



TECHNICAL REPORT

The bacterial challenge: time to react

A call to narrow the gap between
multidrug-resistant bacteria in the EU and
the development of new antibacterial agents

ECDC/EMA JOINT TECHNICAL REPORT

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ECDC/EMEA Joint Working Group

The Mandate (full document in Annex A):

'The ECDC/EMEA Joint Working Group is agreed by the ECDC and the EMEA to oversee and to facilitate, follow-up and be part of the work aimed at producing a report on the gap between the increasing prevalence of multidrug resistant bacteria and antibacterial drug development aimed at treating such infections.'

- The Working Group was given this task on 28 February 2008.
- The Working Group included two members nominated by the Committee for Medicinal Products for Human Use (CHMP) and Paediatric Committee (PDCO) at the European Medicines Agency (EMA), respectively; two members from the Advisory Forum at the European Centre for Disease Prevention and Control (ECDC), and a member of staff from the EMA and the ECDC, respectively. In addition, two co-opted independent experts, including one member from 'Action on Antibiotic Resistance' (ReAct), were selected for their clinical/microbiological expertise in the fields of interest.
- The EMA/CHMP adopted the Technical Report at its meeting on 23 July 2009 and again circulated for information on 20 August 2009. The draft report was presented to the ECDC Advisory Forum on 13 May 2009 and input from the Advisory Forum on the final report was sought through a written procedure on 20 August 2009.

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Declarations of interest: Declarations of interest for members of the working group and external reviewers are available from EMA upon request.

In this report, the terms 'antibiotics' and 'antibacterial agents' have been used interchangeably.

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Abbreviations and acronyms

AMR	Antimicrobial resistance
CHMP	Committee for Medicinal Products for Human Use at EMEA
DG ENTR	Directorate-General for Enterprise and Industry
DG RTD	Research Directorate-General
DG SANCO	Directorate-General for Health and Consumers
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
ENB	<i>Enterobacteriaceae</i>
EphMRA	European Pharmaceutical Market Research Association
ESBL	Extended-spectrum beta-lactamase
ESCMID	European Society for Clinical Microbiology and Infectious Diseases
EU	European Union
GNB	Gram-negative bacilli
IDSA	Infectious Diseases Society of America
IV	Intravenously
MESH	Medical Subject Headings
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
PBP	Penicillin-binding protein
PDCO	Paediatric Committee at EMEA
PO	Per os, by mouth
PRSP	Penicillin-resistant <i>Streptococcus pneumoniae</i>
ReAct	Action on Antibiotic Resistance
VISA	Vancomycin-intermediate <i>Staphylococcus aureus</i>
VRSA	Vancomycin-resistant <i>Staphylococcus aureus</i>
WHO	World Health Organization

Foreword

The introduction of antibacterial agents (commonly referred to as antibiotics) led to a revolution in the management of bacterial infections. Today, emerging and increasing resistance to antibiotics has become a threat to public health in Europe and globally. Only 70 years after their introduction, we are now facing the possibility of a future without effective antibiotics for several types of bacteria that cause infections in humans.

In 2001, the European Commission presented its 'Community Strategy against Antimicrobial Resistance'. It proposed 15 actions in the areas of surveillance, prevention, international cooperation and research and development of new antibacterial agents. Later in the same year, European Union (EU) Health Ministers adopted a Council Recommendation on the prudent use of antimicrobial agents in human medicine¹.

While surveillance of resistance, infection control measures and strategies to prevent the occurrence of infections are central to combating antibacterial resistance trends, patients still get infected and there is a particular lack of antibacterial agents to treat infections caused by bacteria that are resistant to many of the available treatments (i.e. multidrug-resistant bacteria).

In 2004, a report from the World Health Organization on 'Priority Medicines for Europe and the World'² identified infections caused by resistant bacteria as the number one disease requiring priority medicines based on the potential public health impact if effective new antibiotics were not developed. The report suggested that Europe should play a global leadership role in this area.

In 2007, the European Centre for Disease Prevention and Control (ECDC), the European Medicines Agency (EMA) and the international network Action on Antibiotic Resistance (ReAct) entered into a discussion on the need to produce a report that reviewed and documented the gap between infections caused by multidrug-resistant bacteria in the EU and the development of new antibiotics to treat them. An ECDC/EMA Joint Working Group was established in 2008 to prepare this report.

The objective of this report is to give an account of facts and figures that would allow reasonable predictions of the gap between bacterial resistance in the EU and the likely availability of new treatments that would be effective against multidrug-resistant bacteria in the near future. As such, this technical report is made available to the European Commission, and particularly to DG SANCO, DG ENTR and DG RTD, for consideration. The report will also serve as a basis for discussions at the expert conference on 'Innovative Incentives for Effective Antibacterials' scheduled for 17 September 2009, as part of the Swedish EU Presidency.

We note with satisfaction the timely availability of the final report endorsed by the main scientific Committees in the two agencies and would like to thank the working group for its achievement.

Zsuzsanna Jakab, ECDC Director

Thomas Lönngren, EMA Executive Director

¹ Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine (2002/77/EC). Available from: http://antibiotic.ecdc.europa.eu/PDFs/I_03420020205en00130016.pdf

² http://whqlibdoc.who.int/HQ/2004/WHO_EDM_PAR_2004.7.pdf

Executive summary

Main findings:

There is a gap between the burden of infections due to multidrug-resistant bacteria and the development of new antibiotics to tackle the problem.

- Resistance to antibiotics is high among Gram-positive and Gram-negative bacteria that cause serious infections in humans and reaches 25% or more in several EU Member States.
- Resistance is increasing in the EU among certain Gram-negative bacteria such as recently observed for *Escherichia coli*.
- Each year, about 25 000 patients die in the EU from an infection with the selected multidrug-resistant bacteria.
- Infections due to these selected multidrug-resistant bacteria in the EU result in extra healthcare costs and productivity losses of at least EUR 1.5 billion each year.
- Fifteen systemically administered antibacterial agents with a new mechanism of action or directed against a new bacterial target were identified as being under development with a potential to meet the challenge of multidrug resistance. Most of these were in early phases of development and were primarily developed against bacteria for which treatment options are already available.
- There is a particular lack of new agents with new targets or mechanisms of action against multidrug-resistant Gram-negative bacteria. Two such agents with new or possibly new targets and documented activity were identified, both in early phases of development.
- A European and global strategy to address this gap is urgently needed.

In 2007, the European Centre for Disease Prevention and Control (ECDC), the European Medicines Agency (EMA) and the international network Action on Antibiotic Resistance (ReAct) entered into a discussion on the need to document the gap between the frequency of multidrug-resistant bacterial infections in the EU and the development of new antibiotics. As a result, an ECDC/EMA Joint Working Group was established in 2008 to give an account of facts and figures that would allow reasonable predictions of the extent of the gap in the coming years.

The following antibiotic-resistant bacteria were selected because they frequently are responsible for bloodstream infections and because the associated antibiotic resistance trait is, in most cases, a marker for multiple resistance to antibiotics:

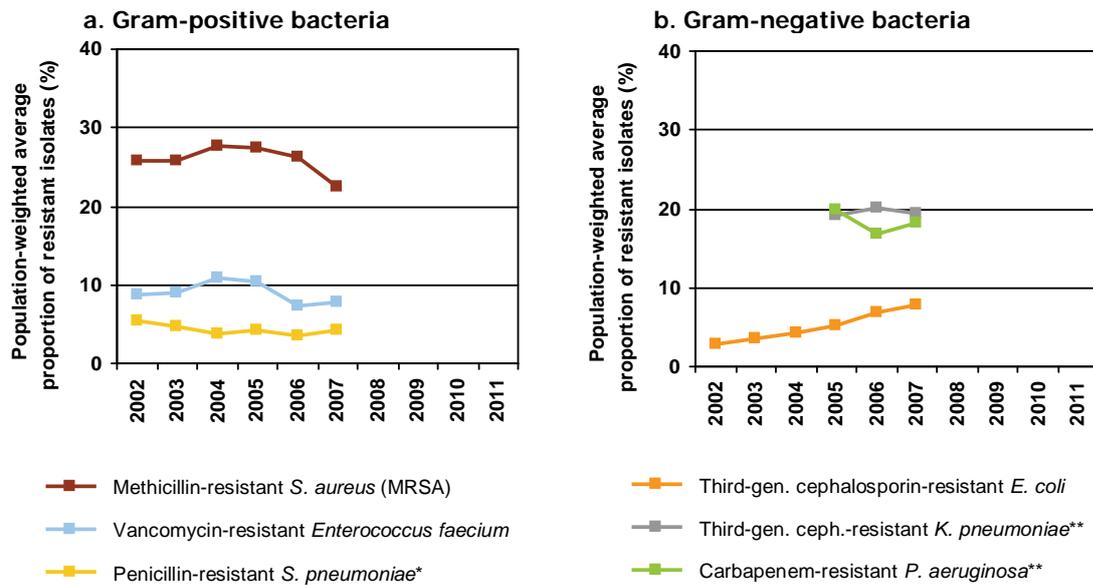
- *Staphylococcus aureus*, methicillin resistance (MRSA);
- *S. aureus*, vancomycin intermediate resistance and vancomycin resistance (VISA/VRSA);
- *Enterococcus* spp. (e.g. *Enterococcus faecium*), vancomycin resistance (VRE);
- *Streptococcus pneumoniae*, penicillin resistance (PRSP);
- *Enterobacteriaceae* (e.g. *Escherichia coli*, *Klebsiella pneumoniae*), third-generation cephalosporin resistance;
- *Enterobacteriaceae* (e.g. *K. pneumoniae*), carbapenem resistance; and
- Non-fermentative Gram-negative bacteria (e.g. *Pseudomonas aeruginosa*), carbapenem resistance.

Trends and burden of infections due to multidrug-resistant bacteria in the EU

Data on these selected antibiotic-resistant bacteria in invasive infections (mainly bloodstream infections) were available from the European Antimicrobial Resistance Surveillance System (EARSS) for EU Member States, Iceland and Norway for each year during the period 2002–2007.

The trends in the proportion of antibiotic-resistant isolates among blood isolates of the selected bacteria frequently responsible for bloodstream infections in Europe are shown in Figure E1.

Figure E1. Population-weighted, average proportion of resistant isolates among blood isolates of bacteria frequently responsible for bloodstream infections, EU Member States, Iceland and Norway, 2002–2007.



* *S. pneumoniae*: excluding Greece, which did not report data on this bacterium to EARSS.

** *K. pneumoniae* and *P. aeruginosa*: excluding Belgium and Slovakia, which did not report data on these bacteria to EARSS.

In 2007, the average proportion of *Staphylococcus aureus* blood isolates that showed resistance to methicillin (% MRSA) was the highest proportion of antibiotic-resistant isolates among the selected bacteria frequently responsible for bloodstream infections in the European Union. However, this proportion has been decreasing in recent years (Figure E1). This is due to decreasing MRSA trends in several Member States, likely due to action plans at national level as documented for France, Slovenia and United Kingdom. The average proportion of MRSA has reached a level close to that of the selected antibiotic-resistant Gram-negative bacteria.

The proportion of *S. aureus* blood isolates that showed intermediate resistance to vancomycin (VISA) was very low (less than 0.1%) in EU Member States, Iceland and Norway. No vancomycin-resistant *S. aureus* isolates were reported to EARSS in 2007 (data not presented on Figure E1).

In contrast, the average proportion of *Escherichia coli* – the most common Gram-negative bacteria responsible for infections in humans – blood isolates showing resistance to third-generation cephalosporins has been rising steadily.

At the same time, there is no sign of decreasing resistance to third-generation cephalosporins in *Klebsiella pneumoniae* or to carbapenems in *Pseudomonas aeruginosa* (Figure E1).

In 2007, the proportion of *K. pneumoniae* blood isolates from EU Member States, Iceland and Norway that showed resistance to carbapenems was, in general, very low (median=0%) with the exception of Greece, where it reached 42% (data not presented on Figure E1).

The human and economic burden of antibiotic-resistant bacteria could only be estimated for the following five antibiotic-resistant bacteria: MRSA, vancomycin-resistant *Enterococcus faecium*, third-generation cephalosporin-resistant *E. coli* and *K. pneumoniae* and carbapenem-resistant *P. aeruginosa*.

The study confirmed that MRSA was the most common, single, multidrug-resistant bacterium in the European Union. However, the sum of cases of common, antibiotic-resistant Gram-positive bacteria (mostly MRSA and vancomycin-resistant *Enterococcus faecium*) was comparable to that of common, antibiotic-resistant Gram-negative bacteria (third-generation cephalosporin-resistant *E. coli* and *K. pneumoniae*, and carbapenem-resistant *P. aeruginosa*).

Overall, it was estimated that in 2007 approximately 25 000 patients died from an infection due to any of the selected five antibiotic-resistant bacteria in the European Union, Iceland and Norway. In addition, infections due to any of the selected antibiotic-resistant bacteria resulted in approximately 2.5 million extra hospital days and extra in-hospital costs of more than EUR 900 million.

Subsequently, an estimate was made of loss of productivity due to these infections. Based on 2007 data, outpatient care costs were estimated at about EUR 10 million and productivity losses due to absence from work of infected patients were estimated at more than EUR 150 million, each year. Productivity losses due to patients who died from their infection were estimated at about EUR 450 million each year. Overall, societal costs of infections due to the selected antibiotic-resistant bacteria were estimated at about EUR 1.5 billion each year.

There are many reasons (e.g. limited range of included bacteria, outpatient infections not being considered, average cost of hospital care which does not take into account special patient care such as intensive care) to support a conclusion that these figures correspond to an underestimate of the human and economic burden of infections due to antibiotic-resistant bacteria.

Research and development pipeline of antibacterial agents

In order to assess the state of the antibacterial drug development pipeline, two commercial databases (Adis Insight R&D and Pharmaprojects) were queried for antibacterial agents in clinical development worldwide. It was decided not to perform an in-depth exploration of agents that had not yet reached clinical trials due to the high attrition rate during preclinical testing and the scarcity of data available for review.

Whenever possible, agents identified by the search were assessed for their antibacterial activity against the selected bacteria based on actual data available in the databases or in the literature. In the absence of actual *in vitro* data, reviewers also took into account reasonable assumptions of the activity of some agents based on the properties of similar agents (i.e. of the same class or with a common mechanism of action) in order to construct a 'best-case scenario'.

Additionally, for each agent, reviewers were requested to indicate whether it was of a new class or belonged to an existing class of antibiotics and to indicate whether it:

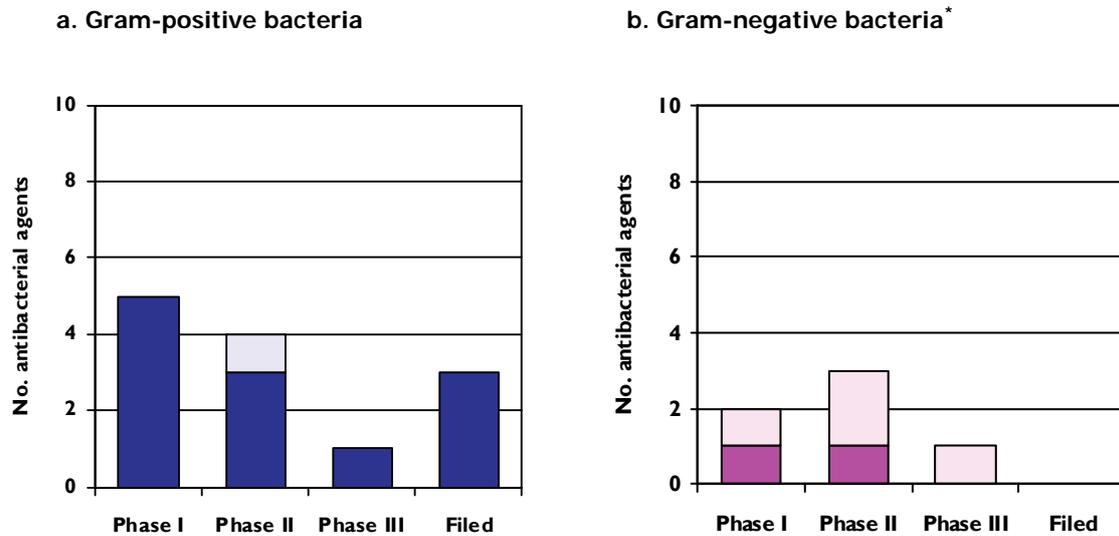
- acted on the same target and in the same way as that of at least one previously licensed antibacterial agent;
- acted through a known mechanism of action on a new target; or
- acted through a new mechanism of action.

The main results from this analysis were as follows:

- Of 167 agents identified by the searches, there were 90 antibacterial agents with *in vitro* activity in a best-case scenario (based on actual data or assumed based on class properties of mechanism of action) against at least one organism in the panel of bacteria selected for their public health importance.
- Of these 90 agents, 24 were new presentations of licensed antibacterial agents and 66 were new active substances.
- Of the 66 new active agents, only 27 were assessed as having either a new target or a new mechanism of action, thus potentially offering a benefit over existing antibiotics.
- Of these 27 agents, there were 15 that could be systemically administered.
- Of the 15 agents with systemic administration, eight were judged to have activity against at least one of the selected Gram-negative bacteria.
- Of the eight with activity against Gram-negative bacteria, four had activity based on actual data and four had assumed activity based on known class properties or mechanisms of action.
- Of the four with activity against Gram-negative bacteria based on actual data, two acted on new or possibly new targets and none via new mechanisms of action.

