Europe to tackle antimicrobial resistance

The European Commission has launched a new approach to antimicrobial resistance which aims to strengthen existing efforts to fight this unrelenting public health issue.

The five-year action plan on antimicrobial resistance (AMR) issued in mid-November by the European Commission marks the start of a new "holistic" approach to addressing this increasingly urgent public health issue, which is the cause of about 25,000 deaths annually in the EU.[1]

The document was released after the Council of the EU in December 2009, and the European Parliament in May 2011, urged the Commission to establish an EU-wide plan to combat AMR, including a strategy for developing new, effective antibiotics.

The plan notes that despite the growing threat of AMR and the ongoing efforts to tackle it that began over a decade ago, weak market incentives as well as the growing cost of developing novel antibiotics have discouraged investment in this area. As a result, only a few new antibiotics are currently under development (see the November/December 2010 issue of *MedNous* for previous articles on antibiotic development efforts).

In particular, the inappropriate use of therapeutic antimicrobials in human and veterinary medicine, the use of antimicrobials for non-therapeutic purposes (eg for growth promotion of food-producing animals) and the pollution of the environment by antimicrobials have limited the EU's progress in the battle against AMR.

It is on this basis that the Commission formed its 12-point action plan, which is described as a "substantial reinforcement of current measures...together with a new set of rigorous measures". Its multi-sectoral approach is in line with the EU's One Health biosecurity initiative that focuses on the link between animal and public health.

Appropriate use, prevention and control

The Commission's proposed actions focus on five main objectives, the first of which is to ensure the appropriate use of antimicrobials in both human and veterinary medicine. This is the cornerstone of EU policy against AMR.

The other proposed actions are to prevent and control infection; develop new antimicrobials and/or appropriate alternatives; promote global collaboration; and boost research and innovation.

Among the Commission's plans for the first objective is the implementation of recommendations from a 2002 Council document on the prudent use of antimicrobials in human medicine that still have not been taken up effectively.[2] By 2015, it will publish a report identifying the progress made and ongoing shortfalls in this area.

Particular emphasis will be placed on improving the sustainability of national surveillance systems on AMR and facilitating access to surveillance data at local and regional levels. Furthermore, more pressure will be placed on member states to implement prescription-only requirements for antimicrobial agents.

Implementing control measures against AMR in nursing homes and long-term care facilities is another focal point of the strategy, as are educating and training healthcare workers. Furthermore, the Commission says that there needs to be better assessment and monitoring of strategies and control measures at the national level.

As for veterinary medicines, although there is co-operation among the animal health industry, veterinarians and farmers to promote prudent use of antimicrobials, "between Member States significant differences exist in the sales of antimicrobials that cannot be explained by the animal husbandry practices", notes the Commission. In addition, there is an increasing concern about the use of certain antimicrobials in the veterinary sector, such as third and fourth generation cephalosporins, which are critical for humans.

To address this and other veterinary issues associated with AMR, the action plan states that the regulatory framework on veterinary medicines and on medicated feed (via the review package foreseen in 2013) should be strengthened to ensure appropriate warnings and guidance are placed on the labels of veterinary antimicrobials. In addition, restrictions on the regular and off-label use of certain new or critically important antimicrobials for humans in the veterinary sector should be considered.

The authorisation requirements for veterinary medicines should also be revisited to sufficiently address the risks and benefits of antimicrobial medicines, the Commission says. Moreover, it believes that new recommendations for prudent use in veterinary medicine should be introduced using the same approach the Council has used in its recommendations for antimicrobial agents in human medicine.

Another important piece of the puzzle is to prevent the spread of diseases – both in veterinary and human settings – in order to reduce the use of antimicrobials. In the veterinary setting (ie for farm animals), the Commission envisions a new Animal Health Law that would focus on the prevention of diseases, the reduction of antibiotics use and the replacement of animal health provisions based on disease control.

In the human healthcare setting, the action plan states that prevention and control efforts should concentrate on following up with the Council's 2009 recommendation on patient safety that addresses the prevention and control of healthcare associated infections.[3]

R&D of new antibiotics

The plan acknowledges the ongoing gap between the increasing problems related to multi-resistant bacteria in the EU and the urgent need to develop new antimicrobials to meet medical needs. It calls for the promotion, in a staged approach, of "unprecedented" collaborative research and development efforts.

