



Critical shortage of new antibiotics in development against multidrug-resistant bacteria—Time to react is now[☆]

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ABSTRACT

Two commercial databases (Pharmaprojects and Adis Insight R&D) were queried for antibacterial agents in clinical development. Particular attention was given to antibacterial agents for systemic administration. For each agent, reviewers were requested to indicate whether its spectrum of activity covered a set of selected multidrug-resistant bacteria, and whether it had a new mechanism of action or a new target. In addition, PubMed was searched for antibacterial agents in development that appeared in review articles. Out of 90 agents that were considered to fulfil the inclusion criteria for the analysis, 66 were new active substances. Fifteen of these could be systemically administered and were assessed as acting via a new or possibly new mechanism of action or on a new or possibly new target. Out of these, 12 agents were assessed as having documented *in vitro* activity against antibiotic-resistant Gram-positive bacteria and only four had documented *in vitro* activity against antibiotic-resistant Gram-negative bacteria. Of these four, two acted on new or possibly new targets and, crucially, none acted via new mechanisms of action. There is an urgent need to address the lack of effective treatments to meet the increasing public health burden caused by multidrug-resistant bacteria, in particular against Gram-negative bacteria.

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1. Introduction

In recent years, several reports from the scientific community have raised concerns that antibacterial drug development will not adequately address the problems posed by antibiotic resistance among important bacterial pathogens (Boucher et al., 2009; Bradley et al., 2007; Cars et al., 2008; IDSA, 2004; Nathan, 2004; Norrby et al., 2005; Spellberg et al., 2004; Tickell, 2005). In its First European Communicable Disease Epidemiological Report, the European Centre for Disease Prevention and Control (ECDC) rated antimicrobial resistance as one of the most important infectious disease threats in Europe because of the increase in infections due multidrug-resistant bacteria in Europe (Amato-Gauci and Ammon, 2007). The recent emergence, in European hospitals and globally, of bacteria that are totally, or almost totally, resistant to currently available antibiotics is even more threatening since treatment options for infected patients are extremely limited (Lepape and Monnet, 2009; Nordmann et al., 2009; Souli et al., 2008). In a recent joint technical report, ECDC and the European Medicines Agency (EMA) in

collaboration with Action on Antibiotic Resistance (ReAct) estimated that at least 25,000 patients die each year in the EU from an infection due to multidrug resistant bacteria (ECDC/EMA, 2009). Antibiotic resistance is also a major public health issue in low and middle income countries. One study indicates that 70% of hospital-acquired neonatal infections could not be successfully treated by the regimen recommended by the World Health Organization (WHO) (Zaidi et al., 2005). A recent study in Tanzanian children confirmed that ineffective treatment of bloodstream infections due to antibiotic resistant bacteria predicted fatal outcome independently of underlying diseases (Blomberg et al., 2007). In that hospital-based study, crude mortality from bloodstream infections caused by Gram-negative bacteria was 43%. Reducing the consequences of antibiotic resistance requires a multifaceted approach, including rational use of existing antibacterial agents and control of the spread of resistant micro-organisms in hospitals and the community. Although these measures are essential to preserve the effectiveness of existing antibiotics, implementation has generally been weak and the prevalence of bacterial resistance, including multi-drug resistance, continues to increase. Development of new antibacterial agents with activity against multi-drug resistant bacteria is therefore perceived as a critical public health need.

In 2006, a think-tank group on Innovative Drug Development from the EMA's Committee on Human Medicinal Products (CHMP) was set up to allow EU regulators, industry and academia to discuss different aspects of drug development (EMA, 2007). Arising from this discussion, an ECDC-EMA Working Group was constituted in 2008 to carry this work forward. An important focus of their efforts was to assess the gap between the burden of disease imposed by multi-drug resistant bacteria and the development of new antibacterial agents. The aim of the present study was to provide, as accurately and as comprehensively as possible, an account of the status of the antibacterial drug development pipeline by documenting and characterising the activity of new agents that have entered clinical development. Particular attention was given to antibacterial agents for systemic administration.

