuse in patients and farm animals [8]. In Switzerland, the overall prevalence of MDR among E. coli isolates at a single hospital in 2011 was still low (6.5%) compared with the numbers reported by the WHO and was similar in the community (5.7%), hospital (7.8%) and specialised outpatient clinic (5.3%) settings [9]. However, using data from the Swiss Antibiotic Resistance Surveillance database (ANRESIS) [10], Kronenberg et al. also showed that the prevalence of MDR increased significantly between 2004 and 2011 from 1% to 5.8% for E. coli and from 1.1% to 4.4% for K. pneumoniae [11].

Unfortunately, development of new antibiotics against these resistant bacteria did not progress at the same speed, and even lagged behind. This worrisome trend leaves physicians with a limited therapeutic arsenal for an increasing number of resistant pathogens and the absence of therapy for some PDR pathogens. Although a few new antibiotics might be available in Switzerland in the next couple of years, these new agents are not based on completely new mechanisms of action as they do not attack new bacterial targets. Nevertheless, through modified economic incentives and updated regulatory guidance, R&D of new antibiotics is slowly taking off again, as we describe in this narrative review.

The crisis of antibiotic research and development

During the flourishing years of antibiotic development in the 1940s and 50s, 12 different classes of antibiotics were discovered, but only seven have been discovered since, the last one being the lipopeptides in the 1980s [12]. Despite this discovery void, the panel of antibiotics available for clinicians to treat susceptible infections still remains large. Many of these antibiotic compounds belong to a known class, but were chemically modified from the original compound to increase the number of susceptible pathogens or to be insensitive to a particular mechanism of resistance. This flourishing era was followed by a steep decline in numbers of new antibiotics approved during the 1990s and 2000s. Indeed, difficulties in the development of new anti-biotics spanning the whole spectrum of drug development appeared: drug discovery challenges [12], regulatory hurdles [13, 14], difficulties in conducting clinical trials [15] and economic disincentives [16, 17]. It also led large pharmaceutical companies to desert this area for more lucrative and less scientifically and economically challenging therapeutic areas, like cardiology and oncology [18]. Although this inverse trend (increasing AMR rates / decreasing availability of efficient antibiotics) has been known for a long time, many alerts and calls to action were needed to raise the awareness around the problem and trigger policy initiatives.

MDR pathogens with unmet medical need

The starting point to raising awareness around the AMR issue and setting priorities for R&D of new antibiotics was to define resistant pathogens for which the highest unmet medical need exists or, in other words, resistant pathogens that have the potential to pose the most serious threat to public health. A first list of six key pathogens was created in 2008 under the acronym “ESKAPE pathogens” [19]: Enterococcus faecium, S. aureus, K. pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species. In 2014, the United States Food and Drug Administration (FDA) released a final list of a total of 21 target pathogens (table 1) with high unmet medical need [20]. As highlighted in the table, the unmet need is highest for XDR or PDR strains [21]. Importantly, this list shows that AMR is not a problem restricted to the healthcare setting only, but that common community-acquired infections such as urinary tract infections, gonorrhoea and tuberculosis are increasingly caused by MDR or XDR pathogens. Since January 2012, when the Generating Antibiotic Incentives Now (GAIN) act came into effect in the United States, development of a new antibiotic agent active against one or several pathogens on this list allows a Qualified Infectious Disease Product (QIDP) designation to be obtained. This offers several incentives such as priority review of the new drug application file by the FDA and an economic incentive in the form of 5 additional years of market exclusivity if a marketing authorisation is obtained. Other economic incentives have been put in place recently in the United States. Funds from the Biomedical Advanced Research and Development Authority (BARDA), which are public, nonrefundable funds given to companies to develop specific compounds for potential bioterrorism threats, are now extended to compounds active against MDR, XDR and PDR pathogens [22]. Consequently, the overall United States budget for 2016 to fight AMR almost doubled to about 1.2 billion dollars.

Concerted actions against AMR and promotion of research and development of new antibiotics: recent policy initiatives and regulatory changes

The crisis of AMR needs to be tackled from various angles and most importantly, there needs to be a global political
will leading to policy, legal and regulatory changes if our society wants to keep up with the issue. Essential determinants impacting R&D of new antibiotics are displayed in figure 1. Thanks to the mobilisation and lobbying activities of several independent initiatives, awareness of the AMR problem has finally risen since 2010 and the second step of concerted action is advancing. The initiatives that have played a key role in raising global awareness on AMR include the independent global network ReAct [23], the World Alliance against Antimicrobial Resistance (WAAAR) [24] and Antibiotic Action [25].