Figure E2 shows the information on these 15 antibacterial agents. Notably, only five of these agents had progressed to clinical trials to confirm clinical efficacy (Phase 3 or later of clinical development).

Figure E2. New systemic antibacterial agents with a new target or new mechanism of action and *in vitro* activity based on actual data (dark colour bars) or assumed *in vitro* activity based on class properties or mechanisms of action (light colour bars) against the selected bacteria (best-case scenario), by phase of development (n=15).



Note: *In vitro* activity based on actual data is depicted at the bottom of each column in darker colour. Assumed *in vitro* activity based on class properties or mechanisms of action (where applicable) is depicted in a lighter colour at the top of each column.

* Two carbapenems have been omitted from Figure E2b since they 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 and are therefore included in Figure E2a.

The burden of bacterial resistance in the EU is already substantial and is likely to increase. Based on current data, it is expected that particular problems will arise in the coming years due to resistance among Gram-negative bacteria.

At the same time, there are very few antibacterial agents with new mechanisms of action under development to meet the challenge of multidrug resistance. There is a particular lack of new agents to treat infections due to multidrug-resistant Gram-negative bacteria.

This report has identified a gap between the burden of infections due to multidrug-resistant bacteria and the development of new antibacterial agents to tackle the problem. A European and global strategy to address the gap is urgently needed. Measures that spur drug development need to be put in place.

1 Introduction

1.1 Multidrug resistant bacteria: an increasing concern

1.1.1 What is antibacterial resistance?

Antibacterial agents inhibit the growth of bacteria and may rapidly kill them by disrupting one or more of their essential cellular functions. For example, depending on the type of antibacterial agent, the mechanism of activity may result in:

- inhibition of the production of proteins or cell wall materials;
- inhibition of DNA replication;
- disruption of cell membrane activities that maintain chemical balance.

Bacteria are usually grouped according to various attributes such as the structure of their outer coverings and their metabolic functions. The primary classification of bacteria is based on their staining properties, which, for almost all types of bacteria, divides them into Gram-positive or Gram-negative groups. Those called Gram-positive have a cell membrane plus a thick layer of cell wall material (peptidoglycan) lying outside the membrane. In contrast, Gram-negative bacteria have a cell membrane, a relatively thin layer of peptidoglycan and then an outer membrane. These major structural differences result in different patterns of susceptibility to antibacterial agents because the outer coverings of the bacteria affect access to the sites where they exert their activity. Therefore, each group of bacteria is usually susceptible to the actions of only a limited range of antibacterial agents and show inherent (i.e. normal) resistance to the actions of others.

Moreover, bacteria have the ability to acquire resistance to one or more antibacterial agents to which they would normally be susceptible. Acquired resistance can arise by mutations that can occur during replication or by gaining genes encoding a mechanism of resistance from other bacteria [1]. The ease with which resistance can be acquired varies between bacterial types. Unfortunately, some of the types of bacteria that are normally not susceptible to many antibacterial agents are also easily able to acquire resistance to others. The result is multidrug resistance. In extreme cases, bacteria can show resistance to most or all of the agents that would commonly be used to treat them.

In addition, each acquired mechanism of resistance may render the bacterium resistant to many or all antibacterial agents of the same type (class) and sometimes confers resistance to agents from many classes. This is called cross-resistance. The genes encoding some mechanisms of resistance are sometimes linked in such a way that they are transferred all together between organisms. This is often referred to as co-resistance.

Each time an antibacterial agent is used to treat an infection, there is a risk that the agent will select, in the population of infecting bacteria, for bacteria that are resistant to it, thus causing unresolved infection in the patient who was treated. The agent will also select for resistant bacteria in the patient's commensal flora, thus resulting in colonisation by resistant bacteria, which may subsequently be responsible for another infection at the same or another body site. In both cases, these resistant bacteria will have the possibility to spread to other patients, especially within hospitals. Thus, increasing rates of resistance to an antibacterial agent and to all other agents that are rendered inactive by common mechanisms of resistance is an inevitable consequence of its use. In the last 10–20 years, multidrug resistance has emerged in many frequently encountered pathogenic bacteria. In extreme cases, these bacteria are not susceptible to any licensed antibacterial agent or are susceptible only to those that are more toxic to the patient than the more commonly used drugs.

1.1.2 What are the consequences of resistance and multidrug resistance?

Multidrug-resistant bacteria represent a major threat to the success of almost all branches of medical practice. Some patients are especially vulnerable to acquiring multidrug-resistant bacterial infections as a consequence of treatments for underlying illnesses, such as organ transplant patients, haemodialysis patients and those with various types of cancer [2-7].

Bacterial resistance potentially complicates the management of every infection, no matter how mild it may be at the time of first presentation. For example, bladder infections in young women should be very easy to treat with commonly used antibacterial agents but the appearance of multidrug resistance among organisms often associated with these infections means that physicians have to resort to other agents that may not be so well tolerated and may even have to be given intravenously when usually oral agents are efficient.

Physicians in the EU are increasingly faced with infections for which antibacterial treatment options are very limited. However, the overall burden of infections caused by multidrug-resistant bacteria is not well documented in the EU. There is a lack of data on the morbidity and mortality attributable to antibacterial resistance, including the economic impact on individuals as well as on healthcare systems and societies.

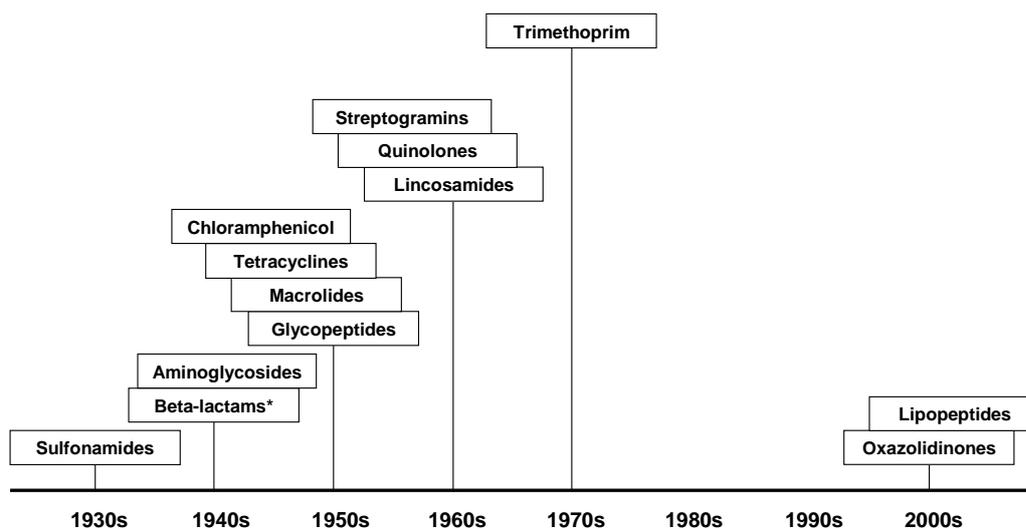
Multidrug resistance among bacteria is a global problem and organisms are easily carried across international boundaries. All regions of the world [8] are already experiencing the effects of multidrug resistance on clinical practise. Therefore, stimulating the development of new antibiotics has far-reaching potential benefits.

1.1.3 Antibacterial resistance and the response from the pharmaceutical industry

The launch of every antibiotic has been and will be followed by resistance in the targeted bacteria. Therefore, there is a constant need to develop new agents to keep up with the acquisition of resistance among pathogenic bacteria.

For approximately four decades (from the 1940s up to the 1970s) the pharmaceutical industry provided a steady flow of new antibiotics, including several with new mechanisms of action that circumvented the problems caused by bacterial resistance to earlier agents. Since then, only three systemically-administered antibiotics (quinupristin-dalfopristin, linezolid and daptomycin), including two from new classes (oxazolidinones and lipopeptides,) have been marketed in the EU to treat infections caused by multidrug-resistant Gram-positive bacteria. The other systemically-administered antibiotics that have reached the EU market during this period belong to existing classes of antibiotics and are not efficacious against the majority of organisms already resistant to other agents in the same class.

Figure 1. Discovery of new classes of antibiotics.



Source: [4, 9-10]

* Penicillins were the first beta-lactams. Other frequently used agents of the beta-lactam class include cephalosporins and carbapenems, developed in the 1960s and 1980s, respectively.

Meanwhile, multidrug resistance among Gram-negative bacteria has been increasing relentlessly. International and local surveillance networks such as the European Antimicrobial Resistance Surveillance System (EARSS)³, as well as numerous reports in the literature [11-13] provide evidence that the frequency of infections caused by multidrug-resistant Gram-negative bacteria is escalating in many countries. In some Gram-negative bacteria, acquired resistance to three or more classes of antibiotics that are commonly used to treat infections is often reported [14]. Therefore, there is particular concern regarding the paucity of new agents with activity against Gram-negative bacteria that have reached the market in the last decade. Those that have been marketed do not show efficacy against Gram-negative bacteria with resistance to most or all beta-lactam drugs.

³ http://www.rivm.nl/earss/result/Monitoring_reports/

1.2 Time to react

The growing gap between the increasing frequency of infections caused by multidrug-resistant bacteria and the decline in research and development of new antibiotics is now threatening to take us back to the pre-antibiotic era. Strategies to curtail the spread of multidrug-resistant bacteria have met with limited success. While effective implementation of these strategies may reduce the rate of increase in infections caused by multidrug-resistant bacteria, a reversal of the existing problems cannot be expected. The continued development of effective antibiotics must be considered as a 'common good' [15-16]. An analysis of the antibacterial agents currently under development in view of current resistance patterns and trends is a starting point for discussing incentives for the development of urgently needed new treatments.

1.3 The response from ECDC and EMEA

One of the aims of the EMEA Road Map 2010 is to foster research and innovation in the pharmaceutical industry across the European Union. In this context, an 'EMEA/CHMP think-tank group on innovative drug development' was set up in 2006. The purpose was to offer stakeholders the possibility to present and discuss informally their views on evolving strategies in drug development. The report from the think-tank⁴ describes the technical and scientific highlights of all these consultations, incorporates reflections and draws recommendations from the think-tank group. In this process, the paucity of new antibacterial agents, which has been the subject of several reports, including the *Antibiotic Innovation Study*⁵ from the international network Action on Antibiotic Resistance (ReAct) in 2005, attracted considerable attention. During this EMEA/CHMP think-tank discussion with industry and academia, the idea of an analysis of the gap between the frequency of infections caused by multidrug-resistant bacteria in the EU and the development of new antibiotics was raised.

ECDC was established in 2005 with the mission to identify, assess and communicate current and emerging threats to human health posed by infectious diseases. In its first Annual Epidemiological Report, published in 2007⁶, ECDC identified antimicrobial resistance as one of the most serious public health problems, globally and in Europe. Antimicrobial resistance, together with healthcare-associated infections, was consequently selected as one of the priority work areas in the *ECDC Strategic Multi-annual Programme 2007–2013*⁷ with the objective of significantly contributing to the scientific knowledge base on antimicrobial resistance and its health consequences, its underlying determinants, the methods for its prevention and control, and the design characteristics that enhance effectiveness and efficiency of its prevention and control programmes.

In 2007, ECDC, EMEA and ReAct entered into a discussion on the need to provide a comprehensive technical report to the European Commission on the pipeline of antibacterial medicinal products in development. In particular, to describe the frequency, trends and burden of disease associated with multidrug-resistant bacteria in the European Union and to assess the pipeline of new agents in development that might have clinically useful activity against them. Production of a joint report was included as a priority project for 2008 and 2009 in the ECDC's programme on antimicrobial resistance and healthcare-associated infections and for EMEA. The assessment of the pipeline of antibacterial drug development was performed in co-operation with ReAct and was conducted under a memorandum of understanding between Duke University, EMEA and ReAct.

An ECDC-EMEA joint working group was established in 2008 with a mandate to produce the joint report. The mandate, composition, meetings, roles and responsibilities of the joint working group are presented in Annex A and its detailed composition is shown on the verso of the title page.

⁴ <http://www.emea.europa.eu/pdfs/human/itf/12731807en.pdf>

⁵ http://soapimg.icecube.snowfall.se/stopresistance/Innovation_report.pdf

⁶ http://ecdc.europa.eu/en/publications/Publications/0706_SUR_Annual_Epidemiological_Report_2007.pdf

⁷ http://ecdc.europa.eu/en/aboutus/Key%20Documents/07-13_KD_Strategic_multiannual_programme.pdf

2 Trends and burden of infections due to multidrug-resistant bacteria in the EU

Most relevant findings:

- Resistance to antibiotics is high among Gram-positive and Gram-negative bacteria that cause serious infections in humans and reaches 25% or more in several EU Member States.
- Resistance is increasing in the EU among certain Gram-negative bacteria such as recently observed for *Escherichia coli*.
- Each year, about 25 000 patients die in the EU from an infection with the selected multidrug-resistant bacteria.
- Infections due to these selected multidrug-resistant bacteria in the EU result in extra healthcare costs and productivity losses of at least EUR 1.5 billion each year.

2.1 Introduction

Antibiotic resistance is not by itself a disease entity. It encompasses many types of infections, bacteria and antibiotic resistance traits. Although the global nature of the problem is known, the lack of overview of the size and the consequences of multidrug-resistant bacteria means that this public health threat is not fully appreciated and often ignored by policymakers and the public.

Data on antibiotic resistance in various bacteria are available from many countries [17], but summarising the situation for the whole European Union in a simple manner remains a challenge. Additionally, there are studies showing that infections due to antibiotic-resistant bacteria result in higher mortality and extra hospital costs [18,19]. However, there currently is no estimate of the burden imposed by multidrug-resistant bacteria on the EU.

The purpose of this study was to give an overview of the trends of antibiotic resistance in bacteria frequently responsible for infections in humans, as well as estimating the human and economic burden associated with multidrug-resistant bacteria, in the EU, Iceland and Norway.

2.2 Materials and methods

2.2.1 Selection of bacteria

The study focused on bacteria most frequently isolated from blood cultures in Europe [20]. For each bacterium, the resistance traits, which in most cases are markers of multiple resistance to antibiotics, were listed (Table 1). Although they are frequently isolated from blood cultures, coagulase-negative staphylococci, beta-haemolytic and viridans streptococci, *Enterobacter spp.* and *Acinetobacter spp.* were excluded from the study because reliable resistance data were not available.

Table 1. Bacteria frequently responsible for bloodstream infections and resistances used as markers for resistance to multiple antibiotics.

Bacteria ^a	Resistance used as a marker of multiple resistance to antibiotics
Gram-positive bacteria	
<i>Staphylococcus aureus</i>	Methicillin resistance (MRSA) Vancomycin-intermediate resistance and resistance (VISA/VRSA)
<i>Enterococcus spp.</i> (e.g., <i>Enterococcus faecium</i>)	Vancomycin resistance (VRE)
<i>Streptococcus pneumoniae</i>	Penicillin resistance ^b
Gram-negative bacteria	
<i>Enterobacteriaceae</i>	
<i>Escherichia coli</i>	Third-generation cephalosporin resistance ^{c,d} Carbapenem resistance ^e
<i>Klebsiella spp.</i>	Third-generation cephalosporin resistance ^{c,d} Carbapenem resistance ^e
Non-fermentative Gram-negative bacteria	
<i>Pseudomonas aeruginosa</i>	Carbapenem resistance ^e

^a *Coagulase-negative staphylococci, beta-haemolytic and viridans streptococci, Enterobacter spp. and Acinetobacter spp. are among the list of the 10 bacteria most frequently isolated from blood cultures [20], but were excluded from the study because reliable resistance data are not available for these bacteria.*

^b *Most fully penicillin-resistant Streptococcus pneumoniae isolates are resistant to both penicillin and macrolides.*

^c *Resistance to cefotaxime or ceftriaxone or ceftazidime (as in the European Antimicrobial Resistance Surveillance System, EARSS).*

^d *Mostly extended-spectrum beta-lactamase (ESBL)-producing isolates.*

^e *Resistance to imipenem or meropenem (as in EARSS).*

2.2.2 Data source

The European Antimicrobial Resistance Surveillance System (EARSS) is the preferred source of data for multidrug-resistant bacteria in Europe because it includes ongoing surveillance data on antibiotic resistance in bacteria responsible for invasive infections (mostly bloodstream infections) such as *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* causing invasive infections.

EARSS is a network of national antimicrobial resistance surveillance systems in European countries coordinated by the Dutch National Institute of Public Health and the Environment (RIVM). EARSS collects comparable and validated antibacterial susceptibility data for public health action. In 2007, routine data for major indicator bacteria were submitted by more than 900 laboratories serving more than 1 400 hospitals in 31 countries [17].

2.2.3 Assessment of the situation in 2007 and of trends of selected antibiotic-resistant bacteria

Data on the proportion of isolates resistant to antibiotics among selected bacteria responsible for invasive infections (mainly bloodstream infections) in each EU Member State, Iceland and Norway and each year during the period 2002–2007 were extracted from the EARSS interactive database⁸. This proportion represents the percentage of bloodstream infection cases in which, based on *in vitro* laboratory data, the antibiotic (or antibiotic group) would be inactive to treat an infection due to this bacteria.