2. Methods

2.1. Search strategy and selection criteria

2.1.1. Selection of databases

Identification of agents was a joint undertaking between the EMA and the Strategic Policy Unit of ReAct at Duke University (Durham, NC, USA). Three commercial databases were identified for the analysis of the research and development pipeline: Pharmaprojects (T&F Informa UK Limited, London, UK) (Pharmaprojects, 2008), Adis Insight R&D (Wolters Kluwer Health, Amsterdam, NL) (Adis, 2008) and BioPharm Insight (Infinata, Norwood, MA, USA) (BioPharm, 2008). A preliminary sensitivity analysis showed that using Pharmaprojects and Adis Insight R&D for antibacterial agents that had entered Phase II of clinical development resulted in a 10% yield increase in comparison to the use of one database only. The addition of the database BioPharm Insight did not result in any significant yield increase. As a result, Pharmaprojects and Adis Insight R&D were selected to identify antibacterial agents in clinical development.

2.1.2. Search strategy and selection of antibacterial agents

Pharmaprojects and Adis Insight R&D were searched using a data-lock point of 14 March 2008 for agents that had entered clinical development or for which an application had already been filed to at least one national regulatory agency. Agents that had reached clinical trials but were reported as suspended, i.e., put on hold, in accordance with Pharmaprojects' definition, were considered to

still be under active development, and were therefore included in the study. However, agents with a status of "no development reported" or "discontinued" according to the databases' definitions were excluded from the study.

2.1.3. Combined dataset

The results produced by the database searches were matched by compound name, synonyms and originator in order to avoid duplicate entries and to eliminate inconsistencies (e.g., misclassifications) in the combined dataset. If discrepancies in the reported development phase of the agent were found between the databases, the most advanced registered phase was used. Where compounds were marked as "discontinued", "no development reported" or "suspended" in one of the databases, but not in the other, these were considered as still being under active development.

2.1.4. Literature search

PubMed was searched for antibacterial agents in development that appeared in review articles (identified as such by PubMed) published in English between and including January 2006 and January 2009, based on the terms listed in the box.

The search used the following Boolean combinations of Medical Subject Headings (MeSH) terms and also search terms previously described by Talbot et al. (2006):

Anti-Bacterial Agents/therapeutic use [Mesh] AND
Bacteria/drug effects [Mesh] AND
Bacterial Infections/drug therapy [Mesh] AND
Drug Resistance, Bacterial [Mesh]

OR

Anti-Bacterial Agents [Mesh] AND
Drugs, Investigational [Mesh] AND
Humans [Mesh] AND
anti-bacterial agents [Substance Name]

OR

antimicrobial drug development

OR

investigational antimicrobials

OR

novel antimicrobials

If an agent identified through the literature search had not been identified earlier during the database searches, this agent was added to the list for the final analysis, provided that it met the entry criteria.

2.2. Assessment strategy

2.2.1. Inclusion criteria

All chemical or biological agents that were identified by the searches and, to the knowledge of the ECDC-EMA Working Group, were not licensed anywhere in the world, were eligible for assessment if a direct antibacterial effect was documented. Vaccines, monoclonal antibodies and agents which had a mechanism of action involving only immuno-modulation, were excluded.

The selected agents were then assessed for their antibacterial spectrum and included in the analysis if they displayed activity against at least one of the chosen antibiotic-resistant bacteria. These bacteria were chosen because they represent indicators for multidrug resistance in bacteria that are among those most commonly isolated from blood cultures in Europe (Biedenbach et al., 2004):

- Methicillin-resistant *Staphylococcus aureus* (MRSA);
- Vancomycin-intermediate and vancomycin-resistant *S. aureus* (VISA/VRSA);
- Vancomycin-resistant enterococci (VRE);
- Penicillin-resistant *Streptococcus pneumoniae* (PRSP);
- Third-generation cephalosporin-resistant *Enterobacteriaceae*;
- Carbapenem-resistant *Enterobacteriaceae*;
- Carbapenem-resistant non-fermentative Gram-negative bacteria.

