Health Care Without Harm

Antimicrobial resistance

A HCWH Europe position paper

Pharmaceuticals

October 2017

Introduction

What is antimicrobial resistance (AMR)?

Antimicrobial resistance (AMR) develops when microorganisms become resistant to the antimicrobial drugs used to treat them - this leads to treatments becoming ineffective, infections persisting, and an increased risk of infections spreading.[1] AMR is a broad term that refers to resistant viral, parasitic, fungal, or bacterial diseases, but resistance to antibiotics is of particular concern, as it is considered one of the greatest global threats to public health.[2]

Why should society be concerned about AMR?

Each year, antimicrobial-resistant infections cause 25,000 deaths in the European Union[3], 700,000 deaths worldwide[4], and generate annual costs of at least €1.5 billion in the EU alone.[3] The World Health Organization (WHO) reports that 480,000 people worldwide are affected by multi-drug resistant tuberculosis each year, and that the fight against HIV and malaria is also further exacerbated by AMR.[5]

A lack of research and development (R&D) could result in a shortage of alternative antimicrobials in the future. Approximately 10 million annual deaths caused by AMR are forecast for 2050 unless there is significantly more investment in R&D, a reduction in the amount of antimicrobials used, and attention to the control of infectious diseases in both human and veterinary fields.[6]

Antibiotic resistance, "the single greatest challenge in terms of infectious diseases today"[7] represents a threat for developed and developing countries alike.[2,8] Whilst widely acknowledged as a global threat, antibiotic resistance has not yet received enough public and governmental attention.

The spread of AMR

Pharmaceutical disposal - an unrecognised factor of AMR

AMR is primarily caused by inappropriate use and overuse of antibiotics in humans and animals, but increasingly evidence shows that pharmaceutical waste from excretion and disposal (including effluent from the pharmaceutical manufacturing process) is also a concern in the development of resistance.[9-12]

Another significant factor of AMR is disposal of drugs; there is insufficient implementation of collection schemes for unused and expired medicines throughout Europe.[13] Inappropriate disposal of antimicrobials: flushing them down the toilet or the sink for example, results in environmental pollution.[14] Sewage treatment systems are inadequate for the complete removal of active pharmaceutical ingredients in waste water, which can contribute to the spread of resistance.[9, 15, 16]

A reservoir for the spread of resistance

Since their discovery in the 1940s, antibiotics have become essential medicines.[1, 2] Recent studies have proven, however, that antibiotic waste from manufacturing sites doesn't just pollute the

environment, but is also a reservoir of resistant microbes.[10-12, 17-20] According to a 2013 report by the European Executive Agency for Health and Consumers, of all the risks humans face from medicinal product residues in the environment - AMR poses the greatest risk.[21]

Research has demonstrated how antibiotic resistance proliferates in the environment - bacteria are able to share genes with each other through a process called horizontal gene transfer, which can fuel the rapid spread of resistance among pathogens.[22] Through this process, genes that are resistant to antibiotics can move between bacterial cells and species.[23, 24]

Some particular environments are considered 'hot-spots' where antimicrobial resistance is more likely to emerge: 'hot-spots' include areas with poor pharmaceutical manufacturing practices, or where expired or unused drugs are disposed inappropriately e.g. toilets, sinks, or household refuse. Areas where pharmaceuticals are used in aquaculture or agriculture are also considered 'hot-spots'.[10-12, 19, 20] Currently the majority of national and global actions to tackle the spread of AMR do not take into account this release of antibiotics into the environment.