⁸ <http://www.rivm.nl/earss/database/>

Such data were available for methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate and -resistant *S. aureus* (VISA/VRSA), vancomycin-resistant *Enterococcus faecium*, penicillin-resistant *Streptococcus pneumoniae* and third-generation cephalosporin-resistant *Escherichia coli*, carbapenem-resistant *E. coli* for the period 2002–2007, and for third-generation cephalosporin-resistant *Klebsiella pneumoniae*, carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *Pseudomonas aeruginosa* for the period 2005–2007.

Mid-year population data for each EU Member State, Iceland and Norway and each year during the period 2002–2007 were obtained from Eurostat⁹.

To give an overview of the situation for each selected antibiotic-resistant bacteria, data were presented on maps, as well as plotted on graphs where each square represented one country. The trends in the proportion of resistant isolates in each country for the period 2005–2007 were assessed by the Chi-square test for trend (Epi Info™ Version 3.3.2, Statcalc).

Additionally, for each year in the study period 2002–2007 and for each bacteria and antibiotic included in the survey, a population-weighted average proportion (percentage) of resistant isolates was calculated. These data were plotted on two graphs. When data were not available for a particular year, data for the closest available year were used. Data were not available for the whole study period for *S. pneumoniae* in Greece and for *K. pneumoniae* and *P. aeruginosa* in Belgium and Slovakia.

2.2.4 Assessment of the human burden of infections caused by the selected antibiotic-resistant bacteria in 2007

For estimating the burden of antibiotic-resistant bacteria, data were only available on the following five antibiotic-resistant bacteria: MRSA, vancomycin-resistant *Enterococcus faecium*, third-generation cephalosporin-resistant *Escherichia coli* and *Klebsiella pneumoniae* and carbapenem-resistant *Pseudomonas aeruginosa*.

Number of infections

Data on the number of isolates resistant to antibiotics among bacteria responsible for invasive infections (mainly bloodstream infections) in each EU Member State, Iceland and Norway in 2007 were extracted from the EARSS interactive database¹⁰.

Data on the estimated population covered by EARSS for each type of bacteria were obtained directly from country representatives in the EARSS network. For each country, the number of invasive infections (mainly bloodstream infections) due to the selected antibiotic-resistant bacteria was estimated from this reported population coverage. Data for Belgium and Slovakia on *K. pneumoniae* and *P. aeruginosa* were not available. They were replaced by values based on the median incidence of invasive infections due to these bacteria multiplied – for Belgium with the percentage of resistance in 2005–2007 from national surveillance of nosocomial septicaemia¹¹, and for Slovakia with the average percentage of resistance for the EU, Iceland and Norway.

The number of infections due to the selected antibiotic-resistant bacteria (with the exception of vancomycin-resistant *E. faecium* and penicillin-resistant *S. pneumoniae*) from the three other main body sites (respiratory tract, skin and soft tissue and urine), was estimated by applying correction factors corresponding to the relative distribution of infections from these body sites compared to bloodstream, as reported in published literature [21–22].

For third-generation cephalosporin-resistant *E. coli*, the same relative distributions as for third-generation cephalosporin-resistant *K. pneumoniae* were used [22]. For vancomycin-resistant *E. faecium*, the three other main body sites considered were: abdomen (abdominal infections), skin and soft tissue (wounds) and urine [23]. For penicillin-resistant *S. pneumoniae*, the only other body site considered was respiratory tract [24]. Parameters used to estimate the number of infections are shown in Annex B1.

The total number of infections due to the selected antibiotic-resistant bacteria was obtained by adding the number of invasive infections (mainly bloodstream) and of infections from the three other main body sites (respiratory tract, skin and soft tissue and urine).

Number of extra deaths due to these infections

Attributable mortality corresponds to the percentage of deaths that are attributable to infection with an antibiotic-resistant isolate of a given bacteria as compared with infection with an antibiotic-susceptible isolate of the same

⁹ <http://epp.eurostat.ec.europa.eu>

¹⁰ <http://www.rivm.nl/earss/database/>

¹¹ http://www.iph.fgov.be/nsih/surv_sep/beschrijving_fr.asp

bacteria when all other possible causes of deaths have been controlled for. It was calculated with the formula: $attributable\ mortality = ((relative\ risk - 1)/relative\ risk) \times crude\ mortality$. For each selected antibiotic-resistant bacteria, data for calculating attributable mortality of bloodstream infections were obtained from published studies [19,22-23,25-26]. Such data were not available for penicillin-resistant *S. pneumoniae*. When only attributable mortality of bloodstream infections was available from published studies, attributable mortality was estimated by applying correction factors corresponding to the relative mortality of nosocomial infections from these body sites compared to nosocomial bloodstream infection [27]. Parameters used to estimate the number of extra deaths are shown in Annex B1.

The number of extra deaths due to the selected antibiotic-resistant bacteria was estimated by applying attributable mortality to each of the estimates of the number of infections described above.

Number of extra hospital days due to these infections

Extra days spent in a hospital are a direct, short-term effect of infections due to antibiotic-resistant bacteria. For each selected antibiotic-resistant bacteria, the extra length of hospital stay for each infection was estimated as the difference between the average length of hospital stay in patients infected with an antibiotic-resistant isolate of a given bacteria to the average length of hospital stay in patients infected with an antibiotic-susceptible isolate of the same bacteria, as reported in published studies selected because they controlled for other factors affecting length of hospital stay such age, sex, comorbidities, severity of underlying diseases, antibiotic therapy and appropriateness of antibiotic therapy [18,23,25,28-29]. For carbapenem-resistant *P. aeruginosa*, the extra length of hospital stay for bloodstream infections was used for all infections [25]. Such data were not available for penicillin-resistant *S. pneumoniae*. Parameters used to estimate the number of extra hospital days are shown in Annex B1.

The number of extra hospital days due to the selected antibiotic-resistant bacteria was estimated by applying the extra length of hospital stay to each of the estimates of the number of infections described above.

2.2.5 Assessment of the economic burden of infections caused by the selected antibiotic-resistant bacteria in 2007

Principles of cost calculations

Cost-of illness analyses involve the identification, measurement and valuing of resources related to an illness.

The principal features of this study were:

- Time frame: Year (2007)
- Perspective: Societal
- Methodology: Standard prevalence-based
- Approach: Bottom-up

An annual time frame was considered whereby all costs within the most recent year for which data were available were measured. The reference year was 2007, the most recent year for which EARSS data were available. The most recently reported year was used for those few instances where 2007 data were not available.

A societal perspective was adopted considering direct and indirect healthcare costs, as well as productivity losses from absence from work due to illness or premature death.

A prevalence-based study was performed to estimate annual costs. In such studies, costs are measured during one period, usually a year, regardless of the date of onset of illness.

A bottom-up approach was used because only aggregated data on the number of infections due to the selected antibiotic-resistant bacteria were available. This approach estimates costs by multiplying the number of cases of an illness by the unit cost of treatment of this illness.

Publications and websites from international organisations, national ministries, bodies and statistical institutes, as well as published literature, were consulted for epidemiological and healthcare utilisation data. If no data were found for a specific country, extrapolations were performed from data from similar countries based on gross domestic product, population and geographical location.

Hospital inpatient care and outpatient care were included in cost calculations for healthcare services. Activities aiming at the prevention of patient-to-patient transmission of antibiotic-resistant bacteria such as the search-and-destroy approach for MRSA that is actually being performed in some EU countries, e.g. the Netherlands, but is not routine in all EU Member States, were not included.

Non-health service costs include productivity losses, informal care costs, patient travel costs and out-of-pocket expenses. Little data is available on informal care, patient travel and out-of-pocket expenses. As a consequence, only productivity losses from absence from work due to illness or premature death were estimated.

Hospital inpatient care costs

Total hospital inpatient care costs were estimated by multiplying the number of extra hospital days, as calculated above, by an average cost for a hospital day in the EU in 2007 of EUR 366. The average cost of a hospital day was obtained from the European Commission [30] and converted to 2007 prices using the health component of the harmonised index of consumer prices (HICP)¹².

Outpatient care costs

In this study, outpatient care corresponded to one consultation with a general practitioner after hospital discharge. An estimate of the cost of this consultation was obtained from published literature [31]. These data were not available for Bulgaria and Romania, Iceland and Norway, for which costs of similar countries were used. All costs were converted to 2007 prices using the health component of the harmonised index of consumer prices (HICP)¹³.

Productivity losses

Productivity losses include the foregone earnings from absence from work due to illness or premature death.

For each country, productivity losses due to absence from work were estimated by multiplying the number of days being absent from work due to infection with an antibiotic-resistant bacteria by the daily earnings and employment rates in 2007, assuming that the number of days being absent from work was equal to the number of extra hospital days due to the infection. A friction period, i.e. the period until another worker from the pool of unemployed has fully replaced the worker who is absent due to illness, was not taken into account because absence from work due to infection is generally not long enough for a worker to be replaced.

Productivity losses from premature deaths from infection due to antibiotic-resistant bacteria correspond to the likely earnings that patients who died would otherwise have received from paid employment. For each country, they were estimated by calculating age-specific products of the following:

- estimated number of extra deaths attributable to antibiotic-resistant bacteria in 2007;
- population distribution in 2007, by age;
- probability of dying, by age;
- number of remaining work years at time of death, by age;
- average annual gross earning in 2007; and
- employment rate in 2007¹⁴.

Because these productivity losses will be incurred in the future, earnings were discounted using a 3.5% annual rate to obtain present values [32]. Additionally, since the age distribution of patients with an infection due to antibiotic-resistant bacteria is different from that of the general population and skewed towards older age, a correction factor of 0.37 was applied, based on the percentage of individuals aged less than 65 years in the general population and among patients with a healthcare-associated infection as reported in a national prevalence survey¹⁵.

Total productivity losses were obtained by adding productivity losses for each selected type of antibiotic-resistant bacteria and for each country.

2.3 Results

2.3.1 Antibiotic resistance situation in 2007 and trends

The population-weighted, average proportions (percentages) of resistant isolates among the selected bacteria are presented in Figure 2. This is an attempt to summarise the general antibiotic resistance situation in the EU, Iceland and Norway. However, for each selected antibiotic-resistant bacteria, there were large variations between countries from less than 1% to more than 50% resistant isolates in many instances. These maps, as well as graphs presenting the distribution of country data, are presented in Figures 3 and 4.

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Overall, the average proportion of MRSA in the EU, Iceland and Norway was high (22%), although it has been decreasing in recent years (Figure 2a). There were large intercountry variations, from less than 1% in Denmark,

¹² <http://epp.eurostat.ec.europa.eu/portal/page/portal/hicp/data>

¹³ <http://epp.eurostat.ec.europa.eu/portal/page/portal/hicp/data>

¹⁴ Eurostat. <http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home>

¹⁵ http://www.invs.sante.fr/publications/2009/enquete_prevalence_infections_nosocomiales/enquete_prevalence_infections_nosocomiales_vol1.pdf

Iceland, Norway and Sweden to more than 25% in 10 countries (Figure 3a). Between 2005 and 2007, the proportion of MRSA significantly decreased in eight EU Member States (Figure 3a). These decreasing trends are likely due to increased prevention and control at national level, as documented for France, Slovenia and United Kingdom [33-35].

Vancomycin-intermediate and vancomycin-resistant *S. aureus* (VISA/VRSA)

The proportion of *S. aureus* isolates that showed intermediate resistance to vancomycin (VISA) was very low in the EU, Iceland and Norway. Overall, it represented less than 0.1% of *S. aureus* bloodstream isolates reported to EARSS by these countries, corresponding to only four confirmed isolates, reported by France (n=1), Ireland (n=1) and the Netherlands (n=2). No vancomycin-resistant *S. aureus* isolates was reported to EARSS in 2007.

Vancomycin-resistant *Enterococcus faecium*

The average proportion of *Enterococcus faecium* isolates that showed resistance to vancomycin was below 8% in the EU, Iceland and Norway (Figure 2a). There was a large intercountry variation, from less than 1% in 14 countries to more than 25% in Ireland, Greece and Portugal, with very few significant variations over the period 2005–2007 (Figure 3b).

Penicillin-resistant *Streptococcus pneumoniae*

The average proportion of *S. pneumoniae* isolates in the EU, Iceland and Norway, that showed full resistance to penicillin was 4% in 2007 (Figure 2a). Intercountry variation showed a much narrower range than for other bacteria, with most countries reporting a proportion below 10% (Figure 3c). Only a few countries showed an increasing or decreasing trend over the period 2005–2007 (Figure 3c).

Third-generation cephalosporin-resistant *Escherichia coli*

The average proportion of third-generation cephalosporin-resistant isolates among *Escherichia coli* – the most common Gram-negative bacterium responsible for infections in humans – is rising steadily in the EU, Iceland and Norway and reached 8% in 2007 (Figure 2b). Indeed, 13 countries showed a significant increase in this proportion during the period 2005–2007 (Figure 4a). There was a large intercountry variation in the proportion reported in 2007, from 1–5% in 12 countries to more than 25% in Romania (Figure 4a).

Third-generation cephalosporin-resistant *Klebsiella pneumoniae*

The average proportion of third-generation cephalosporin-resistant isolates among *K. pneumoniae* in the EU, Iceland and Norway remained high (19%) in 2007 (Figure 2b). There was a large intercountry variation, from less than 5% in Estonia, Finland, Iceland, Norway and Sweden to more than 25% in 11 countries, but only a few countries showed increasing or decreasing trends over the period 2005–2007 (Figure 4b).

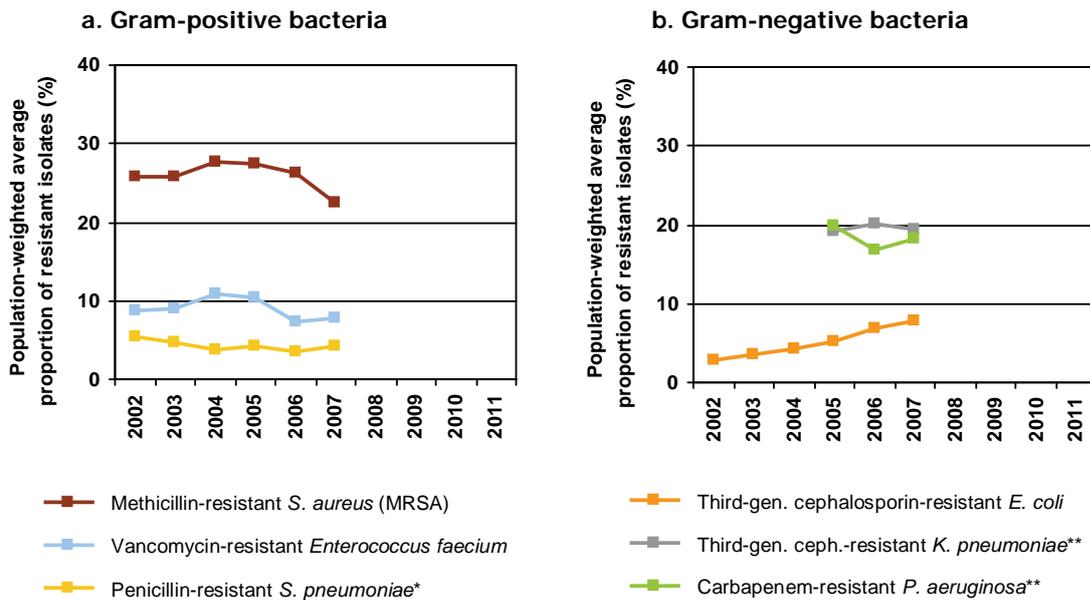
Carbapenem-resistant *K. pneumoniae*

Carbapenem resistance was still absent from *K. pneumoniae* isolates from blood cultures in most EU Member States in 2007 and only six countries reported such isolates. Five of these countries reported only a few isolates: Cyprus (n=1; 3%), France (n=1; <1%), Germany (n=3; 2%), Italy (n=4; 1%) and United Kingdom (n=1; <1%). Greece was a notable exception with 410 reported carbapenem-resistant *K. pneumoniae* isolates, which corresponded to 42% of reported *K. pneumoniae* isolates. The situation in Greece has been attributed to the spread of a hyperepidemic, carbapenemase-producing clone, as well as the spread of the *bla*_{VIM-1} resistance gene cassette and ecological pressure due to antibiotic use [13,36].

Carbapenem-resistant *Pseudomonas aeruginosa*

The average proportion of carbapenem-resistant isolates among *P. aeruginosa* in the EU, Iceland and Norway remained high (18%) in 2007 (Figure 2b). There was a large intercountry variation, from less than 5% in Denmark, Iceland and the Netherlands to more than 25% in the Czech Republic, Greece, Italy and Lithuania, but only a few countries showed increasing or decreasing trends over the period 2005–2007 (Figure 4c).

Figure 2. Population-weighted, average proportion of resistant isolates among blood isolates of bacteria frequently responsible for bloodstream infections, EU Member States, Iceland and Norway, 2002–2007.



* *S. pneumoniae*: excluding Greece, which did not report data on this bacterium to EARSS.