Agents that were being developed only to treat other bacteria not included in this list, e.g., agents that appeared to be under development only to treat tuberculosis or infections due to *Helicobacter pylori* or *Chlamydia trachomatis*, were excluded from the assessment.

2.2.2. Assessment procedure

Agents identified by the searches were divided into five batches and each batch was allocated to a team of two reviewers, including one from the ECDC-EMA Working Group and one external reviewer chosen for their experience in the field. Reviewers were unaware of the identity of their team counterparts. Each reviewer independently assessed their allotted list of agents and assigned an antibacterial spectrum of activity and a level of novelty to each agent following the methodology below. As a final step, all assessments were discussed in the ECDC-EMA Working Group in order to resolve possible discrepancies.

The two outcome parameters considered for the assessment were the spectrum of *in vitro* activity and novelty of the agent using the approaches and definitions given below. Reviewers based their assessment on information available in the two databases as well as any information that they could find in the public domain.

In vitro activity of each agent against the selected bacteria was assigned based on the following approaches:

- Data on *in vitro* activity was reviewed whenever available. For agents belonging to a known class where actual data on *in vitro* activity was not reported, assumptions on activity were made based on the properties of the known antibiotic class or of the mechanism of action involved.
- For agents from known classes, the assessment of *in vitro* activity disregarded any known potential for cross-resistance and co-resistance with other classes.
- When assessing *in vitro* activity, individual reviewers made a judgment based on MICs regarding the potential for the agent to be clinically active against the selected bacteria. It was decided not to take into account any pharmacokinetic data or pharmacokinetic/pharmacodynamic (PK/PD) analyses when scoring the potential antibacterial activity of the agents, since the amount of available data was very variable. However, if there was already information on non-clinical or clinical efficacy, these data were factored into the assessment.
- For formulations intended for topical administration or inhalation, the assessment took into account the possibility that very high local concentrations of the antibacterial agent might be achieved.

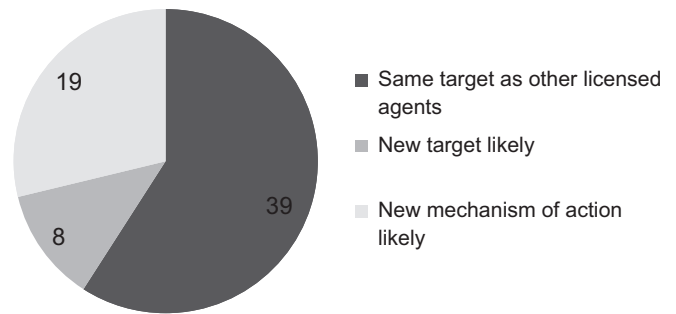


Fig. 1. Novelty of new antibacterial agents.

Novelty was rated according to the following criteria:

- Substance with a new mechanism of action known or very likely;
- Substance with a known mechanism of action that likely acts on a new target;
- Substance that acts on the same target as that of at least one previously licensed antibacterial agent.

3. Database searches

3.1. Overall findings from the database searches

In total, 167 agents were identified through search of the two selected databases and were examined by the reviewers. Only 90 of these agents were considered to fulfil the inclusion criteria for the analysis, of which 24 were new presentations of licensed antibacterial agents and 66 were new active substances.

Fig. 1 displays these 66 new active substances which, in a best-case *in vitro* activity scenario; i.e., based on actual as well as assumed *in vitro* activity based on class properties, could have activity against the selected bacteria.