The pharmaceutical industry is known to contribute to antimicrobial contamination of the environment through their manufacturing practices.[11, 25, 26] Many pharmaceutical producers, attracted by cheaper labour and capital costs and weaker environmental protection laws, have outsourced their manufacturing outside of Europe.[25, 27] Active pharmaceutical ingredients (known as APIs) are the substances within medicine that are biologically active in order to have an effect on the patient (human or animal). China is the world's largest producer and exporter of APIs, currently supplying up to 90% of all antibiotic APIs; the majority of these are then processed in India before being sold on to markets worldwide.[25, 27, 28]

The unmonitored discharge of API-rich effluent into rivers and waterways in China and India has been shown to contribute to the proliferation of resistant bacteria.[10, 25, 26] This is not only problematic for local populations' health; the resistant bacteria can also spread across the world through international trade and travel.[25, 29] Normally the highest source of antimicrobials in the environment is excretion from humans and animals, yet in areas of pharmaceutical manufacturing, direct emissions of APIs are proven to be a much greater source. Every day 44kg of ciprofloxacin is discharged within effluent running into the Godavari River in China – water in this river contains concentrations of ciprofloxacin 1000 times higher than the amount required to kill certain bacteria.[26]

Currently there is little published information available concerning global quantities of APIs produced every year and where they are produced. The lack of data and transparency on these issues is cause for concern that low prices for pharmaceuticals could be indicative of low manufacturing standards, resulting in environmental pollution.[6] Problematically, current legislation fails to properly address this issue: The European Medicines Agency's "Guideline on the environmental risk assessment of medicinal products for human use" states that before receiving market authorisation, pharmaceutical products should undergo an environmental risk assessment.[30] This requirement does not apply, however, to antimicrobials placed on the market before 2006 when the guidelines came into force, and no risk assessments on the development of AMR in the environment are required. There is no scientific evidence that products placed on the market before 2006 are of less environmental concern than new products.

A recent study attempts to fill in the research gap and has proposed to establish "safe levels" of APIs in manufacturing waste. These "safe levels" were calculated by estimating the minimal selective concentrations i.e. the lowest concentration of an antibiotic at which resistance can still occur and predicting the no-effect concentrations i.e. the maximum concentration of an antibiotic below which no resistance can occur.[31]

The health sector's contribution to the AMR crisis

Millions of inappropriate antibiotic prescriptions are written every year, which further fuel the development of resistance.[32] Inappropriate prescribing occurs for a number of reasons: due to a lack of information doctors may prescribe a drug for a resistant infection, or prescribe antibiotics for a viral infection, and second or third-line antibiotics are sometimes prescribed when a first-line antibiotic would have sufficiently worked. Without rapid diagnostic tests, doctors still prescribe antibiotics based on immediate assessments of patients' symptoms; in many cases, antibiotics are prescribed prophylactically because they are cheaper in comparison with available diagnostic tests.[6]

When standard treatments don't work anymore, infections become harder or impossible to control, thus increasing the risk of infections spreading; combined with prolonged illness and lengthier hospital stays, the risk of fatality grows.[2]

Information regarding over-the-counter i.e. non-prescription sales of antibiotics is inconsistent and difficult to obtain in many countries. Despite a European Union Council recommendation that antibiotics are used as prescription-only medicines in Member States[33], it is believed that in some areas of Southern and Eastern Europe 20%-30% of antibiotics consumed are non-prescription.[6, 34]

Antibiotics and antibiotic-resistant bacteria are present in both hospital and municipal sewage systems, and while the healthcare sector may be thought of as a large source of pharmaceuticals in wastewater, hospitals only account for less than 10% of pharmaceuticals in the municipal wastewater (by weight).[15, 35] Excretion of drugs and poor disposal practices in the community means there are larger quantities of pharmaceuticals in municipal waste water.

Statistics have shown that awareness campaigns are effective in informing and educating their audiences about important health issues including antibiotic-use.[36] One successful campaign to reduce antibiotic-use during the 2000 influenza season in Belgium resulted in a 36% reduction in the prescription of antibiotics.[37]

Antibiotic use in food production contributes to the spread of resistance

When used to treat infections in agriculture and aquaculture, antimicrobials, especially antibiotics, are very important for animal health and welfare, as well as food security. At the global level, however antimicrobials are mostly used to prevent infections and compensate for poor animal husbandry practices and/or to promote growth.[6, 38] The exact quantity of antimicrobials used in food production worldwide is unknown due to insufficient data, but it has been shown that in some regions - antimicrobials are used more often for animals than for humans - in the U.S. more than 70% (by weight) of the antibiotics considered medically important for human health are used in livestock.[39]