To this end, the Commission plans to launch a programme with the European Federation of Pharmaceutical Industries and Associations (EFPIA) for research into new antibiotics

aimed at improving the R&D efficiency through the open sharing of knowledge. This will take place within the context of the Innovative Medicines Initiative (IMI), Europe's largest public-private initiative aimed at developing new approaches to overcome scientific bottlenecks in the R&D of innovative medicines.

The Commission also envisages the establishment of an overarching framework agreement with the industry that defines the objectives, commitments, priorities, principles and modes of action for longer-term public-private collaboration. Among other things, this will involve making use of funding provided by the IMI and the Seventh Framework Programme for Research and Technological Development (FP7), as well as FP7's successor, Horizon 2020, which will fund projects from 2014-2020.

When asked how long it would take for such a programme to show signs of return on investment, EFPIA's director general, Richard Bergström, told *MedNous*: "It will take time to get the R&D pipeline to where it should be and we must view this as a long-term collaboration...We expect to see a series of work packages and specific projects launched over the course of the next year on a range of R&D issues relevant to antibiotics".

According to GlaxoSmithKline, whose chief executive Andrew Witty is the president of EFPIA, the programme is likely to include supporting clinical trials to evaluate new antibiotics and enhance drug development, and collaborating on preclinical research for the discovery of novel mechanisms to target bacteria.[4]

Another action point in the plan calls for the reinforcement and co-ordination of research efforts. In particular, this would include promoting further research on the development of diagnostic tools, vaccines and other preventive measures, as well as supporting the launch of a Joint Programming Initiative (JPI) to co-ordinate national research activities related to AMR.

Both are already in the works to some degree. In 2010 FP7 issued a call for proposals on the development of novel diagnostic tools for the rapid identification of resistant pathogens in a clinical setting.[5] Moreover, on 6 December 2011, the Competitiveness Council officially approved the JPI on 'The Microbial Challenge – An Emerging Threat to Human Health', meaning all the conditions for its launch are now in place, a Commission spokesperson told *MedNous*.[6]

The JPI is expected to become operational in 2012 and will focus on three main areas: understanding the biology and dynamics of resistance; improving disease prevention through supporting the development of novel antimicrobials, refined treatments and alternative treatments; and rapid diagnosis of pathogens and their resistance.[7]

Funding: IMI and FP7

As mentioned, the IMI will be at the core of the EU's R&D strategy for antibiotics. The IMI's 5th Call will take place in the first half of 2012. One of the two topics currently under consideration for the Call is 'Tackling resistance to antibiotics: building partnerships to progress the discovery and development of novel antibiotic drugs to treat the most urgent infections'.[8]

Though an IMI spokesperson could not say what the budget for the 5th Call would be, she confirmed that moving forward there would be fewer topics per Call than in the past, with the topics being "much bigger (more budget) than the early ones". The total IMI budget for the period 2008-2013 is €2 billion: €1 billion from FP7 and €1 billion of in-kind contributions from EFPIA member companies.

As far as FP7 is concerned, there are a number of projects already under way relating to AMR in addition to the Call for diagnostic tools.

Regulatory considerations

As with all major changes affecting the pharmaceutical sector, there are regulatory considerations that must be addressed if the action plan is to be successful. Indeed, the plan states that the flexibilities in the current pharmaceutical legislation would play a role in the strategy by allowing for the rapid authorisation of new antibiotics; eventually, however, the Commission foresees the implementation of fast-track procedures for these products.

The Commission says it will also work with stakeholders and member states' authorities towards the establishment of adequate market and pricing conditions for new antibiotics.

International collaboration

The plan recognises the need to collaborate on a global level, and one of its action points calls for the development and/or strengthening of multilateral and bilateral commitments. On a multilateral level, this will be achieved through co-operation with WHO EURO (World Health Organization Regional Office for Europe), among other things.

The main bilateral initiative will involve implementing 17 recommendations laid out by the US-EU Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) that were published in September.[9] TATFAR was set up in 2009 to foster greater collaboration on EU and US activities relating to AMR issues (see the April 2011 issue of *MedNous*).

As recommended in the report, TATFAR's mandate has been extended for an additional two years, during which it intends to monitor the implementation of the recommendations via biannual audio conferences.[10]

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