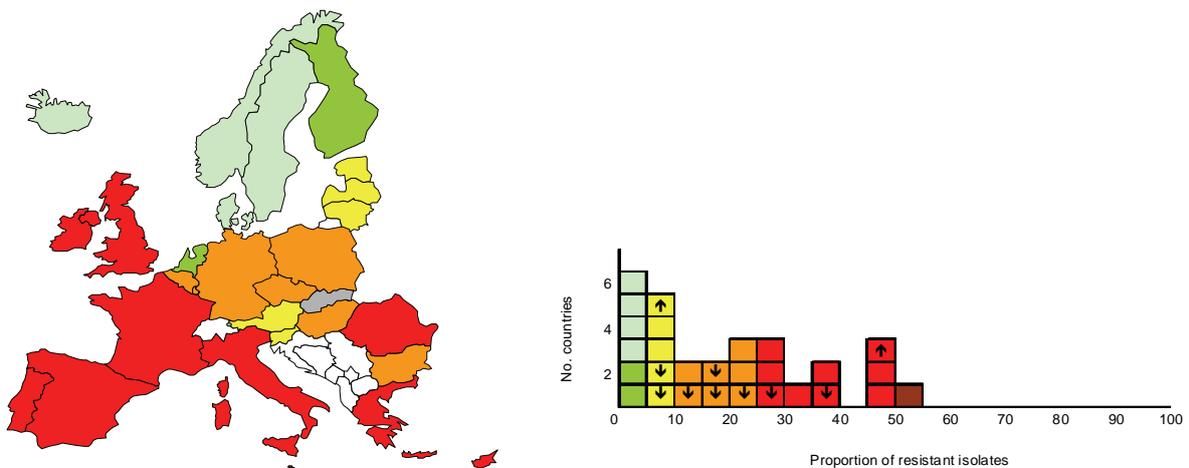
** *K. pneumoniae* and *P. aeruginosa*: excluding Belgium and Slovakia, which did not report data on these bacteria to EARSS.

Figure 3. Proportion of resistant isolates among blood isolates of Gram-positive bacteria frequently responsible for bloodstream infections, EU Member States, Iceland and Norway, 2007 and trends for 2005–2007.

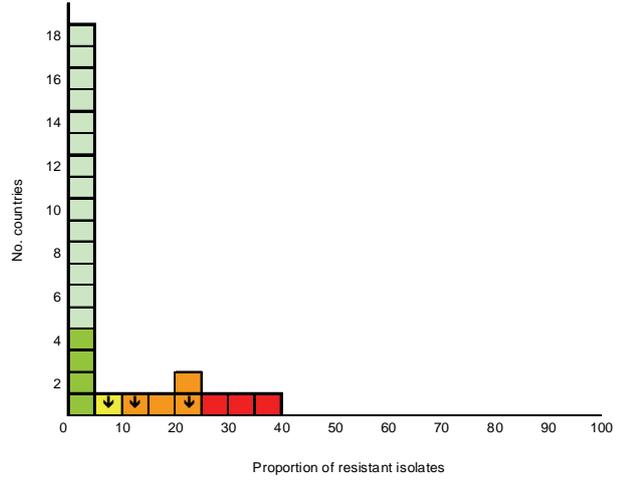
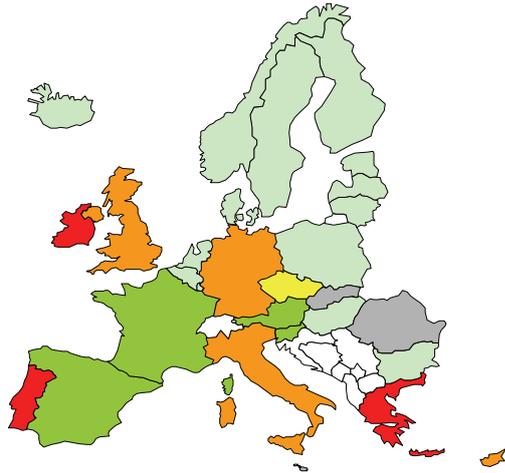
Legend

- <1%
- 1-5%
- 5.1-10%
- 10.1-25%
- 25.1-50%
- >50%
- no data (including countries which reported less than 10 isolates)
- ↑ significant increasing trend
- ↓ significant decreasing trend

a. Methicillin-resistant *Staphylococcus aureus* (MRSA)



b. Vancomycin-resistant *Enterococcus faecium*



c. Penicillin-resistant *Streptococcus pneumoniae*

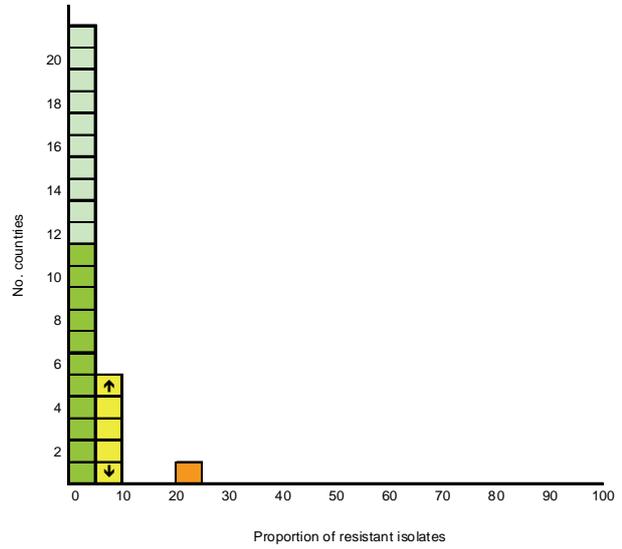
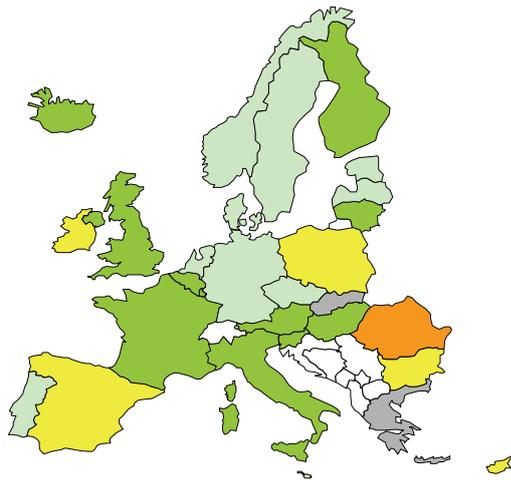
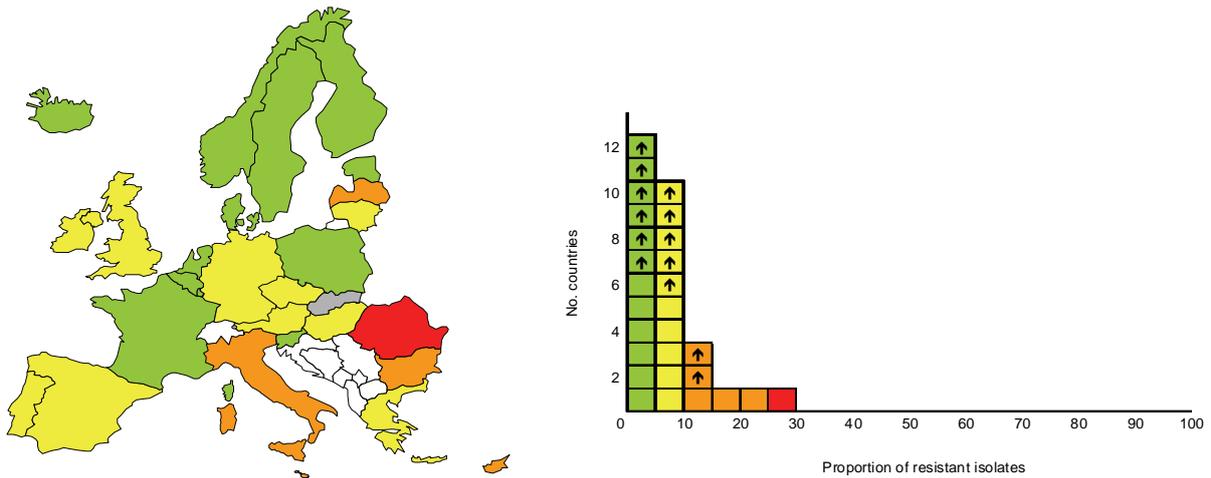


Figure 4. Proportion of resistant isolates among blood isolates of Gram-negative bacteria frequently responsible for bloodstream infections, EU Member States, Iceland and Norway, 2007 and trends for 2005–2007.

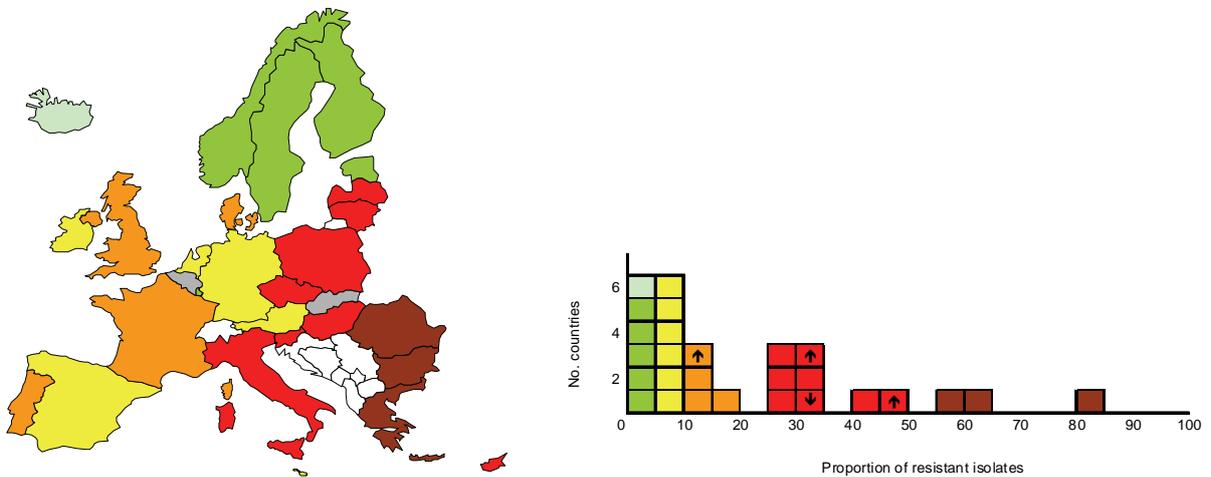
Legend

- <1%
- 1-5%
- 5.1-10%
- 10.1-25%
- 25.1-50%
- >50%
- no data (including countries which reported less than 10 isolates)
- ↑ significant increasing trend
- ↓ significant decreasing trend

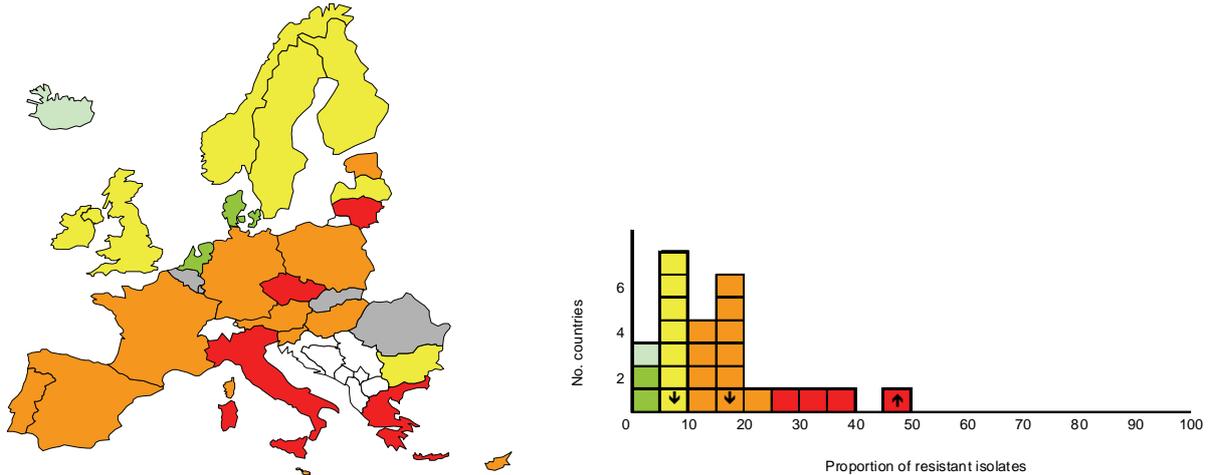
a. Third-generation cephalosporin-resistant *Escherichia coli*



b. Third-generation cephalosporin-resistant *Klebsiella pneumoniae*



c. Carbapenem-resistant *Pseudomonas aeruginosa*



2.3.2 Human burden of antibiotic resistance

The estimated human burden of infections due to the selected antibiotic-resistant bacteria is presented in Table 2.

The study confirmed that MRSA was, in 2007, the most common, single, multidrug-resistant bacterium in the EU as per the estimated number of cases of infection due to this bacterium. However, the sum of cases of antibiotic-resistant Gram-positive bacteria (mostly MRSA and vancomycin-resistant *Enterococcus faecium*) was comparable to that of antibiotic-resistant Gram-negative bacteria (third-generation cephalosporin-resistant *E. coli* and *K. pneumoniae*, and carbapenem-resistant *P. aeruginosa*).

Overall, it was estimated that in 2007 approximately 25 000 patients died from an infection due to any of the selected frequent antibiotic-resistant bacteria in the EU, Iceland and Norway. Notably, about two thirds of these deaths were caused by infections due to Gram-negative bacteria. In addition, infections due to any of the selected antibiotic-resistant bacteria resulted in approximately 2.5 million extra hospital days.

2.3.3 Economic burden of antibiotic resistance

The estimated economic burden of infections due to the selected antibiotic-resistant bacteria is presented in Table 3.

Based on the number of extra hospital days, extra in-hospital costs in 2007 were estimated at more than EUR 900 million in the EU, Iceland and Norway.

Based on 2007 data, outpatient care costs were estimated at about EUR 10 million and productivity losses due to absence from work of infected patients were estimated at more than EUR 150 million, each year. Productivity losses due to patients who died from their infection were estimated at about EUR 450 million each year. Overall, societal costs of infections due to the selected antibiotic-resistant bacteria were estimated at about EUR 1.5 billion each year.

There are many reasons to suggest that these figures correspond to an underestimate of the human and economic burden of infections due to the selected antibiotic-resistant bacteria. These reasons are developed in the discussion section of this chapter.

Table 2. Estimated yearly human burden of infections due to the selected antibiotic-resistant bacteria and percentage of this burden due to bloodstream infections, EU Member States, Iceland and Norway, 2007.

Antibiotic-resistant bacteria ^a	No. cases of infection (four main types) ^b (% bloodstream infections)	No. extra deaths (% from bloodstream infections)	No. extra hospital days (% from bloodstream infections)
<i>Antibiotic-resistant Gram-positive bacteria</i>			
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	171 200 (12%)	5 400 (37%)	1 050 000 (16%)
Vancomycin-resistant <i>Enterococcus faecium</i>	18 100 (9%)	1 500 (28%)	111 000 (22%)
Penicillin-resistant <i>Streptococcus pneumoniae</i> ^e	3 500 (27%)	– ^f	–
<i>Sub-total</i>	<i>192 800 (12%)</i>	<i>6 900 (35%)</i>	<i>1 161 000 (16%)</i>
<i>Antibiotic-resistant Gram-negative bacteria</i>			
Third-generation cephalosporin-resistant <i>Escherichia coli</i> ^d	32 500 (27%)	5 100 (52%)	358 000 (27%)
Third-generation cephalosporin-resistant <i>Klebsiella pneumoniae</i>	18 900 (27%)	2 900 (52%)	208 000 (27%)
Carbapenem-resistant <i>Pseudomonas aeruginosa</i> ^e	141 900 (3%)	10 200 (7%)	809 000 (3%)
<i>Sub-total</i>	<i>193 300 (9%)</i>	<i>18 200 (27%)</i>	<i>1 375 000 (13%)</i>
Total	386 100 (11%)	25 100 (29%)	2 536 000 (14%)

^aData on antimicrobial resistance for *Klebsiella* sp. other than *K. pneumoniae*, *Enterobacter* spp. and *Acinetobacter* spp. were not available from EARSS. Although coagulase-negative staphylococci as well as beta-haemolytic and viridans streptococci are among the 10 most common bacteria isolated from blood cultures [20], they were excluded from the study because reliable resistance data are not available for these bacteria.

^bBloodstream infections, lower respiratory tract infections, skin and soft tissue infections and urinary tract infections.

^cMost fully penicillin-resistant *Streptococcus pneumoniae* isolates are resistant to both penicillin and macrolides.

^dResistant to cefotaxime or ceftriaxone or ceftazidime.

^eResistant to imipenem or meropenem.

^f–, could not be calculated

Table 3. Estimated yearly economic burden of infections (four main types^a) due to the selected antibiotic-resistant bacteria, EU Member States, Iceland and Norway, 2007.

Antibiotic-resistant bacteria ^b	Extra in-hospital costs (EUR)	Extra outpatient costs ^c (EUR)	Productivity losses due to absence from work (EUR)	Productivity losses due to patients who died from their infection (EUR)	Overall costs (EUR)
<i>Antibiotic-resistant Gram-positive bacteria</i>	424 700 000	5 500 000	91 100 000	145 600 000	666 900 000
<i>Antibiotic-resistant Gram-negative bacteria</i>	503 100 000	4 500 000	59 300 000	300 300 000	867 200 000
Total	927 800 000	10 000 000	150 400 000	445 900 000	1 534 100 000

^aBloodstream infections, lower respiratory tract infections, skin and soft tissue infections and urinary tract infections.