Last-resort antibiotics are those prescribed if all other antibiotics have failed; when they are used in livestock this can increase the threat of AMR. Antibiotics lose their efficacy in humans when they are routinely absorbed in low levels in the food chain.[40] This is the case of colistin - whilst not widely used in humans, (as it can cause kidney failure[41]), it remains an important last-resort antibiotic that is administered when an infection hasn't responded to other drugs.[6] The widespread use of colistin in treating animals, however, has led to resistance in animal pathogens which has implications for humans. A recent scientific paper reports the discovery of transferable colistin resistance in both animals and humans in China.[42]

Some frequent antibiotic-use practices in animals are problematic, such as growth promotion, prophylactic use i.e. preventive use in the absence of infection, and metaphylactic use i.e. treating a group animals when only a small number of individuals show signs of infection. Metaphylactic use aims to prevent infections spreading, but it actually leads to gross overuse of antibiotics and contributes to antibiotic resistance.[39] The problem is exacerbated by cramped conditions, allowing resistance to spread rapidly. The most contentious use of antibiotics, however, is non-therapeutic use for growth promotion, which was banned in the EU in 2006[43], but is still permitted for use in the US.

Other, non animal-based food products may also be contaminated with antimicrobial resistant bacteria and/or antimicrobial resistance genes. Ingredients intentionally added during food processing (such as starter cultures, probiotics, bioconserving microorganisms, or bacteriophages), can spread antimicrobial resistant bacteria.[44] Such bacteria can also be spread through cross-contamination (e.g. when raw food is mixed with other ingredients). Whilst cooking processes often kill resistant bacteria, raw food products pose a substantial risk of transferring antimicrobial resistance to humans through consumption.[44]

Actions at the global level

The World Health Organization (WHO) urges Member States to adopt the WHO Global Action Plan on Antimicrobial Resistance as a basis for their own national priorities and specific contexts. This plan, adopted by the 68th World Health Assembly in May 2015, aimed to have national plans in place by May 2017.[45]

The European Commission contributed to the development of the WHO action plan and is currently involved in implementation.[46] The key points of the action plan to tackle AMR include:

- Awareness and education campaigns
- Improving knowledge of AMR through surveillance
- Infection prevention and control measures
- Optimising antimicrobial-use in humans and animals
- R&D and investment.[1]
- Implementing good manufacturing practices - however, this neglects to include environmental criteria.

As part of its Global Action Plan, The WHO recognised the impact that antibiotic use in agriculture can have on the spread of drug resistance, and therefore requires Member States to incorporate actions for dealing with the veterinary use of antimicrobials in their national action plans.[1] This issue has been also recognised by The Food and Agriculture Organisation of the United Nations (FAO) and The World Organisation for Animal Health (OIE) – all three organisations collaborate in sharing responsibilities in tackling AMR.[47] The FAO plays a key role in supporting all actors to adopt measures that minimise the use of antimicrobials and to prevent the development of AMR.[48] The OIE promotes the responsible and prudent use of antimicrobial agents in veterinary medicine and improved knowledge and monitoring of the quantities of antimicrobials used in animal husbandry.[49]

There is also international cooperation among countries through an Intergovernmental Task Force on Antimicrobial Resistance, which reports to the Codex Alimentarius Commission.[50] The EU collaborates closely with the USA, Canada, and Norway to address AMR through the Transatlantic Task Force on Antimicrobial Resistance (TATFAR) established in 2009.[51] The European Commission also collaborates with the Organisation for Economic Co-operation and Development (OECD) to assess the economic impact of AMR.[46, 52]

There is a common consensus at the international level that unnecessary use of antibiotics in animals and agriculture represents a major concern for human health.[6] Recent G7 statements recognised the urgent need for national efforts in sharing best practices and promote the prudent use of antimicrobials.[53, 54, 55, 56] A political declaration to combat the global threats posed by AMR was adopted this year by the 71st United Nations (UN) General Assembly - Member States should develop multisectoral national action plans on AMR, which must be in line with the WHO Global Action Plan.[8]

Actions at the the EU level

The European Commission's Action plan against the rising threats from Antimicrobial Resistance (2011-2016) outlined the main actions for its implementation amongst Member States, and identified areas where measures are most needed.[57] This Action plan aimed to ensure appropriate use of antimicrobials across Member States: within the plan, the European Commission proposed measures to prevent the spread of microbial infections and encouraged innovative research and development of antimicrobial drugs. The plan describes the need for international collaboration to address the risks of resistance spreading via international trade, travel, and the environment. An important target included in this plan was strengthening the regulatory framework on veterinary medicines and on medicated animal feed.[57] Environmental criteria in implementing good manufacturing practices to combat AMR, however, is not included within this action plan either.