Although the bulk of multidrug resistance might lie outside of these regions, the United States and the European Union (EU) are key regions for pharmaceutical companies to register a new drug. New regulatory guidance for infections caused by bacteria with high unmet medical need (i.e., in this case MDR, XDR and PDR bacteria) have been issued by the European Medicines Agency (EMA) and the FDA [26, 27], with the aim to facilitate the approval of new antibiotics. A new risk/benefit balance must be found between approving new antibiotics with limited clinical data, because of the high unmet need, and ensuring patients are treated with new antibiotics that are safe and efficacious. This kind of trade-off has been successfully applied in drug development, for example, to orphan diseases [28, 29]. Furthermore, potential new regulatory pathways being discussed for new antibiotic agents include (1) the Limited Population Drug Approval mechanism [30] and (2) the tiered approach in which different amounts of clinical data are required on the basis of the level of unmet medical need and pathogen-based indications are pursued rather than conventional disease-based indications [31].

Methodological investigations on how to ameliorate trial design for antibiotics are also being addressed by different consortia involving the academic, private and regulatory sectors, such as the Foundation for the National Institutes of Health (FNIH) biomarkers consortium [32] and the COMBACTE project [33], part of the Innovative Medicine Initiative (IMI)’s New Drug for Bad Bugs (ND4BB) programme [34]. IMI is a public-private partnership between the EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Its ND4BB programme launched in 2013 aims to promote R&D of new antibiotics: the TRANSLOCATION and ENABLE projects focus on the discovery stage, the COMBACTE, COMBACTE-MAGNET, COMBACTE-CARE project include clinical trials with new compounds and the sharing of clinical data.

Table 1: Qualified infectious disease product (QIDP) qualifying pathogens: pathogens that have the highest unmet medical need.

<table>
<thead>
<tr>
<th>QIDP qualifying pathogen names [20]</th>
<th>Gram</th>
<th>Type of infection</th>
<th>Hospital acquired</th>
<th>Community acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acinetobacter species¹</td>
<td>Gram−</td>
<td>Opportunistic</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Burkholderia cepacia complex</td>
<td>Gram−</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Campylobacter species</td>
<td>Gram−</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clostridium difficile¹</td>
<td>Gram+</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae (especially Citrobacter, Enterobacter cloacae, Klebsiella pneumoniae, Escherichia coli, Proteus vulgaris, Salmonella, Serratia marcescens, Shigella)</td>
<td>Gram−</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Enterococcus species</td>
<td>Gram+</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>Gram−</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycobacterium tuberculosis complex¹</td>
<td>NA</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Gram−</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>Gram−</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nontuberculous mycobacteria species</td>
<td>NA</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas species¹</td>
<td>Gram−</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus¹,²</td>
<td>Gram+</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Streptococcus agalactiae (group B)</td>
<td>Gram+</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Gram+</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pyogenes (group A)</td>
<td>Gram+</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vibrio cholerae</td>
<td>Gram−</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td><strong>Fungi</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspergillus species</td>
<td>NA</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida species</td>
<td>NA</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coccidioides species</td>
<td>NA</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptococcus species</td>
<td>NA</td>
<td>X</td>
<td></td>
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</tr>
</tbody>
</table>

¹ Key unmet need due to high and increasing prevalence of XDR or PDR strains [21]
² Unmet need primarily for blood, bone and prosthesis infections and not for skin infection.
NA = Not applicable.
development costs from phases I to III, and the DRIVE-AB project, which started in October 2014, aims to develop new economic models for antibiotics while preserving their use [35]. With a total budget for infectious diseases of over 710 million euros [36], such public-private partnerships are an important contribution to a wealth of measures that can be implemented to support the R&D of new antibacterials. Rapid diagnostic test development is another key area and has been recently incentivised through a prize [37]. Other initiatives include the Joint Programming Initiative on Antimicrobial Resistance (JPI-AMR) in the EU [38] and an independent review on AMR commissioned by the United Kingdom government in July 2014 [39]. The latter initiative aims to deliver a list of priority action items that should be agreed internationally to tackle AMR. Last but not least, the recent WHO action plan on antimicrobial resistance (adopted in May 2015) [40] will without a doubt foster attention and trigger a series of actions at a global level.

