EU strategy to fight against Antimicrobial Resistance

OECD workshop on the Economics of Antimicrobial Use in the Livestock Sector and Development of Antimicrobial Resistance
Paris, 12 October 2015

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According to data from 2011, 25 000 patients die annually as a result of infections caused by resistant bacteria in the EU. The costs incurred by drug resistant infections amount to an estimated €1.5 billion annually, due to increases in healthcare expenditure costs and productivity losses.
Resistant bacteria: a natural phenomenon but amplified by other factors

• Inappropriate or over use of therapeutic antibiotics in human and veterinary medicine

• Poor hygiene and infection prevention measures in healthcare settings and at farm level

• Transmission of resistant bacteria from animals to humans through the food chain or direct contact

• Environmental spread caused by contaminated food and water systems and international trade and travel

• Lack of new effective antimicrobials or alternatives
Mechanisms of Antibiotics

Inhibit Cell Wall Synthesis or Function
- Beta Lactams
- Penicillins
- Cephalosporins
- Carbapenems
- Monobactams
- Vancomycin
- Daptomycin
- Polypeptides

Inhibit Nucleic Acid Synthesis or Function
- Inhibit DNA Gyrase +/- Topoisomerase IV: Quinolones
- Inhibits Folate Synthesis: Trimethoprim / Sulfamethoxazole
- Create Free Radicals: Metronidazole, Nitrofurantoin

Inhibit 30S Subunit
- Aminoglycosides
- Tetracyclines
- Tigecycline

Inhibit 50S Subunit
- Macrolides
- Clindamycin
- Linezolid
- Streptogramins
- Chloramphenicol

Inhibit Protein Synthesis

European Commission
DIFFERENT CLASSES OF ANTIBIOTICS - AN OVERVIEW

**Key:**
- **Commonly act as bacteriostatic agents, restricting growth & reproduction**
- **Commonly act as bactericidal agents, causing bacterial cell death**

### 6-Lactams
- **Most widely used antibiotics in the NHS**
- All contain a beta-lactam ring
- **Examples:** Penicillin (shown), amoxicillin and flucloxacillin, cephalosporins (such as cefalexin).
- **Mode of action:** Inhibit bacteria cell wall biosynthesis.

### Aminoglycosides
- **Family of over 20 antibiotics**
- All contain aminosugar substructures
- **Examples:** Streptomycin (shown), neomycin, kanamycin, paromomycin.
- **Mode of action:** Inhibit the synthesis of proteins by bacteria, leading to cell death.

### Chloramphenicol
- **Commonly used in low income countries**
- Distinct individual compound
- **Mode of action:** Inhibits synthesis of proteins, preventing growth.
- No longer a first-line drug in many developed nations (except for conjunctivitis due to increased resistance and worries about safety.

### Glycopeptides
- **Common 'drugs of last resort'**
- Consist of carbohydrate linked to a peptide formed of amino acids
- **Examples:** Vancomycin (shown), teicoplanin.
- **Mode of action:** Inhibit bacteria cell wall biosynthesis.

### Quinolones
- **Resistance evolves rapidly**
- All contain fused aromatic rings with a carboxylic acid group attached
- **Examples:** Ciprofloxacin (shown), levofloxacin, trovafloxacin.
- **Mode of action:** Interfere with bacteria DNA replication and transcription.

### Oxazolidinones
- **Potent antibiotics commonly used as 'drugs of last resort'**
- All contain 2-oxazolidinone heterocycles in their structure
- **Examples:** Linezolid (shown), posizolid, tedizolid, cycloserine.
- **Mode of action:** Inhibit synthesis of proteins by bacteria, preventing growth.

### Sulphonamides
- **First commercial antibiotics were sulphonamides**
- All contain the sulphonamide group
- **Examples:** Prontosil, sulphafurazole (shown), sulphadiazine, sulphoglucose.
- **Mode of action:** Do not kill bacteria but prevent their growth and multiplication. Cause allergic reactions in some patients.

### Tetracyclines
- **Becoming less popular due to development of resistance**
- All contain 4 adjacent cyclic hydrocarbon rings
- **Examples:** Tetracycline (shown), doxycycline, minocycline, oxytetracycline.
- **Mode of action:** Inhibit synthesis of proteins by bacteria, preventing growth.

### Macrolides
- **Second most prescribed antibiotics in the NHS**
- All contain a 14-, 15-, or 16-membered macrolide ring
- **Examples:** Erythromycin (shown), clarithromycin, azithromycin.
- **Mode of action:** Inhibit protein synthesis by bacteria, occasionally leading to cell death.

### Ansamycins
- **Can also demonstrate antiviral activity**
- **Examples:** Gistamycin (shown), rifamycin, naphthyromycin.
- **Mode of action:** Inhibit the synthesis of RNA by bacteria, leading to cell death.

### Streptogramins
- **Two groups of antibiotics that act synergistically**
- Combination of two structurally differing compounds from groups ansamycin A & B
- **Examples:** Quinomycin A (shown), pristinamycin IA.
- **Mode of action:** Inhibit the synthesis of proteins by bacteria, leading to cell death.

### Lipopeptides
- **Instances of resistance rare**
- All contain a lipid bonded to a peptide
- **Examples:** Daptomycin (shown), surfactin.
- **Mode of action:** Disrupt multiple cell membrane functions, leading to cell death.