In June 2017, the European Commission published A European One Health Action Plan against Antimicrobial Resistance (AMR).[58] This second action plan recognises AMR as a growing threat on a global level and aims to strengthen actions containing this crisis and to promote the EU as a best practice region. Within this latest action plan, the European Commission for the first time acknowledges environmental aspects leading to AMR, but only to cover knowledge gaps. There is no mention of the industrial pollution in the supply chain.

The European Commission is currently working on a new regulation on veterinary medicines, which will propose new policy measures to tackle AMR by ensuring proper use of antimicrobial drugs in farming practices. (For further information, please read *Food pathways to antibiotic resistance: A call for international action*)

HCWH Europe recommendations on AMR

AMR currently poses one of the greatest threats to global public health, an important focus for stakeholders worldwide should be to find strategies to improve production standards and minimise the release of antimicrobials into the environment throughout their life cycle (production, use, and disposal).

HCWH Europe therefore urges the European Commission to work with international governments and regulators to establish evidence-based targets for maximum levels of antimicrobial API discharge associated with the manufacture of pharmaceuticals. These targets should be enforced at international level, regardless of products' origins. The goal should be to manage the pharmaceutical waste stream and control API discharge associated with the manufacture of pharmaceutical products.

In this international context, HCWH Europe also calls on the European Commission to develop a guideline with measurable goals, which should include feasible targets and monitoring systems to reduce the overuse and inappropriate use of antimicrobials in human and agricultural practices.

1. Achieve zero discharge and eliminate the release of antimicrobials into the environment from manufacturing plants

Governments need to strengthen laws to eliminate pollution, monitor antimicrobial discharges into the environment rigorously, impose fines, and withdraw licences if needed - the ultimate aim should be a zero discharge policy. National governments and regulators around the world need to expand the regulatory framework for Good Manufacturing Practice (GMP), to include environmental safety. GMP legislation (Directive 91/412/EC[59] and Directive 2003/94/EC[60]) should require antimicrobial production facilities to apply environmental safety standards to achieve a zero discharge and should be validated through an independent auditing system.

2. Enforce the development of minimum manufacturing standards to prevent pharmaceutical waste that leads to AMR

More attention should be paid to environmental safety throughout the regulatory framework for authorisation procedures for medicinal products.[61] Manufacturers need to be held responsible for their antibiotics on the market and they should be held accountable for pharmaceutical pollution that leads to AMR.

Manufacturing standards should be developed amongst all Member States to address this issue. These standards should apply across all stages of the supply chain with transparency regarding the source of APIs, emissions of manufacturing waste containing APIs, and environmental assessment of the discarded APIs. These standards should be applied to products for both human and animal use that are sold in Europe, regardless of where they are produced. Environmental criteria, as a matter of good manufacturing practice, should be included in the market authorisation procedure for medicinal products sold in the EU.

3. Require environmental risk assessment for all antimicrobials

HCWH Europe recommends that an Environmental Risk Assessment (ERA) covering all stages of the pharmaceutical substance's life cycle should be a mandatory part of the marketing authorisation process for antimicrobials.[62]

4. Add requirements to assess the risk for development of AMR

The ERA for antimicrobial substances should include a risk assessment for development of AMR - this would improve current knowledge on risks associated with antimicrobials presence in the environment.[62]

5. Last-resort antibiotics and those medically important for human use should be reserved for human use only

Last-resort antibiotics should not be prescribed for veterinary use, but only for human therapy. HCWH Europe calls upon regulatory bodies and international organisations (WHO, FAO, and OIE) to agree on a harmonised list of last-resort antibiotics that are critical to human health and should be banned from agricultural use.

