

EPHA Briefing on Antimicrobial Resistance

Antibiotics

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Introduction

The discovery of antimicrobial agents, such as antibiotics, has transformed the treatment of infectious diseases in both humans and animals. As growing mobility and trade have increased the risk and incidence of cross-border infections, so antimicrobials have been instrumental in preventing and treating such diseases – an especially crucial function in the facilitation of the single European market. However, as consumption of antimicrobials has increased, the natural processes of adaptation and mutation have resulted in new, resistant strains of common diseases. Unresponsive to traditional treatments, these pose a major threat to public health, as demonstrated by the proliferation of regional and global pandemics.

In 2011, the European Commission stated that 25,000 patients die annually as a result of infections caused by bacteria that exhibit Antimicrobial Resistance (AMR).¹ In addition to the human cost incurred, the loss of productivity and increase in healthcare expenditure costs EU health systems approximately €1.5 billion annually.² In 2012 the World Health Organisation (WHO) warned that without prompt action to reduce the incidence of AMR, we risk returning to a “pre-antibiotic era”, whereby previously minor infections lead to morbidity or even mortality³ – such a situation would seriously challenge the fulfilment of the United Nations Millennium Development Goals set for 2015.⁴

What is Antimicrobial Resistance (AMR)?

Antimicrobials, such as antibiotics, are substances used to kill microorganisms or to prevent them from growing and multiplying.⁵ They are commonly used to treat and prevent a wide range of infectious diseases in both human and veterinary medicine, but are effective only against bacterial infections – they have no impact upon viral diseases.

¹ European Commission Action Plan, 2011

http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf

² European Commission AMR brochure, 2011 http://ec.europa.eu/research/health/infectious-diseases/antimicrobial-drug-resistance/pdf/eu-research-on-antimicrobial-resistance_en.pdf p6

³ WHO factsheet 194 (reviewed 2012), <http://www.who.int/mediacentre/factsheets/fs194/en/>

⁴ In particular Goal 6, “Combat HIV/AIDS, malaria and other diseases”. See United Nations. The Millennium Development Goals. Eight goals for 2015, <http://www.undp.org/content/undp/en/home/mdgoverview.html>

⁵ EFSA. Antimicrobial Resistance. <http://www.efsa.europa.eu/en/topics/topic/amr.htm>



According to the European Centre for Disease Prevention and Control (ECDC),

“Resistance to antimicrobials is a natural biological phenomenon. The introduction of every antimicrobial agent into clinical practice has been followed by the detection in the laboratory of strains of microorganisms that are resistant, i.e. able to multiply in the presence of drug concentrations higher than the concentrations in humans receiving therapeutic doses.”⁶

The proliferation of AMR is occurring across two sectors. In human medicine, antimicrobials are used to treat common infections, as well as in treatments such as organ transplantation and chemotherapy. In veterinary medicine, antimicrobials have been commonly used as growth promoters and are often used to prevent or treat infectious diseases in livestock and companion animals. Whilst policy to address the proliferation of AMR tends to deal with these streams separately, the interaction between the two should not be overlooked – only half of all antimicrobials developed are for use in humans.⁷ Healthy animals result in a healthy food chain, which in turn contributes to healthy nutrition and better health outcomes. Whilst the transfer of AMR from animals to humans remains the subject of scientific investigation, a holistic, ‘one health’ approach is advocated by European Health Ministers.⁸

What causes Antimicrobial Resistance (AMR)?

AMR is a natural phenomenon resulting from the use of antimicrobials to treat infections. However, as a public health threat, its proliferation is caused primarily by over-consumption. The more an antimicrobial is employed to fight a given infection, the faster the infection will mutate and transform into a resistant strain. Inappropriate, irrational and uncontrolled use of antimicrobials is common in both human and veterinary medicine, contributing to the increase of this problem.