^bGram-positive bacteria: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium*. Data for penicillin-resistant *Streptococcus pneumoniae* were not available. Gram-negative bacteria: third-generation cephalosporin-resistant *Escherichia coli* and *Klebsiella pneumoniae* (i.e., resistant to cefotaxime or ceftriaxone or ceftazidime) and carbapenem-resistant *Pseudomonas aeruginosa* (i.e., resistant to imipenem or meropenem).

Data on antimicrobial resistance for *Klebsiella* sp. other than *K. pneumoniae*, *Enterobacter* spp. and *Acinetobacter* spp. were not available from EARSS. Although coagulase-negative staphylococci as well as beta-haemolytic and viridans streptococci are among the 10 most common bacteria isolated from blood cultures [20], they were excluded from the study because reliable resistance data are not available for these bacteria.

^cVisit to general practitioner.

2.4 Discussion

This is the first study that provides an overview of overall trends in antibiotic resistance, as well as estimates of the human and economic burden of infections due to antibiotic-resistant bacteria in the EU, Iceland and Norway. For the study, certain antibiotic-resistant bacteria were selected because they represent markers for resistance to multiple antibiotics. Multidrug-resistant bacteria represent a challenge for therapy since the number of antibiotics that remain active and can be used for treatment is limited.

The study showed that the average proportion of MRSA among *S. aureus* from bloodstream infections, although on average high, has levelled out and even decreased in several countries; a phenomenon that has already been reported by EARSS [17]. Since, in EARSS, the proportion of MRSA is correlated with the incidence of MRSA bloodstream infections [17], this suggests that the incidence of MRSA bloodstream infections is currently decreasing in these countries. Despite this trend, the study also indicated that MRSA was the most common single multidrug-resistant bacterium in the EU, Iceland and Norway. Other common antibiotic-resistant Gram-positive bacteria contributed to a much smaller fraction of the burden of antibiotic-resistant bacteria, although there were variations between countries.

The study also showed that the average proportion of antibiotic-resistant Gram-negative bacteria was high or increasing in the case of third-generation cephalosporin-resistant *E. coli*. These findings corroborate those of independent analyses from EARSS and other reports in the literature showing that infections caused by multidrug-resistant Gram-negative bacteria are becoming increasingly frequent in Europe [11-13,17,37]. Considering this current trend, it is likely that the human and economic burden caused by antibiotic-resistant Gram-negative bacteria will outweigh that of antibiotic-resistant Gram-positive bacteria such as MRSA and will represent a major challenge to appropriate therapy, prevention and control in the foreseeable future.

The number of deaths attributable to infections due to the selected antibiotic-resistant bacteria in the EU, Iceland and Norway was estimated at approximately 25 000 each year; two-thirds being due to Gram-negative bacteria. As a comparison, each year in the EU, about 48 000 persons are killed in a road accident¹⁶, about 37 000 patients die as a direct consequence of a hospital-acquired infection and an additional 111 000 die as an indirect consequence of the hospital-acquired infection [38].

For the United States, the Centers for Disease Control and Prevention made similar estimates of about 99 000 deaths associated with a healthcare-associated infection [39] and 12 000 deaths associated with either MRSA, VRE or *Clostridium difficile* each year [40]. Although they are within the same range, data from the EU and the United States are not immediately comparable since different bacteria were included (e.g. *Clostridium difficile* was not included in the EU study) and US data include cases where antibiotic-resistant bacteria directly and indirectly contributed to patient death whereas this EU study only considered directly attributable deaths.

This study has several limitations. Although EARSS provides the most comprehensive database on antibiotic resistance in Europe, the system itself has some limitations. EARSS does not centrally test bacterial isolates. Efforts are made by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and EU Member States to standardise antimicrobial susceptibility testing in Europe. EARSS organises regular external quality assessment exercises to foster improvement of antimicrobial susceptibility testing in laboratories that participate in EARSS. Nevertheless, EARSS relies on data as reported by Member States according to the EARSS protocol. For some Member States, population coverage is low and EARSS data are not yet geographically representative of the country. Updated data on the estimated population covered by EARSS for each type of bacteria were obtained directly from country representatives in the EARSS network. These data, however, often represent a broad estimate ('best estimate') of population coverage by the EARSS network in each country. Data were missing for only a few countries in the EARSS database. For this study, missing data were replaced by data from the closest available year or by an estimate based on an EU median or average. The number of antibiotic-resistant bacteria included in this study was limited to those bacteria included in EARSS. In particular, EARSS does not perform surveillance of extensively drug-resistant or pandrug-resistant bacteria, i.e. bacteria that are almost totally or totally resistant to antibiotics, which are currently emerging in the EU [14]. Finally, many parameters used in the study were extracted from published literature and may not exactly reflect the value of these parameters in each EU Member State, Iceland and Norway in 2007.

The costs of infections due to the selected antibiotic-resistant bacteria for the EU, Iceland and Norway were estimated at about EUR 1.5 billion each year, with more than EUR 900 million corresponding to hospital costs. Because these costs are based on many assumptions, a nomogram is provided in Annex B1, which allows to calculate yearly in-hospital costs using other values for the total number of infections, the average extra length of

¹⁶ <http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home>

hospital stay per infection and the average cost per hospital day, thus providing a means of testing the sensitivity of the estimates in this study.

In the US, the US Office of Technology Assessment estimated the hospital costs for five major groups of hospital-acquired infections due to antibiotic-resistant bacteria at USD 1.3 billion (in 1992 dollars) [41]. More recently, Spellberg et al. [42] estimated the societal costs of infections due to one single type of antibiotic-resistant bacteria, i.e. multidrug-resistant *P. aeruginosa*, at USD 2.7 billion each year in the US. However, cost comparisons with the US should be made with caution since healthcare is more costly in the US than in the EU [43].

Despite the limitations described earlier, there are many reasons to believe that the human and economic burden of antimicrobial resistance for the EU from this study corresponds to an underestimate. Firstly, population coverage data obtained directly from country representatives in the EARSS network may be overestimated because, in many countries, catchment populations of participating hospitals frequently overlap, which leads to underestimating the total number of infections from these population coverage data. Secondly, data on infections in outpatients are not reported to EARSS and could not be included. This, in particular, includes bacteria such as *Neisseria gonorrhoeae*, for which resistance to first-line agents is increasing in Europe. Thirdly, although the study focused on selected antibiotic-resistant bacteria, there are several other antibiotic-resistant bacteria, e.g. multidrug-resistant *Enterobacter* spp., *Acinetobacter* spp. and coagulase-negative staphylococci that are often responsible for healthcare-associated infection and for which data were not available from EARSS. Fourthly, the study only considered the four main body sites of infection (bloodstream, lower respiratory tract, skin and soft tissue and urinary tract), thus slightly underestimating the number of infections for each of the selected antibiotic-resistant bacteria.

In addition, there are several reasons, other than the above stated underestimation of the number of infections, to believe that the results of the economic burden analysis correspond to an underestimate. Many patients with an infection due to antibiotic-resistant bacteria require intensive care and incur substantially higher hospital costs, since the cost of a day in an intensive care unit is more than twice that of the average cost for a hospital day considered in this study [44]. Infections due to antibiotic-resistant bacteria generally require antibiotics that are more costly than for infections with susceptible bacteria, and these antibiotic costs were not considered. Moreover, in the absence of rapid point-of-care diagnostic tests for multidrug-resistant bacteria, these costly antibiotics are also used empirically to treat many patients with a suspected infection with a multidrug-resistant type of bacteria. These costs were not included. Indirect costs after discharge from the hospital – such as informal care, patient travel and out-of-pocket expenses – were not considered. The costs related to possible disabilities following the infection were also not considered. Finally, the costs of infection control and prevention strategies, such as the search-and-destroy approach for MRSA, were not considered.

In conclusion, and despite its limitations, this study showed that overall, antibiotic resistance in the EU, Iceland and Norway is high, sometimes increasing, and its human and economic consequences are serious. Considering current trends, it is likely that the burden of antibiotic-resistant bacteria will soon shift towards an increasing prevalence of antibiotic-resistant Gram-negative bacteria such as third-generation cephalosporin-resistant *Enterobacteriaceae* and carbapenem-resistant non-fermentative Gram-negative bacteria.

3 Analysis of the research and development pipeline of antibacterial agents

Most relevant findings

- Fifteen systemically administered antibacterial agents with a new mechanism of action or directed against a new bacterial target were identified as being under development with a potential to meet the challenge of multidrug resistance. Most of these were in early phases of development and were primarily developed against bacteria for which treatment options are already available.
- There is a particular lack of new agents with new targets or mechanisms of action against multidrug-resistant Gram-negative bacteria. Two such agents with new or possibly new targets and documented activity were identified, both in early phases of development.

3.1 Introduction

Recent reports suggest that drug development will not adequately address the problems posed by the increasing frequency of antibiotic resistance among common bacterial pathogens [4,45-46]. In contrast, there are other reports that paint a more optimistic picture of the future availability of new antibacterial agents [47-48].

Hence, the aim of this study was to document and characterise the activity of those antibacterial agents that had entered clinical development as accurately and as comprehensively as possible based on information in the public domain. The focus was on antibacterial agents with potential to be clinically active against at least one of the selected panel of antibiotic-resistant bacteria of public health interest. Special emphasis was placed on agents being developed for systemic administration that also appeared to have a new bacterial target and/or a new mechanism of action.

3.2 Methods

3.2.1 Selection of bacteria

In accordance with the trends and burden analysis (see Chapter 2), the same panel of antibiotic-resistant bacteria was selected for the pipeline analysis:

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

3.2.2 Pipeline database search

In a joint undertaking between EMEA (London, United Kingdom) and the Strategic Policy Unit of ReAct at Duke University (Durham, North Carolina, United States), a pipeline search was carried out on 14 March 2008.

Selection of databases

Three commercial databases were identified for the analysis of the R&D pipeline: Pharmaprojects (T&F Informa UK Limited, London, UK), Adis Insight R&D (Wolters Kluwer Health, Amsterdam, NL) and BioPharm Insight (Infinata, Norwood, MA-USA). A pilot sensitivity analysis was performed, following a two-step approach, which compared Pharmaprojects with Adis Insight R&D and Pharmaprojects with BioPharm Insight. The first step consisted of a search for antibacterial agents that had reached phase II of clinical development for any given indication. The second step consisted in evaluating the results obtained in a search for antibacterial compounds in phases I-III of development. The combination of Pharmaprojects with Adis Insight R&D was chosen based on the higher yield provided by this search (see results). The criteria of inclusion into these databases are described in Annex B2.

Search strategy

The database searches followed the Anatomical Therapeutic Chemical (ATC) classification systems of either Pharmaprojects or EphMRA (European Pharmaceutical Market Research Association) for Adis Insight R&D. Both databases were searched for antibacterial agents that had reached phase I, II or III clinical trials. Due to differences in the classification of the databases consulted, the search for antibacterial agents in Adis Insight R&D database had to be extended to include topical antibacterial agents.

The search also included agents for which an application to at least one regulatory agency had already been made. Agents with a status of 'no development reported' or 'discontinued' according to the database definitions were excluded. Agents that had reached clinical trials but were reported as suspended (i.e. put on hold rather than definitely discontinued) were considered to be still under active development, in accordance with the definition by Pharmaprojects (Janet Beal, personal communication) and were therefore included in the search. Details on the relevant definitions used by each of the pipeline database companies can be found in Annex B2.

Pooled dataset

The results produced by the database searches were matched by compound name, synonyms and originator in order to avoid duplicate entries and to highlight any inconsistencies (e.g. misclassifications) in the dataset. If differences on the development phase of the agent were found between the databases, the most advanced phase reported was included in the analysis. Where compounds were marked as 'discontinued' or 'no development reported' in one of the databases, but not in the other, these were considered as still being under active development. Agents reported as 'suspended' in one database but under a clinical phase of development on the other were included in the pooled dataset as being under clinical development.

Sensitivity analysis

To check the completeness of the data, PubMed was searched for literature relevant to the topic, published from January 2006 through January 2009, using the following Boolean combinations of Medical Subject Headings (MeSH) terms, as well as the search terms previously described by Talbot *et al.* [7]: (((("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". Only PubMed-designated reviews published in English were examined. Agents identified through this search were then checked for fulfilment of the inclusion criteria in the Adis Insight R&D database.

3.2.3 Assessment strategy

Scope and inclusion criteria

The agents identified by the searches were divided into two categories: new active substances or new presentations of licensed antibacterial agents, as defined below:

New active substances – All unlicensed (anywhere in the world, to the knowledge of the working group of this report) antibacterial chemical and biological agents with a direct antibacterial effect on at least one of the selected bacteria were considered for further analysis. Agents which had a mechanism of action involving only immunomodulation, vaccines and monoclonal antibodies were excluded.

New presentations of licensed antibacterial agents – Unlicensed presentations of approved active agents were considered for further analysis if there were data to suggest that the new presentation might be active against at least one of the selected bacteria.

Agents in both of the above categories were excluded from the analysis if they were being developed only to treat bacteria not included in the target list (e.g. those that were apparently under development only to treat tuberculosis, *Helicobacter pylori*, *Chlamydia trachomatis* or non-bacterial pathogens such as *Plasmodium spp.*).

Outcome parameters – best case scenario

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. Any information available in the databases or found in the public domain was taken into account.

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

- Actual data on *in vitro* activity were reviewed whenever available. If actual data on *in vitro* activity were not reported for an agent against any of the selected pathogens then assumptions were made regarding likely activity based on the properties of the antibiotic class or of the mechanism of action involved.
- The assessment of *in vitro* activity disregarded any known potential for cross-resistance and co-resistance.

- While *in vitro* activity alone cannot predict *in vivo* efficacy, it was decided not to take into account any available pharmacokinetic data or PK/PD analyses when scoring the antibacterial activity of agents since the amount of data available was very variable.
- However, if there was already information available on non-clinical or clinical efficacy, these data were factored into the assessment.
- In the case of new agents intended for topical or inhalational administration and new presentations and/or routes of administration of licensed antibacterial agents, the assessment took into account the possibility that very high local concentrations of drug might occur. In the case of licensed agents, the antibacterial spectrum was sometimes considered to be possibly extended beyond that associated with systemic administration of the licensed product.

The assignment of *in vitro* activity, which took into account available data together with assumptions based on class properties or mechanisms of action as well as the route of administration, took the most optimistic view of what the new agent might be able to achieve and represents a 'best case scenario'.

Novelty was rated according to the following:

- a) Substance that acts on the same target as that of at least one previously licensed antibacterial agent;
- b) Substance with a known mechanism of action that likely acts on a new target. Agents displaying a broader range of activity than earlier agents from the same class, implying different target range, were also included here, e.g. beta-lactam agents with activity against MRSA were assumed to be able to bind to PBP 2' (PBP 2a). In some cases it was acknowledged that activity reported against organisms resistant to earlier agents from the same class might not actually represent a different target range but could be due only to evasion of resistance mechanisms by the new agent. However, in the absence of information to allow for differentiation, these agents have been counted in this category. In addition, beta-lactamases that appeared to inhibit enzymes not inhibited by licensed inhibitors were also included in this category;
- c) Substance with a new mechanism of action known or very likely.

Assessment procedure

Anti-infective compounds identified by the searches were divided into five batches and each batch was allocated to a team of two reviewers, including one from the working group and one external reviewer selected 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 to each an antibacterial spectrum of activity and a level of novelty using the approaches and definitions detailed above. All assessments were discussed in the ECDC/EMA Joint Working Group in order to resolve any discrepancies between reviewers' opinions.

3.3 Results

3.3.1 Selection of databases based on pilot sensitivity studies

In the first step of the sensitivity analysis (i.e. based upon antibacterial agents that had reached at least phase II of clinical development), combining the results from the Pharmaprojects and Adis Insight R&D databases resulted in an increase in the number of identified agents by 10%. In the second step of the sensitivity analysis, the addition of information from the BioPharm Insight database into the Pharmaprojects database provided no additional information.

3.3.2 Pooled dataset

The results from the searches for antibacterial agents, including topical agents, in phases I, II, III and pre-registration were pooled and matched as described above. In total 167 agents were identified through the searches and were examined by the reviewers.

3.3.3 Sensitivity analysis

The search for information on antibacterial agents in development yielded 320 PubMed-designated review articles of which 29 were considered relevant and were subsequently analysed. The only extra agent that potentially fulfilled the study inclusion criteria was the novel efflux-pump inhibitor MP-601,205 [49]. However, this agent does not possess any direct antibacterial activity by itself and at the time of the data search, no clinical study involving co-administration of this efflux pump inhibitor with an antibacterial agent had commenced. Therefore it was excluded from the analysis.

3.3.4 Overall findings

After completion of the assessment by the reviewers, 90 out of 167 agents in the pooled dataset were considered to fulfil the inclusion criteria for the analysis. Of these 90 agents, 24 were new presentations of licensed antibacterial agents and 66 were new active substances (see also flow chart Annex B2).

