6.1 Antibacterial drug resistance
See Background Paper 6.1 (BP6_1AMR.pdf)

Background and developments since 2004

The 2004 Priority Medicines Report underlined the major threat to global health from increasing resistance to antimicrobial drugs: “The discovery of antibiotics in the mid-twentieth century led to a revolution in the management and treatment of infectious diseases. Today, we are witnessing the emergence of drug resistance along with a decline in the discovery of new antibacterials ... As a result, we are facing the possibility of a future without effective antibiotics ...”. 1

In 2013 the situation remains a continuing cause for concern:

- Gram-negative bacteria are now showing increasing resistance to antibiotics. In Europe, bacteria including *Escherichia coli* and *Klebsiella pneumonia* collected from normally sterile sites (blood or cerebrospinal fluid) have demonstrated resistance to antibiotics.
- The number of new molecular entity (NME) antibiotics approved by the U.S. Food and Drug Administration (FDA) has remained very low over the past two decades (see Background Paper 6.1, Annex 6.1.21). Ten new antibacterials (i.e. excluding antivirals, antifungals, antiprotozoals and vaccines) were approved by the FDA between 2004 and 2012 and 13 were approved between 1996 and 2003. These are NMEs, which are defined by the FDA as medications containing an active substance that has never before been approved for marketing in any form in the United States. There have been no novel mechanism agents for Gram-negative organisms for decades.
- Research has revealed that there is a low possibility, if at all, of reversing antimicrobial resistance (AMR) once it has been established in both community and non-community settings.2
- There is now more extensive data supporting the increasing economic burden of AMR - due in part to the doubled increase in hospital length of stay, additional discharge costs to facilities, extra medical care needed and productivity loss. The societal costs to the EU, Norway and Iceland due to AMR in 2007 were estimated to be in excess of €1.5 billion per year.3

There have also been a number of success stories since 2004. Surveillance programmes have been initiated at local, national, and international levels. Successful programmes have led to better interventions aimed at assessing AMR and ensuring more appropriate antibiotic prescribing. The adoption in November 2011 of the Communication from the Commission to the European Parliament and the Council on an Action Plan against the rising threats from Antimicrobial Resistance has significantly strengthened and coordinated action against AMR.
The Action Plan has 12 concrete actions to combat AMR and two of these in particular should be noted, the actions on collaborative antibiotic research and development (Action 6) and coordination of research efforts (Action 11.)

There have been major improvements in the development of diagnostic tools. Inexpensive and readily available diagnostic tools are now available for a variety of infectious diseases. Some of these tools are able to distinguish between viral and bacterial infections, while others are able to distinguish between bacterial species (see Background Paper 6.1, Annex 6.1.7). Point-of-care diagnostics remain an unmet need.

Since 2004, various national and international organizations have responded to the issue of AMR through numerous meetings, task forces, workshops, and publications (see Background Paper, Annex 6.1.1). Several major publications addressing AMR and its public health threat are in print.5,6,7

One success in efforts to slow the development of AMR in Europe is the overall decline in the prevalence of methicillin-resistant Staphylococcus aureus (MRSA) in this region since 2005 (see Figure 6.1.1). However, this decline has not occurred in all European countries (see Background Paper, Annex 6.1.10).

Figure 6.1.1: Proportion of methicillin-resistant Staphylococcus aureus isolates in participating countries, 2005 and 2010

Control strategies

European Union
European Union efforts to combat AMR are extensive and have expanded (see Background Paper 6.1, Annex 6.1.15). In 2011, the European Commission (EC) issued an “Action plan against the rising threats from Antimicrobial Resistance”. The EC proposed the implementation of a five-year Action Plan to combat AMR, based on 12 key actions. In particular, the actions related to research activities promoting public-private collaborative research and development to bring new antibiotics to patients (Action 6) and the reinforcement and coordination of research efforts (Action 11) are already well advanced in their implementation. The Innovative Medicines Initiative (IMI) has recently launched a €223.7 million programme to combat AMR. Under its 7th Framework Programme (FP7), the EC currently funds numerous projects that aim to develop control strategies, diagnostics, drugs and new therapies. There are numerous national antibiotic stewardship campaigns, including the European Antibiotics Awareness Day.

The European Technology Platform on Nanomedicine has also been established in an effort to create diagnostic tools that can identify a disease at the earliest possible stage – thereby facilitating the appropriate use of antibiotics. Top Institute (TI) Pharma, a non-profit organization whose mandate and vision is based on the 2004 Priority Medicines Report, has also provided support for projects concerning MRSA and multidrug-resistant (MDR) pathogens.

World Health Organization
The WHO has been heavily involved in the range of national and global activities outlined above. In addition, the WHO has published various recommendations to deal with AMR (see Background Paper 6.1, Annex 6.1.18).