In human medicine, inappropriate and excessive consumption occurs in a number of situations. Health professionals are liable to mis-prescribe antibiotics, for example to treat viral infections, against which they have no effect. Furthermore, where the causative micro-organism (that which is responsible for the disease) cannot be identified, doctors often prescribe broad-spectrum antibiotics, designed to treat many infections.⁹ This increases the rate at which whole groups of micro-organisms become resistant to the given antimicrobial. At the patient level, the occurrence of AMR is increased by over-consumption, particularly in countries where prescription-only rules for antimicrobials are not implemented and patients are, in effect, self-medicating. The problem is further

⁶ WHO Strategy, 2001 http://www.who.int/csr/resources/publications/drugresist/en/EGlobal_Strat.pdf

⁷ WHO Report, 2000 <http://www.who.int/infectious-disease-report/2000/>

⁸ Council Conclusions of 22 June 2012 http://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/lsa/131126.pdf

⁹ ECDC overview http://www.ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/Pages/index.aspx



exacerbated by frequent disposal of antimicrobials, which enter the soil and the water system when put into landfill sites.¹⁰

In animal medicine, over-consumption and inappropriate use also contributes to the growing incidence of AMR.¹¹ Antimicrobials are used in livestock in much the same way as in humans – to prevent infectious diseases through vaccination or to treat diseases once they have been diagnosed. Such usage can be prophylactic (preventative) or metaphylactic (for treatment of disease and to avoid spread) and this application is sometimes described as ‘growth promotion’, referring to the use of antimicrobials to improve the quality of the product and prevent common infectious diseases.¹² Whilst this practice has been banned in some countries, it continues in others, increasing the rate of local resistant strains which can then spread to other areas.¹³ Such herd-treatment of large quantities of livestock is necessitated by intensive farming practices and poor standards of hygiene, which increase the risk of infection and therefore make vaccination and treatment essential.¹⁴

Why is Antimicrobial Resistance (AMR) a problem?

Globally, AMR has been detected in numerous microorganisms including bacteria, viruses, protozoa and fungi, raising worldwide concerns about future progress in the fight against diseases such as malaria, tuberculosis and HIV/AIDS. In some areas of the world – most notably South-East Asia – 98% of all gonorrhoea cases are multi drug-resistant which in turn contributes to the sexual transmission of HIV.¹⁵ Recent pandemics, though largely viral rather than bacterial diseases, have highlighted the risks of and potential consequences of global outbreaks.

In the EU, many member states are reporting increasing incidence of Hospital-Acquired Infections (HAIs), such as methicillin resistant *Staphylococcus aureus* (MRSA) and other ‘superbugs’, which are resistant to traditional antimicrobials. Similarly, rates of AMR in pathogens causing, for example, pneumonia or urinary tract infections, is also increasing across the EU. As these bacteria become increasingly resistant, doctors are forced to resort to the prescription of so-called ‘last-line’ antibiotics – these would normally only be used when no other treatments are available, but are equally susceptible to AMR mutations if over-consumed.

These trends put pressure on the development of new, more effective antimicrobials, which in turn pushes up the expenditure of health systems as they are forced to purchase more expensive drugs and treat a growing number of previously uncommon diseases.

¹⁰ The evolving threat of antimicrobial resistance’ World Health Organisation
http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf p33

¹¹ 2012. WHO The evolving threat of antimicrobial resistance Options for action.
(<http://www.who.int/patientsafety/implementation/amr/publication/en/index.html>)

¹² Hughes and Heritage, undated ‘Antibiotic growth-promoters in food-animals’
http://www.fao.org/docrep/ARTICLE/AGRIPPA/555_EN.HTM

¹³ WHO Report, 2000 <http://www.who.int/infectious-disease-report/2000/>

¹⁴ EUPRUMA, European Platform for the Responsible Use of Medicines in Animals
<http://www.epruma.eu/topics/antimicrobials-in-food-producing-animals.html>

¹⁵ WHO Report, 2012 <http://www.who.int/infectious-disease-report/2000/>



Current action and research to combat Antimicrobial Resistance (AMR)