6. Restrict prophylactic and metaphylactic use of antimicrobials in livestock

Antimicrobial drugs, especially antibiotics, must not be used to improve performance (e.g. physiological and reproductive performance) or to compensate for poor animal husbandry. HCWH Europe recommends that the EU should adopt the position of the European Parliament's Environment and Public Health Committee on prophylactic and metaphylactic use of antimicrobials in livestock.[63] Prophylactic use of antimicrobials should be limited to single animals and only when prescribed by a veterinarian. Metaphylactic use should also be restricted: only individual animals that are clinically ill or show a high risk of infection should receive antimicrobial treatment. Sick animals should also be physically separated from the healthy to reduce the risk of infections spreading.

7. Work towards developing legislation for Member States to enforce regulations that prevents over-the-counter sales without prescription

It is the role of the EU regulatory body to establish legislation for prescription-only use of antibiotics and ensure that this is enforced nationally in Member States. This measure should record and monitor the data regarding quantities of antibiotics sold for both human and veterinary use.

8. Develop guidelines for informed prescription practices to reduce the unnecessary use of antibiotics

Better prescription practices need to be developed and implemented to reduce the problem of resistance spreading. Governments across the EU must legislate that doctors' decisions to prescribe antibiotics must be evidence-based and supported by up-to-date surveillance information and that testing technology is applied when available.[6]

9. Support the establishment of a harmonised collection scheme system for antimicrobials throughout the EU

At the EU level, guidelines are needed to support the setup and improvement of take back schemes foreseen in Directive 2004/27/EC.[64] Take back schemes should be expanded and strengthened across the EU to prevent unused antibiotics reaching the environment. Collaboration between Member States to establish a harmonised collection scheme system for antimicrobials should be encouraged through common guidelines and targets.

10. Promote research into environmentally-responsible ways to treat sewage and prevent the release of antibiotic resistant bacteria

Further research is needed on how to improve the wastewater treatment to prevent antibiotic resistant bacteria being released into the environment without resorting to the use of toxic chemicals.

11. Promote research into environmentally-responsible waste disposal methods

Further research is needed on how to improve antibiotic waste disposal methods to prevent the release of toxic chemicals in the environment.

12. Develop EU-wide awareness campaigns to:

a. Educate the public on correct consumption and disposal of antimicrobials

Educational campaigns could help promote proper disposal practices and help patients understand that demanding antimicrobials from health professionals or buying them over-the-counter without the necessary knowledge is harmful as it contributes to AMR.

b. Train health professionals on responsible prescribing practices

Healthcare professionals can influence patients' use of antimicrobials, and they should be actively involved in reducing the misuse and overuse of this category of drugs. For example, doctors can optimise prescription practices to ensure that antibiotics are prescribed and dispensed of prudently. Pharmacists are also well placed to advise patients about how to follow a correct therapy of antibiotic drugs, and to help reduce the risk for accumulation of unused antibiotics that become waste and can end up in the environment.

Hospitals and health systems should become leaders in educating staff, patients, and communities about the link between healthy and sustainable food to long-term wellbeing. Health professionals can also play an important role in advocating for policy changes at the hospital administrative level to prioritise purchasing antibiotic-free meat.

c. Educate farmers on the responsible use of antimicrobial drugs

Farmers and agricultural workers should also be educated about the consequences of unnecessary antimicrobial-use in agriculture.