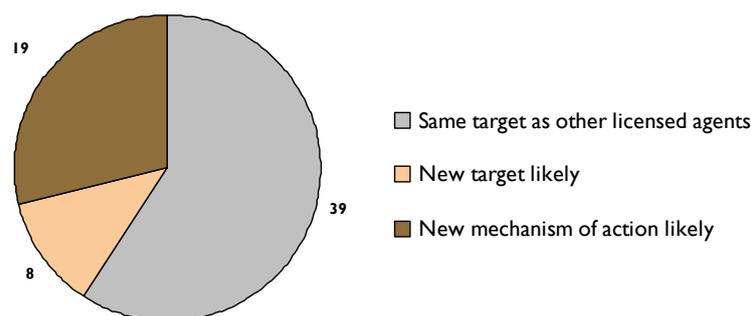
3.3.5 New presentations of licensed antibacterial agents

Of the 24 new presentations of licensed antibacterial agents, 11 were assigned *in vitro* activity that went beyond the known spectrum of activity of the licensed presentation based on optimistic assumptions of what might be achieved by using a different route of administration. These 11 agents comprised topical or inhalational presentations of ciprofloxacin, tobramycin or amikacin, mainly being developed for *P. aeruginosa* infection. They were assessed as possibly having activity against PRSP based on the higher concentrations that could be achieved in the eye or in the respiratory tract. A list of those 11 agents is provided in Annex B2 (List A).

3.3.6 New active substances

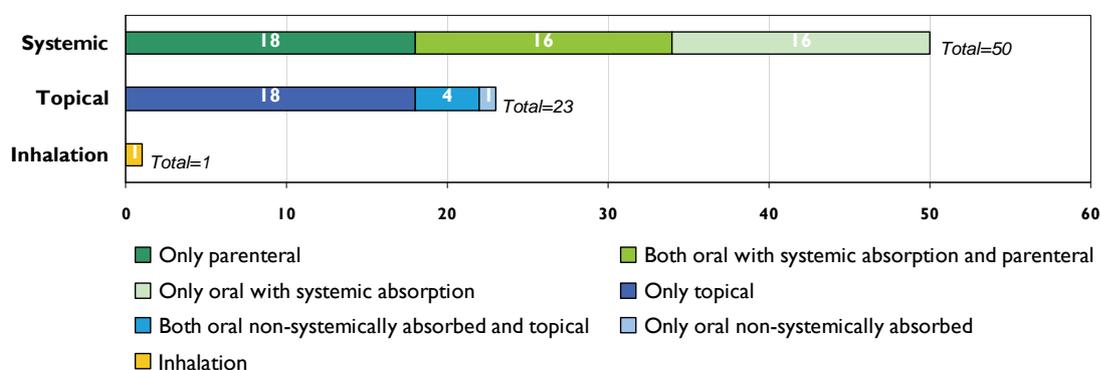
Of the 66 new active substances, 30 (45%) were in phase I of development, 16 (24%) in phase II, nine (14%) in phase III, eight (12%) had been filed with a regulatory agency and three (5%) were reported to have been suspended from further development. Twenty-seven (41%) of these 66 compounds were assessed as having either a new target or a new mechanism of action, thus displaying some degree of novelty (Figure 5). A list of those 39 agents that were assessed as acting on the same target via the same mechanism of action as that of at least one previously licensed antibacterial agent is provided in Annex B2 (List B).

Figure 5. Novelty of new antibacterial agents which, in a best-case scenario (*in vitro* activity based on actual data and assumed *in vitro* activity based on known class properties or mechanisms of action), could have activity against the selected bacteria (n=66, as of 14 March 2008).



An analysis by route of administration (Figure 6) showed that, at the time of the search, 50 of these 66 agents were formulated for systemic administration (34 for oral and 33 for parenteral administration).

Figure 6. Route of administration^a of new antibacterial agents which, in a best-case scenario (*in vitro* activity based on actual data and assumed *in vitro* activity based on known class properties or mechanisms of action), could have activity against the selected bacteria (n=66, as of 14 March 2008).



^a Some agents have several possible routes of administration.

A list of agents with new mechanism of action or new target and topical administration can be found in Annex B2 (List C). Agents that have a new mechanism of action or a new target and that can be systemically administered are shown in Figure 7. It should be noted that the 15 agents in this figure result from adopting the best-case scenario approach described above, i.e. taking into account the agents with actual data available and also those with the likelihood of activity based on known class properties or mechanisms of action.

Figure 7. 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 activity based on known class properties or mechanisms of action (◐), by phase of development (n=15, as of 14 March 2008). Total represents the number of agents active against each of the selected bacteria in a best-case scenario.

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	●							I
PZ-601*	●	●	●	●	●			I
ME 1036*	●	●	●		●			I
NXL 101	●	●	●	●				I
Friulimicin B	●	●	●	●				I
Oritavancin	●	●	●	●				Filed
Telavancin	●	●	●	●				Filed
Ceftobiprole medocaril [†]	●	●	●					Filed
Ceftaroline fosamil [†]	●	●	●					III
Tomopenem [‡]	●	◐	●		●	●	●	II
hLF1-11	●	●			◐	◐	◐	II
Lactoferrin	●	●			◐	◐	◐	I
Talactoferrin-alfa	◐	◐			◐	◐	◐	II
Opebacan					◐	◐	◐	III
NXL 104/ceftazidime [§]					●	●	●	I
●	12	9	8	5	3	2	2	
◐	1	3	1	1	4	4	4	
Total	13	12	9	6	7	6	6	

Abbreviations:

- 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 beta-lactamase inhibitor NXL104 displays additional enzyme inhibition resulting in a broader range of activity than earlier agents.

Note: Phase of development refers to the highest phase of development, regardless of indication.

Table 4 describes the individual characteristics of the antibacterial agents presented in Figure 7.

Table 4. 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*
WAP 8294A2	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 inhibitors / DNA topoisomerase inhibitor	New MoA	IV, PO
Friulimicin 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	Chelating agent / immunomodulation	New MoA	IV, PO
Lactoferrin	Chelating agent / immunomodulation	New MoA	IV, PO
Talactoferrin-alfa†	Chelating agent / immunomodulation	New MoA	PO, Top
Opebacant†	Membrane permeability enhancer/immunomodulation	New MoA	IV
NXL104/ ceftazidime	Beta-lactamase inhibitor + cell-wall synthesis inhibitor	New target	IV

* Information on routes of administration is uncertain in early drug development.

† Agents with only assumed *in vitro* activity.

3.4 Discussion

This study is believed to be the first systematic review of available commercial databases that compile publicly-available information on antibacterial agents in clinical development.

The focus of the study was to give a detailed description of agents with some degree of novelty. These agents may have the potential to become useful in the treatment of infections due to the selected multidrug-resistant bacteria. They may also have the potential to become useful in the treatment of other bacteria of public health importance that were not included in this study such as *Neisseria gonorrhoeae* or fluoroquinolone-resistant Gram-negative bacteria.

A decision was made to take an optimistic approach to the identification of agents potentially active against the selected panel of antibiotic-resistant bacteria. For example, the pooled dataset was built taking into consideration the most optimistic phase of development reflected in the databases used (i.e. the highest phase of clinical development was taken; and reports on clinical development were preferred over those of suspension or discontinuation of studies). The possibility of cross- and co-resistance was not taken into account when assessing *in vitro* activities. Also, assumptions were made on *in vitro* activity based on class properties in the absence of data in order to present a best-case scenario. All of these approaches could have lead to the pipeline looking 'healthier' than it actually is.

Based on this optimistic approach, the main results from the analysis conducted by the ECDC/EMA Working Group were as follows:

- Of 167 agents identified by the searches, there were 90 antibacterial agents with *in vitro* activity in a best-case scenario (based on actual data or assumed based on known class properties or mechanisms of action) against at least one organism in the panel of bacteria selected for their public health importance.
- Of these 90 agents, 24 were new presentations of licensed antibacterial agents and 66 were new active substances.

- Of the 66 new active agents, 27 were assessed as having either a new target or a new mechanism of action, thus potentially offering a benefit over existing antibiotics.
- Of these 27 agents, there were 15 that could be systemically administered. These 15 agents included 13 for which actual data indicated *in vitro* activity against at least one of the selected bacteria, and two additional agents for which activity was assumed due to known class properties or mechanisms of action.
- Of the 15 agents with systemic administration, eight were judged to have activity against at least one of the selected Gram-negative bacteria.
- Of the eight with activity against Gram-negative bacteria, four had activity based on actual data and four had assumed activity based on known class properties or mechanisms of action.
- Of the four with activity against Gram-negative bacteria based on actual data, two acted on new or possibly new targets and none via new mechanisms of action.

The data search was done on 14 March 2008. These results therefore represent the state of the antibacterial drug pipeline at the search date. Since this date, development was discontinued for several agents. Other agents moved from preclinical to clinical development.

Overall, these findings corroborate earlier reports [3,45-46] on the lack of antibacterial drug development to tackle multidrug resistance. In particular, the results of the current analysis indicate that there is a general lack of agents that act on new targets or possess new mechanisms of action.

The IDSA has also attempted to give a systematic account of what is in the antibacterial pipeline, restricted to agents in phase II of clinical development. These reports used the following sources to identify drug candidates: the Pharmaceutical Research and Manufacturers Association survey of medicines in development for treatment of infectious diseases abstracts from the Interscience Conferences on Antimicrobial Agents and Chemotherapy 2002–2004; the websites of the 15 major pharmaceutical and the seven largest biotechnology companies identified by Spellberg *et al.* [6] and literature referenced in the PubMed database from January 2003 to December 2007. In contrast, this study takes also into account investigational agents in phase I of clinical trials. In addition, the databases used in the present analysis state screening all of the sources used by IDSA plus considering additional specialised literature as well as having regular direct communication with companies (see Annex B2).

There are many reasons for the current situation, including difficulties encountered in identifying new bacterial targets and the possibility that the majority of targets amenable to antibacterial activity have already been identified [50]. It is no surprise then that the majority of the investigational agents identified by the searches were directed against the same target and had the same mechanism of action as at least one licensed agent. Almost a third of those with activity against the selected panel of bacteria were new presentations of licensed antibacterial agents. Only 11 out of the 24 new presentations of licensed agents were thought likely to possess an extended spectrum of activity (and only against penicillin-resistant *S. pneumoniae*) as a result of the new route of administration.

It could be argued that there are a number of agents in preclinical development that could improve the gloomy picture presented here. However, it was decided not to include an in-depth exploration of the preclinical pipeline given the high attrition rate of compounds during this phase of development and also due to the scarcity of data available for review. Moreover, it should be noted that the databases used excluded information on agents that were, so far, under development only by academic groups. The search criteria contained EphMRA or EphMRA-derived ATC codes, which are assigned by the database companies and could be subject to variability. Both of these limitations were minimised by performing the literature search for reviews on PubMed and by selecting broader criteria for the main search as described previously.

Multidrug-resistant Gram-negative bacteria constitute a major challenge for the future [45]. Therefore, the lack of systemically administered agents with activity against Gram-negative bacteria displaying new mechanisms of action found in this study is particularly worrisome, and more so when the high attrition rates for agents in early stages of clinical development [50] is taken into consideration. In fact, it is unclear if any of these identified agents will ever reach the market, and if they do, they may be indicated for use in a very limited range of infections. Even if a public health driven approach for R&D of antibacterial agents is commenced in the near future the burden of resistance will inevitably increase during the next years. 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.

4 Conclusions

- There is a gap between the burden of infections due to multidrug-resistant bacteria and the development of new antibiotics to tackle the problem.
- Resistance to antibiotics is high among Gram-positive and Gram-negative bacteria that cause serious infections in humans.
- Resistance is increasing among certain Gram-negative bacteria.
- Infections caused by multidrug-resistant bacteria are associated with excess morbidity and mortality.
- Infections caused by multidrug-resistant bacteria are associated with substantial extra costs.
- Very few antibacterial agents with new mechanisms of action are under development to meet the challenge of multidrug resistance.
- There is a particular lack of new agents to treat infections due to multidrug-resistant Gram-negative bacteria.
- A European and global strategy to address this gap is urgently needed.

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Glossary

Antimicrobial agents: medicinal products that kill or stop the growth of living microorganisms and include **antibacterial agents** (more commonly referred to as **antibiotics**), which are active against bacterial infections.

Antibacterial (antibiotic) resistance: is the ability of a bacterium to survive and even replicate during a course of treatment with a specific antibiotic. Failure to resolve an infection with the first course of antibiotic treatment may mean that the infection may spread, may become more severe and may be more difficult to treat with the next antibiotic that is tried.

- **Intrinsic resistance:** natural resistance of bacteria to certain antibiotics.
- **Acquired resistance:** normally susceptible bacteria have become resistant as a result of adaptation through genetic change.
- **Multidrug resistance:** corresponds to resistance of a bacterium to multiple antibiotics.

Attrition rate: the number of antibacterial agents moving out of development over a specific period of time.

Bacteria are microorganisms and can be divided into categories according to several criteria. One way to classify bacteria is based on staining them using a method that divides most bacteria into two groups – **Gram-positive** and **Gram-negative** – according to the properties of their cell walls.

Bloodstream infection: presence of bacteria in the blood, in quantities that allow isolation from blood samples in the laboratory.

Burden of disease: refers to the overall impact of disabling clinical or public health conditions at the individual level, or at the societal level or to the economic costs of diseases.

Carbapenemase: enzyme produced by some bacteria causing resistance to carbapenems, a class of antibiotics.

Cephalosporins: a class of antibiotics. The class is often divided into generations to indicate incremental increase in spectrum of antibacterial activity. Third-generation cephalosporins, for example, have a broad spectrum of activity and further increased activity against Gram-negative bacteria as compared to previous generations of cephalosporins.

Clinical development of antibacterial agents: see annex B.

Clinical trial: a research activity that involves the administration of a test regimen to humans to evaluate its efficacy and safety.

Commensal flora: the natural bacteria that live on and in a healthy person.

Comorbidities: the presence of one or more diseases or disorders in addition to a primary disease or disorder.

Drug (antibiotic) formulation: the composition of a dosage form, including the characteristics of its raw materials and the operations required to process it. Examples are **oral formulation** (by mouth), **intravenous formulation** (by infusion into a vein).

Extended-spectrum beta-lactamase (ESBL): enzyme produced by Gram-negative bacteria causing resistance to most beta-lactams, including most penicillin and cephalosporins.

Enterobacteriaceae: a family of Gram-negative bacteria. Examples of common *Enterobacteriaceae* are *Escherichia coli* and *Klebsiella pneumoniae*.

Gram-positive bacteria: bacteria that are stained purple or violet by Gram staining.

Gram-negative bacteria: bacteria that cannot retain the purple stain of Gram staining and are stained pink as a result of Gram staining.

***In vitro* activity:** activity tested outside the living body and in an artificial environment.

Morbidity: any departure, subjective or objective, from a state of physiological or psychological well-being.

Mortality rate: an estimate of the portion of a population that dies during a specified period.

Multidrug resistance: occurs when a bacterium is resistant to the action of many types of antibiotics. This severely limits the choice of antibiotics that would be suitable for treatment.

Non-fermentative bacteria: bacteria that do not ferment sugars, which distinguishes them from fermentative bacteria.

Nosocomial (hospital-acquired) infection: an infection occurring in a hospital or another healthcare facility, when the infection was not present or incubating at time of admission.

Pharmacokinetics: study of the rate of drug action, particularly with respect to the variation of drug concentrations in tissues with time, and the absorption, metabolism and excretion of drugs and metabolites (i.e. what the body does to the drug).

Pharmacodynamics: study of the physiological effects of drugs on the body (or on microorganisms within or on the body), the mechanisms of drug action and the relationship between drug concentration and effect (i.e. what the drug does to the body or microorganisms).

PK/PD: Pharmacokinetics/pharmacodynamics.

Phases of clinical trials of antibiotics: see annex B.

Preclinical development of antibiotics: see annex B.

Priority medicines: those medicines which are needed to meet the priority healthcare needs of the population ('essential medicines') but which have not yet been developed. In this Report, a 'priority' medicine for a priority disease is by definition also a significant improvement over already marketed agents.

Soft tissue: tissues that connect, support, or surround other structures and organs of the body, e.g. tendons, ligaments, muscles, fibrous tissue.

Systemic (or systemically administered) antibiotics: compounds administered parenterally (e.g. intravenously) or systemically absorbed after oral administration.

Systemic infection: an infection in which the pathogen is distributed throughout the body rather than concentrated in one area.

Topical antibiotics: antibiotic applied to body surfaces, e.g. to treat skin infections.

Annex A: Mandate, composition, meetings, roles and responsibilities

Mandate

The ECDC/EMEA Joint Working Group is agreed by the ECDC and the EMEA to oversee, facilitate, follow-up and be part of the work aimed at producing a report on the gap between the increasing prevalence of multidrug-resistant bacteria and antibacterial drug development aimed at treating such infections. The Scientific Committees of the ECDC and the EMEA will finally adopt the Technical Report prior to publication.

Composition and meetings

1. Core members of the Joint Working Group

- Two members appointed by each of the Scientific Committees from ECDC and EMEA, respectively.
- One representative from the administrative staff of EMEA and ECDC, respectively.
- Two co-opted independent experts. They will be selected by the working group for their clinical/microbiological expertise in the field of interest.
- The paid consultant employed to run the project.

2. Observers

- One observer from each of DG Enterprise, DG SANCO, DG Research and ESCMID¹⁷.