In 2001 the WHO published its Global Strategy for Containment of Antimicrobial Resistance,¹⁶ describing what AMR is and what strategies should be implemented to control the escalation of the problem. In the same year, the European Commission issued its Community Strategy against Antimicrobial Resistance¹⁷ - through this strategy the Commission intended to improve on four key areas: surveillance, prevention, research, and international cooperation. As a result, EU-wide recommendations and guidelines were adopted, including the 2001 Council Recommendations on the prudent use of antimicrobial agents in human medicine.¹⁸ In 2006, acknowledging the link between AMR in human and veterinary medicine, the Commission introduced a ban on the use of antimicrobials for growth promotion in animal husbandry and called for the monitoring of zoonotic AMR (resistance that is transmitted between animals and humans).

Whilst AMR has been recognised as a problem of increasing scale, until recently there was relatively little action to counter it. In June 2008, the Council adopted a set of conclusions¹⁹ calling upon the Commission to promote cooperation, followed by a further set of conclusions in 2009 encouraging innovative incentives for effective antibiotics.²⁰ In 2011 the European Parliament adopted a resolution calling on the Commission to produce an EU-wide plan to tackle the proliferation of AMR²¹ and an Action Plan²² was subsequently published in November 2011. In January 2012, the Council of the European Union issued a Recommendation on the prudent use of antimicrobial agents in human medicine and the Danish Presidency of the European Council also enshrined AMR as one of its priority work streams for the first half of 2012. Most recently, a Danish Presidency conference in Copenhagen gathered the principal stakeholders and called for urgent action.²³

In an attempt to raise public awareness, AMR was made the focus of the 2011 World Health Day²⁴ organised by the WHO in April. In a similar vein the ECDC has been organizing, since 2008, an annual Antibiotic Awareness Day.²⁵ The most recent of these prompted European Commissioner for Health and Consumer Policy, John Dalli, to declare AMR as one of the biggest public health risks facing Europe today. The WHO's latest publication evaluates the progress made since the release of the Global Strategy in 2001.²⁶

The European Food Safety Authority (EFSA) and European Medicines Agency (EMA) are also active players in the battle against AMR, with the former involved in monitoring and analysis in the food chain, data collection and risk assessments, while the EMA publishes reports on European Surveillance of Veterinary Antimicrobial Consumption (ESVAC).

¹⁶ WHO Strategy, 2001 http://www.who.int/csr/resources/publications/drugresist/en/EGlobal_Strat.pdf

¹⁷ COM/2001/0333, available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2001:0333:FIN:EN:PDF>

¹⁸ Council Recommendation November 2001

http://europa.eu/legislation_summaries/public_health/threats_to_health/c11569_en.htm

¹⁹ Council Conclusions 22 May 2008 <http://register.consilium.europa.eu/pdf/en/08/st09/st09637.en08.pdf>

²⁰ Council Conclusions 1 December 2009 <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:302:0010:0011:EN:PDF>

²¹ See <http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P7-TA-2011-0238+0+DOC+XML+VO//EN>

²² Action Plan against AMR 15 November 2011

http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf

²³ <http://eu2012.dk/en/Meetings/Conferences/Mar/Bekaempelse-af-antibiotikaresistens---en-faelles-indsats>

²⁴ For more information on World Health Day, see <http://www.who.int/world-health-day/2011/en/index.html>

²⁵ For more information on the Antibiotic Awareness Day, see <http://ecdc.europa.eu/en/EAAD/Pages/Home.aspx/>

²⁶ WHO Report, 2012 <http://www.who.int/patientsafety/implementation/amr/publication/en/index.html>



EFSA and ECDC also produce joint annual EU Summary Reports on AMR resulting from zoonotic infections and food-borne outbreaks.