Current systemic compounds active against MDR pathogens recently or in the process of being registered

What is the current pipeline status and are any new antibiotic agents likely to reach Swiss pharmacies in the next 2 years? First, as listed in table 2, five systemic compounds have been approved since May 2014 in the United States (ceftolozane-tazobactam [41], oritavancin [42], tedizolid [43], dalbavancin [42] and ceftazidime-avibactam [44]). All had QIDP designation, meaning they are active against at least one of the pathogens with high unmet medical need (table 1). Four of these five new antibiotics or antibiotic combinations have pending marketing authorisations at the EMA and three of them (ceftolozane-tazobactam, oritavancin and tedizolid) have been submitted to the Swiss Agency for Therapeutic Products (Swissmedic). One new antibiotic agent, cefepibrepro [45], was approved in the EU at the end of 2013 and in Switzerland at the end of 2014, after unusually long regulatory approval delays [46]. Importantly, four of these six compounds have activity mainly against Gram-positive pathogens and will, therefore, be useful for treatment of meticillin-resistant Staphylococcus aureus (MRSA) infections. As MRSA infection rates are decreasing in many parts of Europe [47, 48], these new compounds are enlarging our arsenal but clearly not tackling the key emerging resistant Gram-negative pathogens. Only cefotaxime-tazobactam, which has a submission pending in Switzerland, partially covers MDR Gram-negative pathogens such as extended spectrum β-lactamase (ESBL)-producing strains. Importantly for MDR Gram-negative infections, ceftazidime-avibactam was approved in January 2015 in the United States for complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI), but restricted to patients who have limited treatment options [49]. Avibactam is the first new β-lactamase inhibitor (BLI) approved in two decades. Using the new regulatory guidance and QIDP designation registration process, the antibiotic combination was approved on the basis of data for ceftazidime alone, supplemented by in-vitro and phase II data for ceftazidime-avibactam in the targeted indications [49]. Phase III trials are planned to be completed in 2015 [50]. Although the label is currently restricted because of the limited availability of data, it will help to preserve use of the drug and development of resistance. It remains to be seen whether, once data from ongoing phase III or postmarketing studies are available for broad spectrum antibiotics such as ceftazidime-avibactam, pharmaceutical companies will try to expand the label, leaving it to countries’ public health systems to decide upon and put in place conservation measures for these precious new antibiotics.

Current systemic compounds active against MDR pathogens in phase III and their potential use in Switzerland

As of June 2015, six compounds are in phase III for the systemic treatment of severe bacterial infections. They all have QIDP designation. While delafloxacin [51] and solithromycin [52] will most likely play a role in management of Gram-positive infections [53], four of the six other compounds that could be available in Switzerland within the next 3–5 years have activity against MDR Gram-negative pathogens with key unmet medical needs (table 2 and [21]): ceftazidime-avibactam [44], meropenem+RPX7009 [54, 55], eravacycline [56] and plazomicin [57]. Notably, three of these are also active against carbapenem-resistant Enterobacteriaceae (meropenem+RPX7009, eravacycline and plazomicin).

In Switzerland, there are a few published small-scale outbreaks [58] and reports of imported cases of carbapenem-resistant Enterobacteriaceae (CRE) from endemic countries [58–63]. Thus, the need for new therapeutic agents is so far very limited, but this will likely change in the coming years as more and more infections with CRE will occur with the global spread of XDR/PDR Gram-negative bacteria [64]. As current treatment options for CRE are limited to, for example, colistin, fosfomycin, tigecycline or combination therapies [65], compounds active against such XDR bacteria such as eravacycline, plazomicin or meropenem+RPX7009 will hopefully be available to treat patients by that time. The need is very different in Switzerland for ESBL-producing strains, which are now widely present in the community. Indeed, local studies have shown that carriage of ESBLs is observed in 5.8% of screened healthy people [66] and 4.8% of patients at admission [67]. Most ESBL-producing Enterobacteriaceae are resistant to fluoroquinolones and cotrimoxazole, limiting orally available therapeutic options for more severe ESBL infections. Fosfomycin and nitrofurantoin remain highly active for uncomplicated UTI, which led to new Swiss treatment guidelines for uncomplicated UTI: the recommended first-line antibiotic changed from a quinolone agent to fosfomycin or nitrofurantoin [68, 69].
The current early antibiotics development pipeline: overview of promising compounds in phase I and II of clinical development

As listed in the inventory of antibiotics in clinical development kept by the Pew Charitable Trusts antibiotics and innovation project [70], there are currently 37 antibiotics overall in clinical development from phase I to registration for systemic bacterial infections (including *Clostridium difficile* infection). Ten compounds are in phase I and 18 in phase II. All of these have QIDP designation, meaning that they are active against at least one QIDP-qualifying pathogen. Based on published calculated failure rates for all therapeutic areas [71, 72], only 1 in 9 or 10 compounds entering phase I can be expected to obtain market approval. This ratio could be even smaller for innovative antibiotics displaying new mechanisms of action.