3.2. Findings from the literature review

The literature search for information on antibacterial agents in development yielded 29 articles (Abbanat et al., 2008; Aliphass et al., 2006; Bishop and Howden, 2007; Boucher et al., 2009; Bush et al., 2007; Drew, 2007; Falagas and Karageorgopoulos, 2008; French, 2008; Korbila and Falagas, 2008; Kwa et al., 2008; Leeds et al., 2006; Lo et al., 2008; Lomovskaya et al., 2007; Mesaros et al., 2007; Moreillon, 2008; O'Neill, 2008; Page, 2007; Pan et al., 2008; Poulakou and Giamarellou, 2007; Projan and Bradford, 2007; Scheinfeld, 2007; Song, 2008; Talbot, 2008; Talbot et al., 2006; Theuretzbacher and Toney, 2006; Van Bambeke et al., 2007; Vergidis and Falagas, 2008; Vicente et al., 2006; Yang and Kerdel, 2006) that were considered relevant to the topic of antibacterial agents in development and were subsequently analysed. From these articles, the single additional agent that potentially fulfilled the study inclusion criteria was a novel efflux-pump inhibitor MP-601,205 (Lomovskaya et al., 2007). However, this agent does not possess any direct intrinsic antibacterial activity and, at the time of the data-lock point, no clinical study involving co-administration with an antibacterial agent had commenced. It was therefore excluded from the analysis.

3.3. Characteristics of the new active substances

Of the 66 new active substances, 30 were in Phase I of clinical development, 16 in Phase II, nine in Phase III, eight had been filed to a regulatory agency and three were reported to have been

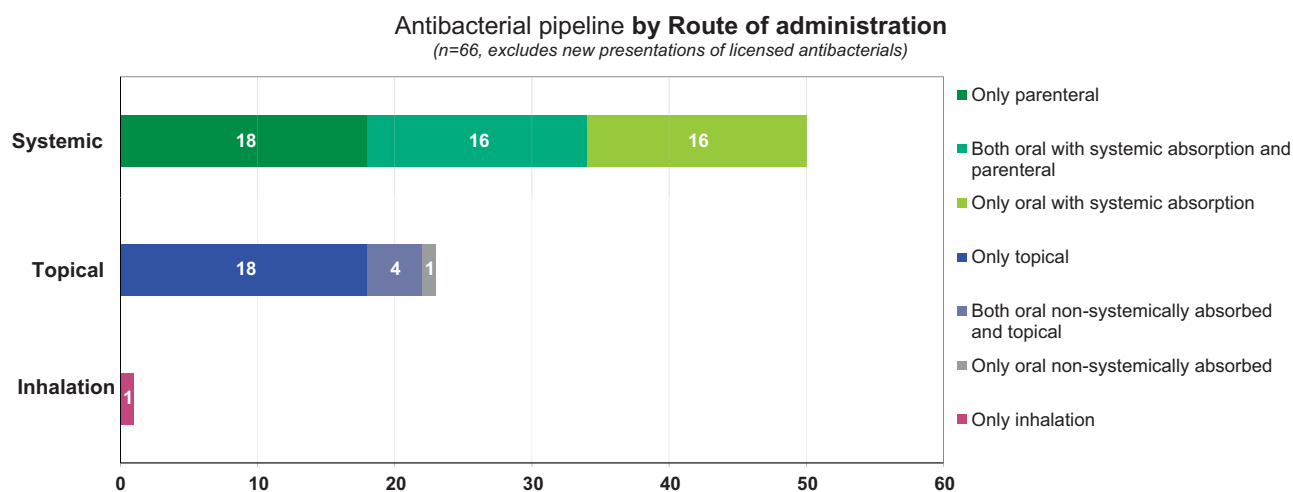


Fig. 2. Routes of administration of new antibacterial agents (n = 66, excludes new presentations of licensed antibacterials) Please note that some agents have several possible routes of administration.

suspended from further development. An analysis by route of administration (Fig. 2) showed that, at the time of the search, 50 of these 66 new active substances were formulated for systemic administration (16 for oral, 18 for parenteral, and the remainder for either oral or parenteral administration).