In relation to research objectives, the Seventh Framework Programme (FP7, 2007-2013) is currently funding over 30 projects in diverse pathogens covering drug discovery, development of diagnostics, the effects of antimicrobial use, controlling and monitoring the spread of AMR, and basic research on pathogens, to be continued under Horizon 2020.²⁷ FP7 also contributes to the Innovative Medicines Initiative (IMI), a public-private partnership that supports the development of better and safer medicines. In 2012, the Commission released a Recommendation for a Joint Programming Initiative (JPI) on AMR.²⁸

Surveillance and data collection is conducted primarily by the ECDC, which coordinates two main projects:

- European Antimicrobial Resistance Surveillance System (EARSS) This is a program of statistics control from all Member States and it is the biggest system of public financing for surveillance of antimicrobial resistance in the EU. It includes 900 public health laboratories serving more than 1,400 hospitals in Europe, equating to an estimated population of 100 million European citizens. Reports are published annually containing up-to-date information on antimicrobial resistance.²⁹
- Eurosurveillance This is a European scientific journal dedicated to epidemiology, surveillance, prevention and control of communicable diseases. The journal is published on a weekly basis, but ad hoc articles, news items and press releases are also distributed regularly. The journal occupies a key role in communicating to the community.³⁰

How can Antimicrobial Resistance (AMR) be reduced?

Some key challenges exist in the fight to control AMR, some of which are being addressed in the Commission's Action Plan:

- Promotion of appropriate and prudent use in humans and animals (livestock);
- Prevention of infections;
- Use of combination therapies;
- Increased hygiene in hospitals and in food production;
- Innovation and development of new antimicrobials and vaccines;
- Improving surveillance;
- Better and targeted communication, education and training;
- Closer international cooperation; and
- Monitoring and evaluation of actions taken.

²⁷ For a summary of these, see "EU Research on Antimicrobial Resistance: EU projects 2007-2010", available at http://ec.europa.eu/research/health/infectious-diseases/antimicrobial-drug-resistance/pdf/eu-research-on-antimicrobial-resistance_en.pdf

²⁸ C(2011) 7660 final, "Recommendation on the research Joint Programming Initiative "The Microbial Challenge – An Emerging Threat to Human Health"

²⁹ ECDC. About the network. (http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/about_EARS-Net/Pages/about_network.aspx)

³⁰ Eurosurveillance. About us. (<http://www.eurosurveillance.org/Public/AboutUs/AboutUs.aspx>)



Data show that there are wide variations in AMR between different EU countries, related to the level of consumption of antibiotics in both humans and animals.³¹ Scandinavian countries are generally at the lower end of the scale, whilst Southern European countries record much high levels of antibiotic consumption and, consequently, of AMR.³²

A reduction in AMR requires that human and animal health are not seen in isolation and that policy reflects the interconnectedness of livestock, food chains and human health. This is reflected in the Commission's continuing promotion of holistic, "One Health" approach in the fight against AMR. In particular, action is needed in the following areas:

Awareness raising amongst health professionals

General practitioners are often under considerable pressure to offer quick solutions to avoid absences from work and school – as a result, many resort to prescribing antibiotics instead of exploring more appropriate forms of treatment.³³ For example, more than half of antibiotics prescribed for respiratory infections are unwarranted because viruses are the cause.³⁴ As 'gatekeepers', pharmacists also play an important role, by promoting best dispensing practices, informing patients about the need to fully dispose of left-over doses appropriately and avoid self-medication. They can also inform patients about and monitor possible side effects, adverse reactions and drug interactions. Since community pharmacists and nurses are often the first point of call for sick patients, their role in educating the public and discouraging antibiotic use where it is unnecessary is significant.³⁵ Advising patients about AMR is relevant for doctors, nurses and all other health professionals.