As mentioned earlier, pharmaceutical companies massively left the antibiotics field in the 1990s. Importantly, some of the large pharmaceutical companies that had left are back in the antibiotics R&D field. In Switzerland, the two largest Swiss pharmaceutical companies Novartis and Hoffmann-La Roche have restarted R&D activities for antibiotics. Roche started a partnership in 2013 with Polyphor to develop RG7929 (POL 7080), a compound active against MDR Gram-negative bacteria and in particular MDR *P. aeruginosa* [73]. Two phase II clinical trials with this compound

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**Table 2: Late-stage pipeline: systemic antibiotics recently approved, in registration or in phase III of clinical development.**

<table>
<thead>
<tr>
<th>Drug (brand name) - Company</th>
<th>Antibiotic class</th>
<th>Activity spectrum/resistant pathogens targeted</th>
<th>Phase and indication¹</th>
<th>Regulatory status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftaroloxone+ tazobactam [41] (ZerbaxaTM) – Cubist Pharmaceuticals / Merck Sharp &amp; Dohme</td>
<td>Cephalosporin + BLI</td>
<td>Gram–, including MRSA, VRSA, penicillin- and cephalosporin-resistant Pseudomonas aeruginosa, ESBL-producing strains</td>
<td>Approved for cUTI and cIAI, in phase III for VAP and phase I for paediatric use</td>
<td>Approved December 2014</td>
</tr>
<tr>
<td>Tedizolid phosphate [43] (SivextroTM) – Cubist Pharmaceuticals / Merck Sharp &amp; Dohme</td>
<td>Oxazolidinone</td>
<td>Gram+, including MRSA and linezolid-resistant MRSA</td>
<td>Approved for ABSSSI, in phase III for HAP/VAP and for ABSSSI in adolescents</td>
<td>Approved June 2014</td>
</tr>
<tr>
<td>Dalbavancin [42] (DalvanceTM/XyaldaTM) – Actavis / Durata Therapeutics</td>
<td>Glycopeptide</td>
<td>Gram+, including MRSA</td>
<td>Approved for ABSSSI, in phase III for CABB and phase I and III for paediatric use</td>
<td>Approved May 2014</td>
</tr>
<tr>
<td>Meropenem+RPX009 [54, 55] (CarbavancTM) – The Medicines Company</td>
<td>Carbapenem + new class of BLI</td>
<td>Gram–, including CRE and particularly KPC</td>
<td>Phase III for cUTI and infections caused by CRE²</td>
<td>NA</td>
</tr>
<tr>
<td>Eravacycline [56] – Tetraphase Pharmaceuticals</td>
<td>Tetracycline</td>
<td>Gram+ and –, including CRE, ESBL-producing strains, MDR Acinetobacter baumanii; VRE, MRSA</td>
<td>Phase III for cUTI and cIAI⁴</td>
<td>NA</td>
</tr>
<tr>
<td>Plazomicin [57] – Achaogen</td>
<td>Aminoglycoside</td>
<td>Gram–, including CRE</td>
<td>Phase III for bloodstream infection and nosocomial pneumonia caused by CRE²</td>
<td>NA</td>
</tr>
<tr>
<td>Delafloxacin [51] – Melinta Therapeutics</td>
<td>Fluoroquinolone</td>
<td>Gram+ and –, including MRSA</td>
<td>Phase III for ABSSSI</td>
<td>NA</td>
</tr>
<tr>
<td>Solithromycin [52] – Cermap Pharmaceuticals</td>
<td>Macrolide</td>
<td>Gram+, including macrolide-resistant strains</td>
<td>Phase III for CABB and uncomplicated gonorrhea, in phase I for paediatric use</td>
<td>NA</td>
</tr>
</tbody>
</table>

¹ Information retrieved from clinicaltrials.gov as of March 2015.
² Personal communication.
³ Completion of trial expected in 2016; clinicaltrials.gov identifiers: NCT02168946 and NCT02166476.
⁴ Completion of trial expected in 2015; clinicaltrials.gov identifiers: NCT01978938 and NCT0184485.
⁵ Completion of trial expected in 2017; clinicaltrials.gov identifiers: NCT01970371.