Twenty-seven of these 66 new active substances were assessed as having either a new mechanism of action or a new target. The remaining 39 agents belonged to known antibacterial classes or groups, i.e., quinolone (15), β -lactam (6 agents), oxazolidinone (3), diaminopyrimidine (2), macrolide (2), pleuromutilin (2), aminoglycoside (1), ansamycin (1), FabI inhibitor (1), glycopeptide (1), metallic ion (1), streptogramin (1), tetracycline (1) and hybrid (oxazolidinone/quinolone and rifamycin/fluoroquinolone) (2). They were thus assessed as acting on the same target as that of at least one previously licensed anti-bacterial agent, and hence not considered for the remainder of this analysis.

Of the 27 new active substances assessed as having a new mechanism of action or a new target, there were 15 agents which could be systemically administered (Table 1, Fig. 3) and thus considered potentially useful for the treatment of serious invasive infections. Of these 15 systemically administered agents, 13 were judged to have activity against at least one of the selected antibiotic-resistant Gram-positive bacteria and eight against at least one of the selected antibiotic-resistant Gram-negative bacteria. Among

antibiotic-resistant Gram-positive bacteria, MRSA was the most often covered by these agents (13 out of 15) and VRE the least covered (5 out of 15). Of the eight agents with activity against antibiotic-resistant Gram-negative bacteria, four had an activity based on actual data and four had assumed activity based on known class properties or mechanisms of action. Of the four agents with activity against antibiotic-resistant Gram-negative bacteria based on actual data, two acted on new or possibly new targets and none via new mechanisms of action.

Table 1 presents the individual characteristics of all 15 antibacterial agents in Fig. 3. Out of these 15 agents, only seven had a new mechanism of action, of which six were antibacterial peptides or proteins as indicated in Fig. 3.

4. Discussion

This study is believed to be the first review to compile publicly available information from commercial databases on antibacterial agents in clinical development and evaluate their novelty and potential use against antibiotic-resistant bacteria of public health interest.

We limited our study to agents in clinical development because these agents are the most likely to reach market within the next 5–10 years. A decision was made to take an optimistic approach to

Table 1

New systemic antibacterial agents with new target or new mechanism of action and *in vitro* activity based on actual data or assumed based on known class properties or mechanisms of action against the selected bacteria (n = 15, as of 14 March 2008).

Name of agent	Mechanism of action (MoA)	Degree of novelty	Route of administration ^a
WAP 8294A2 ^b	Membrane integrity antagonist	New MoA	IV, Top
PZ-601	Cell wall synthesis inhibitor	New target	IV
ME 1036	Cell wall synthesis inhibitor	New target	IV
NXL 101	DNA gyrase inhibitor/DNA topoisomerase inhibitor	New MoA	IV, PO
Friulimicin B ^b	Cell wall synthesis inhibitor	New MoA	IV
Oritavancin	Cell wall synthesis inhibitor/Membrane integrity antagonist	New target	IV, PO
Telavancin	Cell wall synthesis inhibitor/Membrane integrity antagonist	New target	IV
Ceftobiprole medocaril	Cell wall synthesis inhibitor	New target	IV
Ceftaroline fosamil	Cell wall synthesis inhibitor	New target	IV
Tomopenem	Cell wall synthesis inhibitor	New target	IV
hLF1-11 ^b	Chelating agent/immunomodulation	New MoA	IV, PO
Lactoferrin ^b	Chelating agent/immunomodulation	New MoA	IV, PO
Talactoferrin-alfa ^{b,c}	Chelating agent/immunomodulation	New MoA	PO, Top
Opebacan ^{b,c}	Membrane permeability enhancer/immunomodulation	New MoA	IV
NXL104/ceftazidime	β -Lactamase inhibitor + cell-wall synthesis inhibitor	New target	IV

^a Information on routes of administration is uncertain in early drug development. IV, intravenous; PO, oral; Top, topical.

^b Antibacterial substance of peptidic nature with a new mechanism of action known or very likely.