Better infection control in healthcare

Since hospital-acquired infections are a major spur for the spread of AMR, it is vital that high standards of hygiene are observed in hospitals and all other healthcare settings (nursing home, long-term care facilities, etc.). Particular caution must be taken to protect risk groups (e.g. children, the elderly, cancer patients, the chronically ill) susceptible to AMR infections. The 2009 Council Recommendation on patient safety, including the prevention and control of healthcare associated infections³⁶ specifically addresses these problems. In addition, the increasingly creation of multidisciplinary teams or antimicrobial stewardships³⁷ to monitor antibiotic use and restrict prescription of drugs when their bacterial targets become resistant is crucial in the reduction of AMR. Finally, measures to reduce infection must also be undertaken in community healthcare. Since resistance levels in some community infections, such as urinary tract infections are increasing, the necessity of these measures applies as much to community as to hospital settings.

³¹ 'The evolving threat of antimicrobial resistance' World Health Organisation
http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf p34

³² EDCE EARS-Net map of AMR occurrence http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/map_reports.aspx

³³ Antibiotics won't work – but a placebo might' Guardian blog
<http://www.guardian.co.uk/commentisfree/2011/nov/18/antibiotics-cold-placebo>

³⁴ Safe Care Campaign http://www.safecarecampaign.org/Antibiotic_Stewardship.html

³⁵ See PGEU Statement "Community Pharmacists' Contribution to the Control of Antimicrobial Resistance" (2009)

³⁶ For the full text of the Council Recommendation, see
http://ec.europa.eu/health/ph_systems/docs/patient_rec2009_en.pdf

³⁷ For the full text of the Council Recommendation, see
http://ec.europa.eu/health/ph_systems/docs/patient_rec2009_en.pdf

³⁷ As recommended in the Transatlantic Taskforce report
http://ecdc.europa.eu/en/activities/diseaseprogrammes/tatfar/documents/210911_tatfar_report.pdf



Improving health literacy

One major challenge is the education of individuals about the prudent use of antibiotics and the inherent dangers of AMR. This must include warnings about the overuse of antibiotics, which in any case should only be used to treat bacterial infections. In addition, citizens should obtain proper information about the appropriate use of antibiotics, which should only be available upon prescription and when absolutely needed, and must be taken at the correct dosage, intervals and duration. It is also necessary to know what a particular antibiotic consists of, its purpose and effects, and in which case it should be prescribed.³⁸

Promoting other forms of therapy

While it is important that new antibiotics can be brought to the market for the benefit of patients suffering from ever more complicated diseases, the Commission's Communication highlights some of the difficulties in developing new antimicrobials for this purpose.³⁹ Therefore, in the long run, a paradigm shift is necessary to prevent antibiotics becoming ineffective and obsolete. There are already several non-antibiotic approaches to the treatment and prevention of infection (e.g. probiotics, phages phytomedicines) but the scientific evidence base is still unclear.⁴⁰ The growing field of complementary and alternative medicine (CAM) also comprises numerous treatment options for the prevention and treatment of health conditions that can support the move away from the current state of over-prescription of antibiotics. Further research and awareness of these fields is necessary to contribute to a reduction in AMR.

Reduction in the use of antimicrobials in livestock and food production

As in the case of human medicine, the use of antimicrobials in veterinary practice must be reduced in order to stem the proliferation of AMR. Where intensive farming is used to provide meat for human consumption, antibiotics are often used to compensate for the effects of poor sanitation, high stress and overcrowded conditions.⁴¹ The implementation of Good Farming Practices serve a wider purpose that just the reduction of AMR. Factory farming impacts on animals, people and the planet – it endangers health through the spread of AMR, it is unfair in its treatment of animals and its pressure on rural livelihoods, and it is unsustainable in its damage to the environment.⁴²

In relation to the prevalence of resistant strains of common microorganisms, such as E.coli and salmonella, numerous examples can be offered. In 1998 strains of multi drug-resistant Salmonella typhimurium struck 25 people in Denmark, resulting in two fatalities. Epidemiologists eventually traced the micro-organism to pork and to the pig herd where it originated. In the same year 5,000 people in the United States fell ill with multi drug-resistant campylobacteriosis caused by contaminated chicken. The

³⁸ WHO factsheet on rational use of medicines <http://www.who.int/mediacentre/factsheets/fs338/en/index.html>