3. Invitation of additional experts to attend a working group meeting

- Invitation of additional experts is made on a case-by-case basis according to the expertise required to provide advice. The Chairperson, together with the members of the implementation group, will call for additional experts to attend working group meetings or other ad hoc technical meetings that may become necessary.
- The working group may decide to invite representatives of interested parties (e.g. industry organisations) to address and discuss issues of common interest, such as aspects on the drug development pipeline.

Chairperson and Vice-Chairperson

The Chairperson – and in his absence, the Vice-Chairperson – is in charge of the efficient conduct of the business of the working group meetings and shall in particular:

- Plan the work of the working group meetings together with the implementation group and paid consultant.
- Ensure the fulfilment of the mandate of the working group.
- Be in charge of the conduct and running of the meetings.
- Seek confirmation from working group members that no conflict of interest exists in relation with topics raised during meetings.

The Vice-Chairperson will deputise for the Chairperson when the latter is unable to chair either all or part of the working group meeting. On such occasions, the Chairperson will seek the agreement of the Vice-Chairperson as early as possible, prior to the meeting and the implementation group shall be informed immediately.

Election of Chairperson and Vice-Chairperson

Core members of the working group shall elect one of the core members to act as Chairperson and one to act as Vice-Chairperson.

Organisation of meetings

1. Dates for working group meetings will preliminary be set for 2008 with additional ad hoc meetings to be decided as appropriate (see point 7).

¹⁷ European Society of Clinical Microbiology and Infectious Diseases

2. The working group shall meet at the ECDC in Stockholm. Ad hoc meetings may also take place at the EMEA in London.
3. The meetings will be held and minuted in English and sent to EMEA and ECDC Scientific Committees for information.
4. The draft agenda for every meeting shall be circulated, together with the relating documents, by the implementation group/paid consultant, in consultation with the Chairperson, at least seven calendar days before the meeting.
5. When a member of the working group is unable to participate in a meeting, or part of a meeting, he/she must inform the paid consultant/implementation group in advance, in writing.
6. A minimum of five core members are required to attend the working group meeting or the meeting will have to be rescheduled.
7. The proposal for an ad hoc working group meeting and the conduct and objectives of such meeting shall be proposed by the Chairperson in collaboration with the implementation group. The implementation group/paid consultant shall inform the working group on the need for an ad hoc meeting as early as possible.

Roles and responsibilities of the working group

In accordance with its mandate to oversee, facilitate, follow-up and advise on the work aimed at producing a report on the gap analysis, the working group and its Chairman will regularly be kept updated on the progress of the project as set out in this document.

- The main role of the working group will be to advise the implementation group with regard to:
 - definitions of objectives and main output, i.e. the gap analysis and technical reports;
 - overall strategy;
 - definitions of the individual components of the gap analysis;
 - proposals for improvements to reach the objectives;
 - discussions on the scientific methodology for the individual project;
 - content of the technical reports; and
 - giving support to the implementation group and paid consultant as far as meeting the objectives, including the final reports.
- The members shall provide declarations of interest in the area of antibiotic drug development by filling in an agreed form provided by EMEA/ECDC. In addition, members shall declare any conflict of interest as appropriate before or during the working group meetings. At the discretion of the Chairman, the member may be prevented from active participation on certain specific issues.
- The members shall commit to active participation of the activities of the group. Should a member fail to attend two consecutive meetings, replacement of the member will be considered by any of the appointing bodies.

Roles and responsibilities of the implementation group

Under the authority of the working group, the implementation group shall closely oversee and lead the work of the paid consultant responsible for the daily running of the individual projects.

- Provide technical and scientific lead to the paid consultant.
- Provide legal and regulatory lead to the paid consultant.

The composition of the implementation group includes EMEA and ECDC staff representatives, one of the co-opted members and the paid consultant.

Responsibilities of the paid consultant

The overall projects will be run and monitored by a paid consultant. The responsibilities of the paid consultant include the close monitoring of the ongoing projects to ensure timely feedback of the work in accordance with the agreed timetable. The paid consultant will be part of the implementation group and will produce:

1. A regular report on the progress of the different projects, which includes:
 - monthly written updates to the implementation and working groups members; and
 - regular telephone discussions and agreements with members of the implementation group and the working group Chairperson.

2. In consultation with the Chairperson and the implementation group, the relevant documents to be conveyed to the working group, i.e. timely invitations to meetings, provision of agendas, documents and presentations, as appropriate.
3. In liaison with the different study contractors to convey technical and scientific steer to meet the objectives of each project and thereby to ensure high quality output from the projects.
4. The overarching technical report and reports on the subprojects in liaison with the working group members and implementation group.

Observers and contractors

In addition to the observers mentioned above, the working group may admit additional representatives of international organisations, EU scientific committees or political bodies with interests in the issues of antimicrobial resistance as observers during working group meetings.

In addition, contractors of the scientific projects may be invited to discuss and give presentations to the working group.

General provisions

The members of the working group, as well as observers and all experts, shall not disclose any information, which, by its nature, must be covered by professional secrecy (i.e. not to divulge any of the materials discussed at the meetings until such time that this material becomes published, unless otherwise sanctioned by the working group).

Annex B: Additional information on the study on the burden of infections due to multidrug-resistant bacteria and pipeline analysis

B1 Burden study

B1.1 Table of parameters used

Parameter	Unit	Value	Reference
No. MRSA ^a from LRTI ^b / from BSI ^b	Ratio	1.25	[21]
No. MRSA from SSTI ^b / from BSI	Ratio	5.25	[21]
No. MRSA from UTI ^b / from BSI	Ratio	0.75	[21]
Attributable mortality of MRSA BSI	%	9.8	[26]
Attributable mortality of MRSA LRTI	%	7.0	[26-27]
Attributable mortality of MRSA SSTI	%	1.4	[26-27]
Attributable mortality of MRSA UTI	%	0.2	[26-27]
Extra length of hospital stay for MRSA BSI	Days	8	[29]
Extra length of hospital stay for MRSA LRTI	Days	9.4	[29]
Extra length of hospital stay for MRSA SSTI	Days	5	[29]
Extra length of hospital stay for MRSA UTI	Days	6.1	[28]
No. VRE ^c from wound infection / from BSI	Ratio	4.67	[23]
No. VRE from intra-abdominal infection / from BSI	Ratio	1.89	[23]
No. VRE from UTI / from BSI	Ratio	3.44	[23]
Attributable mortality of VRE BSI	%	25	[23]
Attributable mortality of VRE wound infection	%	6	[23]
Attributable mortality of VRE intra-abdominal infection	%	3	[23]
Attributable mortality of VRE UTI	%	9	[23]
Extra length of hospital stay for VRE BSI	Days	15	[23]
Extra length of hospital stay for VRE wound infection	Days	6.2	[23]
Extra length of hospital stay for VRE intra-abdominal infection	Days	2.6	[23]
Extra length of hospital stay for VRE UTI	Days	5.4	[23]
No. penicillin-resistant <i>Streptococcus pneumoniae</i> from respiratory tract infection/ from BSI	Ratio	2.7	[24]
No. third-generation cephalosporin-resistant <i>Klebsiella pneumoniae</i> from LRTI / from BSI ^d	Ratio	1.19	[22]
No. third-generation cephalosporin-resistant <i>K. pneumoniae</i> from SSTI / from BSI ^d	Ratio	0.33	[22]
No. third-generation cephalosporin-resistant <i>K. pneumoniae</i> from UTI / from BSI ^d	Ratio	1.19	[22]
Attributable mortality of third-generation cephalosporin resistant <i>E. coli</i> and <i>K. pneumoniae</i> BSI	%	30	[19]
Attributable mortality of third-generation cephalosporin resistant <i>E. coli</i> and <i>K. pneumoniae</i> LRTI	%	21	[19, 27]

Parameter	Unit	Value	Reference
Attributable mortality of third-generation cephalosporin resistant <i>E. coli</i> and <i>K. pneumoniae</i> SSTI	%	4	[19, 27]
Attributable mortality of third-generation cephalosporin resistant <i>E. coli</i> and <i>K. pneumoniae</i> UTI	%	1	[19, 27]
Extra length of hospital stay for third-generation cephalosporin resistant <i>E. coli</i> and <i>K. pneumoniae</i> infection	Days	11	[18-19]
No. carbapenem-resistant <i>Pseudomonas aeruginosa</i> from LRTI / from BSI	Ratio	16.0	[22]
No. carbapenem-resistant <i>P. aeruginosa</i> from SSTI / from BSI	Ratio	4.67	[22]
No. carbapenem-resistant <i>P. aeruginosa</i> from UTI / from BSI	Ratio	11.3	[22]
Attributable mortality of carbapenem-resistant <i>P. aeruginosa</i> BSI	%	17.7	[25]
Attributable mortality of carbapenem-resistant <i>P. aeruginosa</i> LRTI	%	12.7	[25, 27]
Attributable mortality of carbapenem-resistant <i>P. aeruginosa</i> SSTI	%	2.6	[25, 27]
Attributable mortality of carbapenem-resistant <i>P. aeruginosa</i> UTI	%	0.4	[25, 27]
Extra length of hospital stay for carbapenem-resistant <i>P. aeruginosa</i> BSI ^e	Days	5.7	[25]

^aMethicillin-resistant *Staphylococcus aureus* (MRSA)

^bBSI, bloodstream infection; LRTI, lower respiratory tract infection; SSTI, skin and soft tissue infection (including wounds and surgical site infections); UTI, urinary tract infection

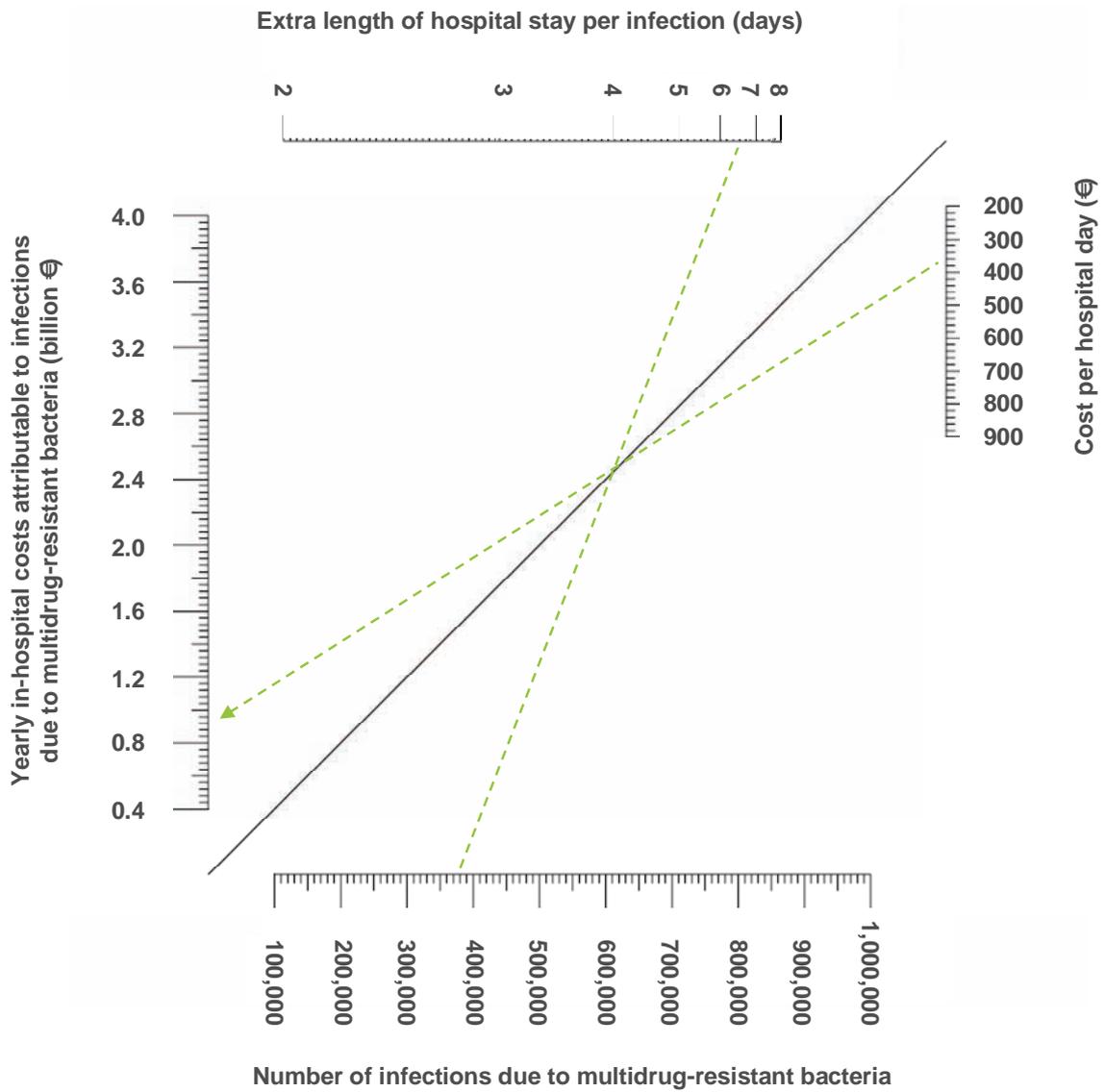
^cVancomycin-resistant enterococci (VRE)

^dThese ratios were also used for third-generation cephalosporin resistant *Escherichia coli*.

^eThis extra length of hospital stay was also used for LRTI, SSTI and UTI.

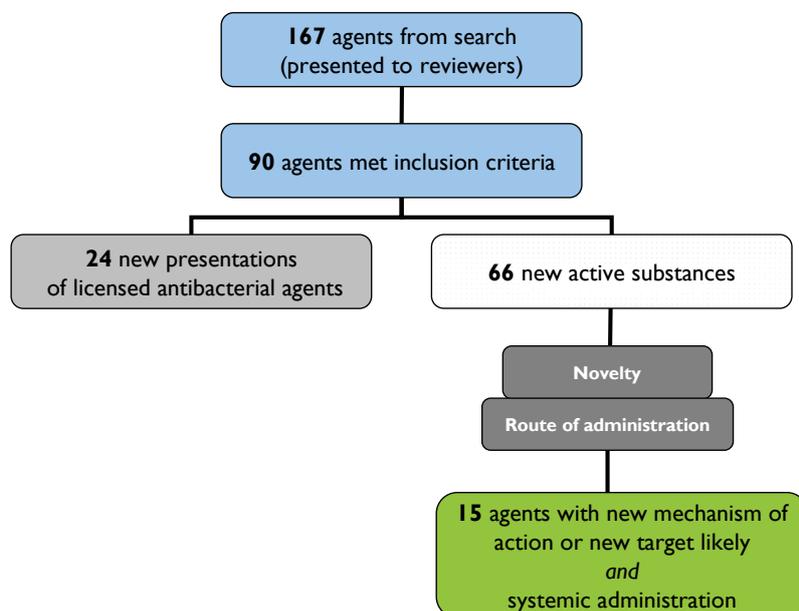
B1.2 Nomogram

This nomogram can be used to calculate yearly in-hospital costs attributable to infections due to multidrug-resistant bacteria with various values for the total number of infections, the average extra length of hospital stay per infection and the average cost per hospital day.



B2 Pipeline analysis

B2.1 Flow-chart of the pipeline analysis



B2.2 Agents with same target as previously licensed agents.

List A. New presentations of licensed antibacterial agents with assigned *in vitro* activity that goes beyond the known spectrum of activity of the licensed presentation, based on optimistic assumptions of the activity that might be achieved by using a different route of administration (n=11, search date 14 March 2008).

Amikacin inhalation
 Amikacin sustained release
 Ciprofloxacin inhalation
 Research programme: liposomal ciprofloxacin inhalation
 SPRC AB01
 Tobramycin liposomal
 Tobramycin inhalational
 Tobramycin/Dexamethasone
 Tobramycin/fosfomicin
 Tobramycin/prednisolone acetate
 Ciprofloxacin otic solution

List B. Agents that were assessed as acting on the same target via the same mechanism of action as that of at least one previously licensed antibacterial agent (n=39, search date 14th March 2008).

AFN 1252	E 5065	RX 1741
AR 709	EDP 420	Sulopenem
BC-3205	Faropenem medoxomil	Tebipenem pivoxil
BC-7013	Finafloxacin	WCK 1152
CBR 2092	Iclaprim	WCK 771A
Cetefloxacin	MCB 3837	Zabofloxacin
Cethromycin	Rifalazil	TD 1792
CS 834	MK 2764	WQ 3034
TR 701	Nemonoxacin	Clinafloxacin
DC 159a	NXL 103	Dalbavancin
DW 286	Ozenoxacin	Trospectomycin
DX 619	PF 3709270	Besifloxacin
E 4767	Ranbezolid	NPI-32101

List C. New topical* 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=12, search date 14 March 2008).

AN 0128
 Bacteriophage, pseudomonal
 Iseganan†
 Lysostaphin cream
 Lysostaphin (topical)
 NVC 422
 Omiganan
 OPT 80
 Pexiganan
 Ramoplanin
 REP 8839
 XOMA 629

* Oral non-systemically absorbed agents have been also counted in this category.

† In addition, Iseganan can also be given via inhalation.