ABSSSI = acute bacterial skin and skin structure infections; BLI = β-lactamase inhibitor; CABB = community-acquired bacterial pneumonia; cIAI = complicated intra-abdominal infections; CRE = carbapenem-resistant *Enterobacteriaceae*; cUTI = complicated urinary tract infections; ESBL = extended spectrum β-lactamase; Gram+ = Gram-positive; Gram– = Gram-negative; HAP = hospital-acquired pneumonia; KPC = Klebsiella pneumoniae carbapenemase; MRSA = meticillin-resistant *Staphylococcus aureus*; VAP = ventilator-acquired pneumonia; VRSA = vancomycin-resistant *Staphylococcus aureus*. 

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**Review article: Current opinion Swiss Med Wkly. 2015;145:w14167**

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Swiss Medical Weekly · PDF of the online version · www.smw.ch Page 5 of 9
are currently recruiting patients (NCT02096315, NCT02096328). In January 2015 Roche also partnered with two other companies to develop the new BLI RG6080 (OP0595), which is currently in phase I [74]. As announced in September 2014 [75], Novartis restarted in-house research activities conducted at the Novartis Institute for Biomedical Research (NIBR) on C. difficile, P. aeruginosa and S. aureus [76]. Smaller Swiss companies are not lagging behind and this is important as most of today’s antibiotic innovation stems from small and medium enterprises, especially in the early phases of research and preclinical development. Basilea Pharmaceutica had cefotibiprole recently approved in the EU and Switzerland and has an active antibiotics pipeline with BAL30072, a monosulfactam compound active against MDR Gram-negative infections currently in phase I. Debiopharm entered into the antibiotics field in 2013, focusing on inhibitors of the new staphyloccocal target FabI. Two of their compounds, Debio 1452 and its produg Debio 1450 are in phase II and I of clinical development, respectively.

Other promising compounds in early clinical development with activity against MDR Gram-negative pathogens include avibactam in combination with aztreonam or ceftaroline and the novel BLI relebactam in combination with imipenem-cilastatin. More details on some of these compounds are reviewed in Butler et al. [77]. Importantly, we must emphasise that all of the above-listed compounds with activity spectrum against Gram-negative MDR pathogens are modified compounds of existing classes. There is a clear need to discover new bacterial targets or new natural compounds. In this regard, the approach of Ling et al. recently described a new technique to discover natural antibacterial compounds from soil bacteria and the discovery of teixobactin, a new inhibitor of the synthesis of peptidoglycan [78].

Conclusion

AMR threatens modern day medicine. Five new systemic antibiotics have been approved since May 2014 in the United States, which is good news but clearly not enough to fight all resistant infections. Four of these have pending marketing authorisations at EMA and three of them at Swissmedic (ceftolozane+tazobactam, oritavancin and tedizolid). One new antibiotic, cefotibiprole, was approved in the EU at the end of 2013 and in Switzerland at the end of 2014. These new antibiotics expand the arsenal of treatments available to clinicians, but do not have new mechanisms of action and are not active against CRE, the MDR Gram-negative pathogens for which there is the highest unmet medical need. There are currently 37 antibiotics in clinical development from phase I to registration, among which some compounds have activity against CRE and could be available in a couple of years if they prove safe and efficacious.

Since 2010, awareness around the AMR issue has dramatically increased and actions have started to be called for or implemented. R&D of new antibiotics is a key component of all programmes aiming at fighting AMR, but it has lagged owing to a plethora of scientific, regulatory and economic challenges. During past years, regulatory guidance has been updated and economic incentives have started to be put in place. This is encouraging both large and small pharmaceutical companies to slowly re-enter the antibiotics field. As R&D is a long process, the real effect of all these measures and restarting R&D activities will only be assessable in 5–10 years in terms of new antibiotics available to treat patients infected with MDR, XDR and PDR pathogens. As AMR is a global issue, coordinated action will now become key in order to optimise the use of resources to develop new antibiotics, as well as to allow their appropriate distribution (where they are most needed in terms of patterns of AMR) and use (to prevent development of AMR).

Acknowledgments: The authors would like to thank Chantal Merey for useful discussions.

Disclosures: The research leading to this review has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115523 [Combating Bacterial Resistance in Europe – COMBACTE] and n° 115618 [Driving re-investment in R&D and responsible antibiotic use – DRIVE-AB], resources of which are composed of financial contribution from the European Union’s 7th Framework Programme (FP7/2007-2013) and EFPIA companies in kind contribution.

SH has received peer-reviewed research grants funded by Pfizer and B. Braun and is a member of the advisory boards of Destiny Pharma, bioMérieux, Novartis and DaVolterra.

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Figure 1
Essential determinants impacting the research and development (R&D) of new antibiotics.
QIDP = qualified infectious disease product.