^c Agents with only assumed *in vitro* activity.

Name of agent	Gram-positive bacteria				Gram-negative bacteria			Phase of development
	MRSA	VISA/VRSA	PRSP	VRE	3 rd Gen Cep. R ENB	Carb. R ENB	Carb. R NF GNB	
WAP 8294A2 ^P	●							I
PZ-601 [*]	●	●	●	●	●			I
ME 1036 [*]	●	●	●		●			I
NXL 101	●	●	●	●				I
Friulimicin B ^P	●	●	●	●				I
Oritavancin	●	●	●	●				Filed
Telavancin	●	●	●	●				Filed
Ceftobiprole medocartil [†]	●	●	●					Filed
Ceftaroline fosamil [‡]	●	●	●					III
Tomopenem [‡]	●	●	●		●	●	●	II
hLFI-11 ^P	●	●			●	●	●	II
Lactoferrin ^P	●	●			●	●	●	I
Talactoferrin-alfa ^P	●	●			●	●	●	II
Opebacan ^P					●	●	●	III
NXL 104/ceftazidime [§]					●	●	●	I
	●	12	10	9	5	4	2	2
	●	1	2	0	0	4	4	4
Total		13	12	9	5	8	6	6

Fig. 3. New systemic antibacterial agents with new target or new mechanism of action and *in vitro* activity against selected bacteria based on actual data or assumed *in vitro* activity. ●, Activity based on actual data. ●, Assumed activity based on known class properties or mechanisms of action. 3rd Gen Cep. R ENB: third-generation cephalosporin-resistant *Enterobacteriaceae*; Carb. R ENB: carbapenem-resistant *Enterobacteriaceae*; Carb. R NF GNB: carbapenem-resistant non-fermentative Gram-negative bacilli. *Are no more active than earlier carbapenems against Gram-negative bacteria. The relative novelty of these agents was based on a better profile of activity against antibiotic-resistant Gram-positive bacteria. †Reported MRSA activity suggests a different binding profile to PBPs than currently licensed cephalosporins. ‡Reported activity against bacteria resistant to earlier carbapenems might not actually represent a different target range but could be due only to evasion of resistance mechanisms by the new agent. §Ceftazidime is a licensed cephalosporin. Only the β -lactamase inhibitor NXL 104 displays additional enzyme inhibition resulting in a broader range of activity than earlier agents. ^PAntibacterial substance of peptidic nature with a new mechanism of action known or very likely. Phase of development refers to the highest phase of development, regardless of indication. Total represents the number of agents active against each of the selected bacteria in a best-case scenario.

the identification of agents potentially active against the selected panel of antibiotic-resistant bacteria. For example, when the combined dataset was built, the possibilities of cross- and co-resistance were not taken into account during the assessment. Furthermore, in the absence of *in vitro* susceptibility data, assumptions on *in vitro* activity based on class properties were made.

Most of the agents identified using this optimistic approach were under development for invasive infections caused by antibiotic-resistant Gram-positive bacteria, especially against MRSA. Only eight agents had potential activity against antibiotic-resistant Gram-negative bacteria and only four based on actual data. Among these four agents, only two acted on new or possibly new targets and none via new mechanisms of action. The lack of novelty among these agents illustrates the current paucity of development of agents active against multi-resistant Gram-negative bacteria. This reflects the difficulties encountered in identifying new bacterial targets and the possibility that the majority of targets amenable to antibacterial activity have already been identified (Payne et al., 2007). Other reports have painted a more optimistic picture of the future availability of new antibacterial agents (Theuretzbacher, 2009; Wong, 2005). However, these reports do not particularly focus on the development of agents against multidrug-resistant bacteria as is the case in this study.