B3. Technical information provided by the pipeline database companies

B3.1 Adis Insight R&D (Wolters Kluwer Health)

Internal processes

Information Sources

Proceedings from 150+ major scientific meetings are monitored routinely and pertinent data presented as posters and abstracts are included in R&D Insight within 10 days of each meeting. News from media releases is added to the database daily from PR Newswire, Business Wire, Canada Newswire, Hugin Online, Japan CNN and direct from company websites that do not use these services.

Additional sources are:

- Direct contact with pharmaceutical company representatives to verify information.
- Company reports and regulatory filings are routinely checked for new and updated information. More than 3 500 companies are monitored.
- Information from ongoing clinical trials is incorporated from international media releases and more than 20 clinical trial registries, such as www.clinicaltrials.gov.
- Scientific journals: more than 1 400 journals are monitored routinely for inclusion

All information sources are evaluated by expert staff for relevance to *R&D Insight*. All staff are provided with comprehensive training by experienced senior editors on the selection of relevant material.

Inclusion and exclusion criteria

All information on drugs being developed by pharmaceutical companies and biotechnology companies, either alone or in collaboration with non-commercial institutions, is entered into the database for all countries, all therapeutic areas and all indications. Information about the following is excluded:

- Medical devices (unless in combination with a drug).
- Generic drugs, unless undergoing reformulation and regulation as new drugs, and biosimilars.
- Drugs launched in all major markets prior to 1995 that do not have new development since launch.

Company profiles – Inclusion criteria

Adis *R&D Insight* contains links to more than 400 company profiles, detailing information about each company's subsidiaries, history, R&D expenditure, licensing agreements, mergers and acquisitions, as well as links to the complete R&D pipeline for each company.

To qualify for the addition of a Company Profile to *R&D Insight* a company must have:

- 10 or more active drugs in development;
- be amongst the top 50 biotechnology companies according to MedAd News (Engel Publishing);
- be a client of Wolters Kluwer Health with five or more products in development; or
- made a specific request to have a company profile included.

Timeliness

- Client queries and requests: response within 24 hours of receipt.
- Media releases: three-day turnaround.
- Scientific conference processing: completion 10 working days post conference.
- Company reports: annual, quarterly and half-yearly reports completed throughout each year as they become available;
- Clinical trial data: incorporated when the data is made available.
- All relevant scientific data added for completeness in advance of regulatory submission (phase III).

EPhMRA codes

These are codes used by the European Pharmaceutical Market Research Association (EPhMRA) classification system. These codes mainly classify products according to their indications and use. Therefore, the same compound may be found in several classes, depending on the product. For example, Naproxen tablets can be classified in M1A (anti-rheumatic), N2B (analgesic) and G2C (if indicated for gynaecological conditions only). The main purpose of the EPhMRA classification system is to satisfy the marketing needs of pharmaceutical companies.

Phase of development – Definitions

Development phase	Definition
Research	The early development of a drug research programme, including lead screening and lead validation. Used when a company has identified a small number of candidates and is conducting early research to identify or optimise lead compounds for further <i>in vitro</i> and <i>in vivo</i> testing.
Preclinical	The drug is being tested <i>in vitro</i> (cells, test tubes) or <i>in vivo</i> (animals). The developer applies for permission to go into clinical testing. The procedure for applying for permission will depend on the country. For example, in the USA, an Investigational New Drug (IND) application must be granted before clinical trials can begin.
Phase 0	Purpose: the drug is being tested in first-in-human trials conducted in accordance with US FDA 2006 Guidance on Exploratory Investigational New Drug (IND) studies. These studies are designed to speed up development of promising drugs by establishing very early on whether the agent behaves in human subjects as was anticipated from preclinical studies. Studies will include the administration of single subtherapeutic doses of the study drug to a small number of subjects (10–15) to gather preliminary data on the agent's pharmacokinetics and pharmacodynamics.
Phase I	Purpose: to identify adverse events and determine efficacy and initial pharmacokinetics. These trials of a new drug or therapy are usually conducted in normal male volunteers. Patients may be evaluated instead of volunteers in phase I trials in order to treat immediately life-threatening and serious conditions for which there is no comparable or satisfactory alternative therapy available. In addition, expanded access programmes allow patients for whom standard therapy is ineffective or contraindicated, and who are ineligible to enter trials, to receive investigational drugs in parallel with controlled trials.
Phase I/II	Purpose: to establish the maximum tolerated dose (phase I) and drug tolerability (phase II) in patients. In life threatening and serious conditions, the second part may confirm preliminary efficacy.
Phase II	Purpose: to provide a measure of efficacy in addition to short-term tolerability and safety. Phase II studies are conducted in patients who have the disease or condition that the drug is intended to treat. Other phase II study objectives include determining the minimum dose that is maximally effective, or that is sufficiently effective without undue toxicity. For the purposes of using R&D Insight, phase II includes phase IIa pilot or feasibility trials, and phase IIb well controlled, pivotal trials.
Phase II/III	Purpose: to address within a single trial objective what is normally addressed through separate trials in phases IIb and III. The aim of having the seamless phase II/III trial design is so that data can be used more efficiently, which may lead to a reduction in the duration of drug development. The trial is designed to assess efficacy and safety of the test drug and most are designed with parallel treatment groups rather than crossover.
Phase III	Purpose: to confirm efficacy and monitor adverse reactions from long-term use. In phase III studies, a drug is tested under conditions more closely resembling those under which the drug would be used if approved for marketing. The goal is to gather additional information about efficacy and tolerability that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labelling. NB. Approval/disapproval decisions are based on the results of adequate and well-controlled (pivotal) studies. To be considered pivotal, a study must meet at least the following four FDA-defined criteria; they must be: (1) controlled – using placebo or a standard therapy; (2) double-blind – when such a design is practical and ethical; (3) randomised; (4) of adequate size – study sample size is a common clinical trial design flaw. For the purposes of using R&D Insight, phase III includes phase IIIa and phase IIIb trials. Phase IIIb trials are usually those undertaken after a regulatory dossier has been submitted.
Pre-registration	All the necessary clinical trials have been completed and the drug is waiting for registration or approval for use by a governing body. For example, a New Drug Application (NDA) has been filed with the FDA in the USA.
Registered	The drug has been registered or approved for use in a particular country, or group of countries such as the European Union countries.
Launched	The drug has been launched and is now marketed in a particular country, or group of countries.
Discontinued	The company has chosen to stop development. This term is usually qualified by the phase at which development was discontinued, for example, discontinued (preclinical).

Development phase	Definition
No development reported	If there has been no activity associated with a drug (no commercial information released, no recently published studies) for 18 months to two years, the term 'no development reported' is assigned. The time frame depends on the last phase of the drug. This is the term used until a drug is confirmed as discontinued, withdrawn or suspended, or activity is resumed.
Withdrawn	The drug has been withdrawn from the market. This term applies to drugs that have been launched but subsequently withdrawn from the market.
Suspended	This term is used when a company has suspended development of a drug, often in order to focus on the development of some other drug. Development has not been discontinued.
Clinical (Phase unknown)	This option is only used when the clinical phase of development is unclear.
Phase groupings	
Active	This group will include all active phases: those which are not discontinued, suspended, withdrawn, or have a no development reported status.
Inactive	This group will include all inactive phases: those which are discontinued, suspended, withdrawn, or have a no development reported status.
Clinical	This group will include all active, clinical phases from phase 0 to launched.
Preclinical	This group will include active, preclinical and research phases.

B3.2 Pharmaprojects (T&F Informa UK Ltd.)

Development status

The following development stages are used throughout Pharmaprojects:

Preclinical	All stages of preclinical investigation including discovery, research, lead optimisation. This is also used where the developmental status is unknown.
Phase I clinical trial	Human pharmacokinetic and volunteer studies.
Phase II clinical trial	Early clinical studies to demonstrate activity in patients.
Phase III clinical trial	Multicentre clinical trials to obtain data for registration.
Clinical trial	In clinical trials, stage unknown
Pre-registration (also known as pre-approval)	Registration documents submitted but not yet approved.
Registered (also known as approved)	Registration obtained but marketing not yet started.
Launched	Product available in at least one market.
Suspended	Development suspended with the possibility of restarting.
Discontinued	Development terminated.
No development reported	No evidence of continuing development reported.
Withdrawn	Withdrawn from marketing.

How the drug profiles are updated

As a drug advances and new information becomes available, its profile is amended and updated. Where there is controversy surrounding important information, this is verified with the developing company before a profile is amended.

The Pharmaprojects editorial staff are continually reviewing worldwide information on new drug development. In addition, a significant amount of new information derives from the work of the editorial team of Pharmaprojects' sister publication *Scrip World Pharmaceutical News*.

Much of the Pharmaprojects data comes directly from the companies themselves, with extensive reference to company websites, reports and press releases.

There is continual two-way communication between Pharmaprojects staff and their contacts in the pharmaceutical and biotechnology industries; both to gather new data and importantly, to verify information obtained from other sources.

Every company with an entry in Pharmaprojects is asked to verify, at least annually, the information relating to its development pipeline.

Pharmaprojects editorial staff attend the major international medical and scientific congresses to gather information often entering the public arena for the first time. Editors use these opportunities to question company personnel attending the congress to ascertain the companies' development plans for any products reported. This ensures that, as far as possible, all new compounds entered into the database are true development candidates.

International research literature is scanned for new developments; however, there is less dependence on journals since, by definition, research information is 'old' by the time it is published.

Criteria for addition to Pharmaprojects of new drug candidates

Here, we look at the criteria used to decide when to add a new product entry on to the database – and, just as importantly, when not to.

The aim of Pharmaprojects is to provide the most accurate picture possible of what is really going on in pharmaceutical research and development worldwide. A vital part of this is deciding whether or not a preclinical compound is a genuine candidate for development as a new drug. Now more than ever, in the days of combinatorial chemistry and mass screening, there are thousands more compounds synthesised than are development candidates. If we added every compound which we came across onto the database, the Pharmaprojects active database would be huge and just as full of inactive compounds as if we did not perform the 'No Development Reported' procedure (see later). So we have to be selective. One of the questions we get asked most often is what are the criteria our editors use to decide whether or not to add a new compound to the active database. Some databases, particularly those that rely heavily on patent applications as data sources, add on many more preclinical drugs than are ever seriously considered as drug development candidates. While it can be useful to alert those in the industry to early research areas in which companies have interests, the downside is that it can give a badly distorted view of what is really in company's portfolios. At Pharmaprojects, we make strenuous efforts to discover whether or not a drug is a serious candidate for development before adding it on to the database to keep ours the most accurate reflection of genuine pipelines.

So how do we do this? Certain data sources themselves can be regarded as confirmation of active development; for example, if a drug appears on the pipeline section of a company's website. Often companies will contact us themselves and provide us with details of new drugs that they wish to see included in their Pharmaprojects pipeline, particularly if the drugs are available for licensing. Company press releases or R&D portfolio presentations are also reliable sources. It gets more difficult if the first appearance of a compound is not in such a source. In such cases where it is not explicitly stated that a compound is in development, we will generally contact the company concerned to see if it is a pipeline compound. However, many companies decline to comment on early development compounds. It is in these cases that we have to use other criteria to decide whether or not to add the compound to the database.

Although we do use a set series of criteria to evaluate the likelihood of a product being in development, we do not use a 'points' system or a formula; rather we combine our analysis on a number of fronts with the years of experience our editorial team has accrued. However, here are a number of points that they will consider.

Firstly, the name of the compound will be considered. If it is obviously an INN, it is more likely to be a serious development candidate. If it is given a more spurious name, for instance one based on the research institute where it was synthesised or discovered, it might be treated with more caution. A lot of information can be gathered from a compound's lab code. For instance, Merck & Co's research compounds begin with an L- code; when they are chosen for development, they are rechristened with an MK- number. The same applies with Abbott and A- codes becoming ABT- codes. Thus an editor coming across an MK- or ABT- code would be inclined to treat this as a potentially serious development candidate. Also, as most companies label their lab codes sequentially, we can get a good idea of the age of a compound, with a higher numbered code more likely to be a new candidate.

A very important consideration is the published source of the data. Most drugs that we have to decide whether or not to include will be those presented at conferences or appearing in journals. The identity of the journal thus has

a bearing. For instance, the Japanese Journal of Antibiotics is a very important source of useful information for us, but it also includes reports on many antibiotics that have been newly isolated, but are not serious candidates for development as medicines. Thus, we have to be careful.

One of the ways in which we are aided in our decision is by actually looking at the scientific data provided and, in particular, its activity. For instance, in the case of an antibiotic, a good rule of thumb is that reasonable activity is indicated by an MIC of less than 1mg/ml. Higher MICs may thus indicate a less active compound that is therefore less likely to be taken forward. However, this would be organism-dependent, with a higher MIC for a multidrug-resistant organism being looked at more seriously.

We can also apply our judgement on other benefits a new drug has or does not have against existing therapies. These may include a better side-effect profile, easier dosing regimen, or a more convenient route of administration. A serious development candidate would be expected to have advantages in at least one area.

Finally, we are more likely to add in a new profile if the drug is in a new therapeutic area for the company involved. In other words, we may feel it is more important to alert to the fact that a company has moved into the analgesic area with its first compound in that field than we would to inform that a 14th preclinical analgesic had been reported by a company. In the latter case, we would probably wish to ascertain from the company whether the drug was a serious lead rather than just another in a series that they have synthesised.

So the combination of good contacts, entry criteria and, above all, editorial experience come together in deciding whether a drug mentioned in the literature merits inclusion in Pharmaprojects. These procedures, along with others such as the 'No Development Reported' programme enable us to provide what we believe is the most accurate picture of what is really in development at the world's pharmaceutical companies.

Keeping our pipelines accurate using the No Development Reported status

The challenge for Pharmaprojects is to bring you the most accurate picture of what is really happening in pharmaceutical R&D. To do this, we must not only add to the active section of the database all compounds that enter development, but we must remove all of those whose development ceases. The latter task is not as easy as it might seem. Although the discontinuation of products in more advanced stages of development is often high-profile news, companies are usually unwilling to make announcements about drug failures at earlier stages. It is perfectly normal for many compounds not to make it past the early stages of development, but quite naturally, a company is not going to send out a press release every time it drops an early drug candidate.

At Pharmaprojects, we will only list a drug as discontinued if this has positively been confirmed by the company. Therefore, we needed to devise a programme to weed out other drugs whose development is not continuing. This involves contacting companies to ask them about drugs that we suspect have been dropped, and having a way to deal with such drugs that the companies decline to comment on. This is where the 'No Development Reported' (NDR) status comes in.

The first stage of the process is to identify which drugs may have dropped out of development. To do this, we look at how long it is since we last obtained new information on a drug. With our extensive contacts at companies, our wide-range of published information and our series of stringent checks to keep our data up-to-date, if nothing new has been heard on a development project for over a year, we begin to suspect that it has halted. Thus, each month, we produce from our internal database a list of compounds that have not been updated for some time, typically 14 to 18 months (it varies slightly due to our publishing schedule). We then get in touch with all of the companies involved, using our extensive network of contacts built up over 25 years, to enquire about the development status of the programmes. In some cases, the companies will confirm that development is ongoing; in some, they will confirm that development has been dropped. But in quite a large number of cases, they decline to comment at all.

The reasons why companies decline to respond to our questioning are many. In some cases, it is company policy never to comment on early development projects. Some companies do not comment on 'negatives', such as lapses of development. In a small number of cases, although the compound has been reported as a development candidate at a meeting, it may never have been a serious candidate, so the company's Investor Relations department or whichever department deals with our queries may have no information on it.

We now have to decide what to do with these compounds whose development appears to have stalled. The NDR category was created to apply to those compounds that are believed to have been dropped, but for which the companies involved have not confirmed discontinuation. Thus these entries can be listed as 'No Development Reported'. They immediately become part of the Ceased data set and do not appear as part of a company's R&D pipeline any more. The passing of a drug to NDR is recorded as a Major Event. In fact, there is a little more editorial discretion than the above would suggest. Compounds in phase II and beyond are often investigated further before being moved to NDR, as since phase II and III trials can take more than 18 months, there may be nothing unusual about the lack of new data reported. Preclinical and phase I drugs are much more likely to be

switched to NDR after the first inquiry, but even here, each one is looked at on a case-by-case basis. For instance, if the text of an entry reads 'Company A and Company B have entered into a 3yr agreement to investigate COX-2 inhibitors', it does not make much sense to mark up the entry as ceased after only 18 months!

Of course, if Pharmaprojects subsequently uncovers evidence that a project marked as NDR is indeed proceeding, it is brought back into active development and 'Development Continuing' is recorded to alert subscribers to this fact. Around 91% of records marked up as NDR never return to active development. Of those that do, most do so within a year of being marked up as NDR. If a profile has been listed as NDR for a year or more, you can thus be 97-98% certain that its development has ceased.

The importance of the 'No Development Reported' process in keeping our company R&D pipelines accurate cannot be overstated. Without this process, we would be giving a totally distorted view of the company's development programme.

At Pharmaprojects, we are committed to reporting only what is really in development at the pharmaceutical companies across the world. This involves much more than just scanning the literature and reporting every compound mentioned as a development drug. This is a complex process that involves vetting which compounds are added and close liaison with all of the pharmaceutical companies. The 'No Development Reported' process is just one of the methods that we employ to provide a truer picture of today's drug R&D.