References

1. WHO (2015). *Global Action Plan on Antimicrobial Resistance.*
2. WHO (2014). *Antimicrobial Resistance Global Report on Surveillance.*
3. European Centre for Disease Prevention and Control/European Medicines Agency (2009). *Technical Report. The bacterial challenge: time to react.*
4. The Review on Antimicrobial Resistance Chaired by Jim O'Neill (2014). *Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations*.
5. WHO (2016). *Antimicrobial resistance. Fact sheet.*
6. The Review on Antimicrobial Resistance Chaired by Jim O'Neill (2016). *Tackling Drug-Resistant Infections Globally: Final Report And Recommendations.*
7. WHO Media Centre (2015). *WHO report finds systems to combat antibiotic resistance lacking.*
8. United Nations General Assembly (71st session) (2016). *Political declaration of the high-level meeting of the General Assembly on antimicrobial resistance.*
9. Küster A and Adler N (2014). Pharmaceuticals in the environment: scientific evidence of risks and its regulation. *Philos Trans R Soc Lond B Biol Sci.* 369 (1656).
10. Larsson DG, de Pedro C and Paxeus N (2007). Effluent from drug manufactures contains extremely high levels of pharmaceuticals. *J Hazard Mater*. 148(3):751-755.
11. Ashbolt NJ, Amézquita A, Backhaus T *et al.* (2013). Human Health Risk Assessment (HHRA) for Environmental Development and Transfer of Antibiotic Resistance. *Environmental Health Perspectives* 121(9): 993-1001.

12. Berendonk TU, Manaia CM, Merlin C *et al.* (2015). T*ackling antibiotic resistance: the environmental framework*. Nature Reviews Microbiology 13(5): 310-317.
13. HCWH Europe (2013). *Unused pharmaceuticals, where do they end up? A snapshot report of European collection schemes.*
14. Center for Disease Dynamics, Economics & Policy (2015). *State of the World's Antibiotics.*
15. Korzeniewska E, Korzeniewska A, Harnisz M (2013). *Antibiotic resistant Escherichia coli in hospital and municipal sewage and their emission to the environmen*t. Ecotoxicology and Environmental Safety 91: 96 -102.
16. Kümmerer K (2010). *Pharmaceuticals in the Environment*. Annu. Rev. Environ. Resour. 35:57–75.
17. Bengtsson-Palme J, Boulund F, Fick J *et al*. (2014) *Shotgun metagenomics reveals a wide array of antibiotic resistance genes and mobile elements in a polluted lake in India*. Frontiers in Microbiology 5:648.
18. Flach CF, Johnnin A, Nilsson I (2015) *Isolation of novel IncA/C and IncN flouruquinolone resistance plasmids from an antibiotic-polluted lake*. Journal of Antimicrobial Chemotherapy 70(10), 2709-2717.
19. Pruden A, Pei R, Storteboom H, Carlson KH (2006) *Antibiotic resistance genes as emerging contaminants: Studies in northern Colorado*. Environmental Science & Technology 40(23): 7445-7450.
20. Pruden A, Larsson DGJ, Amézquita A *et al.* (2013) *Management options for reducing antibiotics and antibiotic resistance genes to the environment*. Environmental Health Perspectives 121(8): 878-885.
21. BIO Intelligence Service (2013). *Study on the environmental risks of medicinal products.* Final Report prepared for the Executive Agency for Health and Consumers.
22. Thomas CM, Nielsen KM (2005) *Mechanisms of, and barriers to, horizontal gene transfer between bacteria*. Nature Reviews Microbiology 3(9): 711-721.
23. Stokes HW, Gillings MR (2011) *Gene flow, mobile genetic elements and the recruitment of antibiotic resistance genes into Gram-negative pathogens*. FEMS microbiology Reviews 35(5): 790-819.
24. Davies J (1994) *Inactivation of antibiotics and the dissemination of resistance genes*. Science 264(5157): 375-382.
25. SumOfUs (2015). *Bad Medicine: How the pharmaceutical industry is contributing to the global rise of antibiotic-resistant superbugs.*
26. Larsson, DGJ (2014). *Pollution from drug manufacturing: review and perspectives. Phil. Trans. R. Soc. B.* 369: 20130571.
27. Nordea (2016). *Impacts Of Pharmaceutical Pollution On Communities And Environment In India.*
28. Pharm Tech (2013). *The Weaknesses and Strengths of the Global API Market*.
29. Lübbert C, Baars C, Anil Dayakar A, Lippmann N et al. (2017). *Environmental pollution with antimicrobial agents from bulk drug manufacturing industries in Hyderabad, South India, is associated with dissemination of extended-spectrum beta-lactamase and carbapenemase-producing pathogens*. Infection 45(4):479-491.
30. European Medicines Agency (2006) *Guideline on the environmental risk assessment of medicinal products for human use*.
31. Bengtsson-Palme J, Larsson DGJ (2016) *Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation.* Environment International 86:140-149.
32. National Institute for Health and Care Excellence (NICE) (2015). *Calls for NHS to curb inappropriate antibiotic prescribing*.
33. Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine (2002/77/EC).
34. Morgan DJ, Okeke IN, Laxmanirayan R et al. (2011). *Non-prescription antimicrobial use worldwide: a systematic review.* The Lancet Infectious Diseases,11, 9, 692-701.
35. Kümmerer K (2009). *The presence of pharmaceuticals in the environment due to human use – present knowledge and future challenges.* Journal of Environmental Management 90: 2354–2366.
36. European Centre for Disease Prevention and Control (ECDC) (2010) *Technical Report: A literature review on health communication campaign evaluation with regard to the prevention and control of communicable diseases in Europe*.