World
China’s activities concerning AMR are rather recent but expanding. In 2004, China created its first AMR surveillance programme and national guidelines for appropriate antibiotic use. Elsewhere, Israel has had success with a national campaign promoting prudent antibiotic use, and numerous other countries have also implemented stewardship campaigns and other control strategies. In India, the Chennai Declaration proposes a plan to create a road map for tackling the challenge of AMR in India.

Other approaches

Vaccines
There are several FDA-approved vaccines addressing bacterial pathogens (see Background Paper 6.1, Annex 6.1.24 and Table 6.1.3). Accumulating literature is providing evidence that vaccination has potential advantages for primary prevention of AMR. Protein-based vaccines usually target multiple immunogenic epitopes, suggesting that several mutations are required before the immune response to the vaccine may no longer recognize the bacterial pathogen. By preventing infections in
the first place, vaccines do not allow bacteria to replicate in the host, thereby limiting the selection process of variants to the initial phases of the infection. However serotype replacement, as observed for pneumococcal strains, can undermine vaccine effectiveness. Bacteriophages may be used in the future for the treatment of antibiotic-resistant organisms.

**Diagnostics**

The development and validation of new diagnostic tests can in principle help determine whether antibiotics should be prescribed at all. When antibiotic treatment is needed, such tools can help determine which antibiotics should be prescribed. In addition, rapid tests can help control the spread of infections if an infection is diagnosed early enough. (See Background Paper 6.1, Annex 6.1.7).

**Alternatives to antibiotics**

Over the past five years progress has been made towards the development of one possible alternative to antibiotics: antivirulence drugs that would not kill but rather deprive bacteria of their virulence functions so that they can be eliminated by the immune system.\(^{13}\)

Another alternative approach was recently demonstrated in a proof-of-concept trial in which bacteriophages were genetically engineered to reverse a pathogen’s drug resistance, thereby restoring its sensitivity to antibiotics.\(^{14}\)

Elsewhere, another approach is based on the broad and diverse biological functions of endogenous peptides called cationic antimicrobial peptides (CAMPs), which are found in most animal cells that host microbes. These CAMPs are currently being widely used as blueprints for the development of innovative therapeutic agents that may be used as antimicrobials.\(^{15}\)

**Incentivizing R&D**

Numerous incentives for drug development have been proposed and implemented (see Background Paper, Annex 6.1.22). The Innovative Medicines Initiative (IMI) has recently launched research calls under the new theme NewDrugs4BadBugs (ND4BB), which aims to bring new antibiotics to patients by funding research in which small and medium-sized enterprises (SMEs) and academics work in close collaboration with large pharmaceutical companies in order to establish a vibrant antimicrobial drug discovery hub. In July 2012, the United States enacted the Food and Drug Administration Safety and Innovation Act (user fee legislation) which included the GAIN Act. The GAIN Act will provide an additional five years of data exclusivity, priority review and fast track status for new antibacterials that target qualifying pathogens.\(^{16}\)

**Remaining challenges**

Although there are some achievements in the containment of AMR in Europe, much remains to be done. For this reason it is concluded that the containment of AMR remains a high priority. Continued action is needed on many fronts: to stimulate basic
and applied research and development of new medicines and other treatment options in response to increased resistance; to reduce inappropriate use through the use of evidence-based public health interventions; to improve prescribing and dispensing practices; and to conduct high-quality surveillance of antibacterial resistance and of antimicrobial consumption patterns in hospitals and the community.

Research needs

Collaborative, global and more concerted efforts are needed to address the public health threat that AMR poses. The EU should continue its extensive contributions and collaborations in this regard and can provide ongoing leadership in research in the following areas:

Diagnostic and therapeutic tools:
- Development and use of cost-effective and point of care diagnostic tools to encourage prudent and appropriate antibiotic use.
- Priority development of antibiotics against Gram-negative bacteria.
- Replenishment of the antibiotic development pipeline, possibly using new business models for R&D, in order to develop new products with novel mechanisms of action to address the already heavy burden of AMR.

Health systems:
- Establishment and implementation of a multi-faceted approach using standardized surveillance coupled with appropriate antimicrobial stewardship campaigns at country level.
- Allocation of public funding to continue providing evidence/data on antimicrobial resistance to treatment for vaccine-preventable diseases in order to assess the potential impact of comprehensive vaccination policies in reducing antimicrobial resistance.

Prescription interventions:
- Promotion of strategies designed to modify physician antimicrobial-prescribing practices towards an approach based on simplicity rather than complexity.
- Approaches to encourage improved adherence to veterinary “judicious use” guidelines.
- Promotion of investment in research and development of future innovative vaccines capable of targeting and preventing antibiotic-resistant bacteria.

References