³⁹ Cf. COM(2011) 748, p.9

⁴⁰ A few examples of studies into the use of homeopathic treatments as an alternative for antibiotics can be seen here: http://www.britishhomeopathic.org/hh_article_bank/in_practice/patient_centred_healthcare/homeopathy_alternative_to_antibiotics.html

⁴¹ Alliance to Save our Antibiotics Report 2011

http://www.ciwf.org.uk/includes/documents/cm_docs/2011/c/case_study_of_a_health_crisis_a_report_for_the_alliance_to_save_our_antibiotics.pdf p4

⁴² Compassion in World Farming – RAW campaign literature <http://www.raw.info/>



same drugs that eventually failed them had also been used in the poultry that turned up on their plates.⁴³

Other bodies of research, however, challenge the link between human and animal AMR. Research by the International Animal Health Organisation (IFAH) suggests that the Danish ban on growth-promoting use of antimicrobials, following the crisis described above, was itself followed by an increase in AMR strains of the relevant pathogen in the EU⁴⁴ and was implemented on the basis of the precautionary principle rather than risk assessment.⁴⁵ Similarly, a number of studies and reports conclude that AMR transferral from animals to humans is not as prolific in practice as laboratory tests indicate. Furthermore, in some cases, instances where antimicrobials are used in both humans and animals, the significance of resistance generated by human use is overlooked.⁴⁶ Finally, studies also show that there is little difference between the duration and intensity of illness caused by resistant and non-resistant strains of a given microorganism, thereby challenging the notion of a high public health cost.⁴⁷

Whilst the scientific linkages and causations continue to be investigated, the future benefit of antimicrobial use for both humans and animals relies on a reduction in the consumption of both sectors. In veterinary medicine, this requires a change in farming practice – “feed for growth” livestock and food production systems marked by intensive farming are breeding grounds for AMR⁴⁸ and ultimately trigger additional health threats caused by poor nutritional quality, insufficient food security and climate change. The promotion of Good Farming Practices and animal husbandry can serve to avoid infections and prevent AMR spread via air, water and soil. Research has also shown that certain food production systems (i.e. organic) are associated with lower levels of AMR and hence create less dependency on antimicrobials.⁴⁹ Immunisation of animals remains an important factor, as supported by the WHO, but should not be a substitute for bacteria-deterrent living conditions.⁵⁰

⁴³ WHO Report 2000 <http://www.who.int/infectious-disease-report/2000/>

⁴⁴ IFAH draft report on tackling antibiotic resistance from a food safety perspective, internal document

⁴⁵ IFAH response to WHO Europe report – internal document

⁴⁶ IFAH response to WHO Europe report – internal document

⁴⁷ Professor Peter Silley, 2012 ‘Towards an understanding of transfer of resistance from animals to man’ Internal report of the IFAH

⁴⁸ Alliance to Save our Antibiotics Report 2011

http://www.ciwf.org.uk/includes/documents/cm_docs/2011/c/case_study_of_a_health_crisis_a_report_for_the_alliance_to_save_our_antibiotics.pdf p4

⁴⁹ Research by Johns Hopkins School of Public Health

<http://ehp03.niehs.nih.gov/article/fetchArticle.action?articleURI=info%3Adoi%2F10.1289%2Fehp.1003350>

⁵⁰ Alliance to Save our Antibiotics Report ‘Case study of a health crisis’

http://www.ciwf.org.uk/includes/documents/cm_docs/2011/c/case_study_of_a_health_crisis_a_report_for_the_alliance_to_save_our_antibiotics.pdf

About EPHA

EPHA is a change agent – Europe's leading NGO advocating for better health. We are a dynamic member-led organisation, made up of public health NGOs, patient groups, health professionals, and disease groups working together to improve health and strengthen the voice of public health in Europe. EPHA is a member of, among others, the Social Platform, the Health and Environment Alliance (HEAL), and the Better Regulation Watchdog. EPHA's Transparency register number is 18941013532-08.



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