37. Goossens H, Guillemot D, Ferech M *et al.* (2006). *National campaigns to improve antibiotic use*. Eur J Clin Pharmacol 62(5):373-9.
38. Landers TF, Cohen B, Wittum TE, Larson EL (2012). A *Review of Antibiotic Use in Food Animals: Perspective, Policy, and Potential*. Public Health Rep. 127(1): 4–22.
39. The Review on Antimicrobial Resistance (2015) *Antimicrobials in agriculture and the environment: Reducing unnecessary use and waste*.
40. Allen HK (2014). *Antibiotic Resistance Gene Discovery in Food-Producing Animals.* Current Opinion in Microbiology 19 (0) 25–29.
41. Spapen H, Jacobs R, Van Gorp V, Troubleyn J, Honoré PM (2011). *Renal and neurological side effects of colistin in critically ill patients*. Ann Intensive Care 1:14.
42. Yi-Yun Liu, Yang Wang, Walsh TR *et al.*, (2016). *Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study.* The Lancet Infectious Diseases 16(2): 161-168.
43. Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, p. 29–43.
44. Verraes C, Van Boxstael S, Van Meervenne E *et al*. (2013). *Antimicrobial resistance in the food chain: A review*. Int J Environ Res Public Health. 10(7):2643-69.
45. United Nations General Assembly (68th session) (2015) Resolutions and Decisions Annexes.
46. European Commission (2016). *Action at a Global Level.*
47. The FAO-OIE-WHO Collaboration (2010). *A Tripartite Concept Note.*
48. FAO (2017) Antimicrobial Resistance.
49. OIE (2017) Antimicrobial Resistance.
50. FAO/Codex Alimentarius (2016). *Ad hoc Codex Intergovernmental Task Force on Antimicrobial Resistance (TFAMR).*
51. Centers for Disease Control and Prevention (2016). *Transatlantic Task Force on Antimicrobial Resistance (TATFAR).*
52. OECD (2016). Antimicrobial Resistance.
53. Declaration of the G7 Health Ministers, 8-9 October, 2015, in Berlin.
54. Leaders' Declaration G7 Summit, 7-8 June 2015.
55. Declaration of the G20 Health Ministers, 19-20 May, 2017, in Berlin.
56. G7 Germany 2015. *Combating Antimicrobial Resistance. Examples of Best-Practices of the G7 Countries.*
57. European Commission (2011). *Action plan against the rising threats from Antimicrobial Resistance.* COM (2011) 748.
58. European Commission (2017) *A European One Health Action Plan against Antimicrobial Resistance (AMR).* COM (2017).
59. Directive 91/412/EC laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products. OJ L228/70, 17.8.91.
60. Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. OJ L 262/22, 14.10.2003.
61. European Commission (2016) *Authorisation procedures for medicinal products*.
62. Agerstrand M, Berg C, Björlenius B *et al*. (2015) *Improving Environmental Risk Assessment of Human Pharmaceuticals*. Environ. Sci. Technol 49: 5336–5345.
63. European Parliament News (2016). *Superbugs: curb use of today's antibiotics, and develop new ones, urge MEPs.*
64. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use.