Overall, our findings corroborate earlier reports on the lack of antibacterial drug development to tackle multi-drug resistance (Spellberg et al., 2004; White, 2005), including those from the Infectious Diseases Society of America (IDSA) (Boucher et al., 2009; Talbot et al., 2006). Spellberg et al. (2004) evaluated the research

and development programs from the 15 major pharmaceutical companies and the seven major biotechnology companies. The commercial databases used in the present analysis also cover the many firms involved in pharmaceutical research and development that are not among the largest, as well as all the supplementary sources that were used in the IDSA studies. In addition, these databases include information from the specialised literature and information directly available from companies. Furthermore, our study took into account all investigational agents in clinical development, i.e., Phases I–III, or for which an application had already been filed to at least one national regulatory agency, whereas the IDSA studies were limited to Phases II and III.

Our study has some limitations. It could be argued that there are many agents in pre-clinical development that may have an activity against multi-drug resistant bacteria. However, there is little data for assessment of compounds in pre-clinical development and these compounds have a high attrition rate. Moreover, it should be noted that the databases that we used did not include information on agents that were, so far, under development only by academic groups. This study describes the situation at the data-lock point of 14 March 2008. Obviously, new compounds have since entered clinical development and been included in the databases while others have been discontinued. We are also aware that, occasionally, information on compounds is only made available in the public domain at a late stage of development.

Multidrug-resistant Gram-negative bacteria represent a major challenge for the future (Boucher et al., 2009). The lack of agents that could be administered systematically and with activity against Gram-negative bacteria displaying new mechanisms of action as

found in this study is of particular concern, especially if the high attrition rates for agents in early stages of clinical development (Payne et al., 2007) are taken into consideration. In fact, it is unclear if any of the agents identified in this study will ever reach the market. Even if a public health driven approach for research and development of antibacterial agents starts in the near future, the burden of antibiotic resistance is likely to continue to increase. Therefore, a European and global strategy to address this serious problem is urgently needed, and measures that spur new antibacterial drug development need to be put in place.

As early as 2004, a report from the World Health Organization on “Priority Medicines for Europe and the World” identified infections caused by resistant bacteria as the number one therapeutic area requiring priority medicines based on the potential public health impact (Kaplan and Laing, 2004). In 2003 and 2005, two EU conferences addressed the role of research and of actions to promote new technologies to fight antibiotic resistance (Cornaglia et al., 2004; Finch and Hunter, 2006). The need for involvement of the public sector into research and development of new antibiotics has been pointed out by both the international network ReAct – Action on Antibiotic Resistance (Tickell, 2005) and the European Academies Science Advisory Council (EASAC, 2007). Our study sends another clear message that the present antibiotic pipeline will not meet the public health needs. The results of this study were presented at the conference “Innovative incentives for effective antibacterials” held in Stockholm during the Swedish Presidency of the EU on 17 September 2009 (Swedish Government, 2009). At the conference, a review of possible regulatory, financial and other incentives to stimulate research and development of new antibiotics was presented (Morel and Mossialos, 2010). In response to the call for action on the urgent need for novel antibiotics, the European Health Council called upon the EU Commission in December 2009 during the Swedish Presidency, to develop a comprehensive action-plan on antibiotic resistance, including concrete proposals concerning incentives to develop new effective antibiotics. This action-plan is to be presented in November 2011. Moreover, a Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was established in November 2009. The goal of the TATFAR is to increase the mutual understanding of EU and US activities and programs on antimicrobial issues, deepen the transatlantic dialogue, provide opportunities to learn from each other, and promote information exchange, coordination and co-operation between the EU and the US. One of the focus areas for the TATFAR is to identify strategies for improving the pipeline of new antimicrobial drugs, diagnostic procedures and techniques, and maintaining existing drugs on the market. The TATFAR aims to conclude its work by March 2011. Incentives to stimulate research and development of novel antibiotics were further discussed at the Conference “the Global Need for Effective Antibiotics-moving towards concerted action” held in Uppsala Sweden, September 2010 (So et al., 2011).

Conflict of interest

All authors, members of the working group and reviewers of agents in the database have declared potential conflict of interest to the EMA. Declarations of interests can be obtained upon request.

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