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http://www.compoundchem.com/2014/09/08/antibiotics/
Political commitments addressing AMR in the EU

• Council Recommendation of 9 June 2009 on the prevention and control of health-care associated infections

• European Parliament Resolutions: 12 May 2011 on antibiotic resistance and 27 October 2011 on the public health threat of antimicrobial resistance

• Council Conclusions on the impact of antimicrobial resistance in the human health sector and in the veterinary sector – a "One Health" perspective – 22 June 2012

AMR: an European and global issue

Decision-makers

- European Commission
- European Parliament
- Council of the European Union
- Regulations; Directives; EC communications / decisions; Council conclusions / resolutions / recommendations

Scientific advice

- Committees
  - CHMP
  - CVMP
  - ESVAC
- Scientific committees
  - SCENIHR
- Networks
  - EARS-Net
  - ESAC-Net

International organisations

- World Health Organization
- Codex Alimentarius
- Food and Agriculture Organization of the United Nations
- World Organisation for Animal Health
- Guidelines, reports

Guidelines, technical reports, scientific advice, recommendations
EU Legislation

Pharmaceutical legislation on medicinal products for human use (Directive 2001/83/EC) introducing the prescription-only requirement for the use of antibiotics in humans and animals

Harmonised monitoring and new case definitions for antimicrobial resistance and healthcare-associated infections (Decision 2013/1082/EU)

Harmonised monitoring of AMR in zoonotic and commensal bacteria in the food chain (Decision 2013/652/EU)

EU legislations on veterinary medicinal products and medicated feed (revision ongoing)

Draft Animal Health Law
The European Commission Strategy on AMR

Communication from the Commission to the European Parliament and the Council
Action plan against the rising threats from Antimicrobial Resistance


- 5 year action plan
- Holistic approach
- 7 key areas
- 12 concrete actions
The 7 Key Areas

1. Ensuring **appropriate use** of antimicrobials in both humans and animals
2. Developing **new effective antimicrobials** or alternatives for treatment
3. **Preventing** microbial infections and their spread
4. **Cooperating with international partners** to contain the risk of AMR
5. **Improving monitoring and surveillance** in human and animal medicine
6. **Reinforcing research** and innovation
7. **Improving communication**, education and training
The 12 actions

Human

1. Appropriate use
4. Prevention of infections
6. New antibiotics
9. Surveillance

Veterinary

2 & 3. Appropriate use
5. Prevention of infections
7. Need for new antibiotics
10. Surveillance

8. International cooperation
11. Research & Innovation
12. Communication, education

Action Plan Progress Report (March 2015)


- Comprehensive report on progress made so far on the 12 actions
- Lists all scientific guidelines, reports and recommendations issues by ECDC, EFSA, EMA
- Links to ongoing research projects
Appropriate use of antimicrobials

Action nº2: strengthen the regulatory framework on veterinary medicines and on medicated feed

• Revision of the Veterinary Medicines Legislation
  - Specific provisions on veterinary antimicrobials to address the health threat of AMR which cover granting of **marketing authorisations for veterinary antimicrobials**, the **use of antimicrobials**, a legal tool to **preserve** certain antimicrobials for human use and a requirement to gather information on the **use of veterinary antimicrobials**

  - Proposal Sept 2014

• Revision of the Medicated Feed Legislation
  - Provides a **prohibition on the preventive use** of antimicrobials included in medicated feed; ensures a **more precise dosage** of antimicrobials administered to farmed animals to avoid sub-therapeutic exposure and establishes **thresholds for residual levels** of antimicrobials in ordinary compound feed

  - Proposal Sept 2014
Appropriate use of antimicrobials

Action nº3: introduce recommendations for prudent use in veterinary medicine

- Scientific recommendations on use in veterinary sector of last resort antimicrobials for humans
  - EMA advice on use of last resort antimicrobials in the veterinary sector
  - Antimicrobial Expert Group in EMA provided recommendations on referrals and responsible use of CIAs

- Reduce overall use of AM in veterinary medicine
Prevent microbial infections & spread

Action nº5: Adoption of a proposal for an EU Animal Health Law

- Animal Health legal framework based on "Prevention is better than cure"
  - Animal Health Law proposal for a regulation lays down responsibilities on:
    - operators to ensure the required level of animal health and biosecurity;
    - veterinary and aquatic animal health professionals to adopt effective measures to prevent the spread of pathogens and to raise awareness;
    - competent authorities to protect animal health, human health and the environment;
  - Proposal provides for an assessment, prioritisation and categorisation of diseases or disease agents
  - Proposal clarifies obligations to ensure appropriate monitoring, surveillance and early detection of pathogens

Milestones / Deadlines

- Agreement on June 2015
Monitoring and surveillance

Action nº10: strengthen surveillance systems on AMR and antimicrobial consumption in animal medicine

- Harmonised surveillance systems
  - **ESVAC** project collects standardised overall sales data and national sales from MSs
  - Harmonisation of surveillance and monitoring of AMR in the food chain

- Surveillance and monitoring of animal pathogens in the Animal Health Law proposal

- EFSA, EMA and ECDC combined information
  - First Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report

**Milestones / Deadlines**

- **2012**
  - Completed

- **Completed**
Ex-post Evaluation of the AMR Action Plan

- Strong political will to continue to combat AMR
- Action Plan to expire in 2016
- The Commission is committed to evaluate the impact of the Action Plan to assess the extent the planned objectives were achieved
- Sustained action at EU level necessary to ensure progress and collaboration with all sectors and global partners
Ex-post Evaluation of the AMR Action Plan

Objectives:

• To identify the achievements and failures in the implementation of the 12 key strategic actions

• To assess the impact of the achievements on the management and control of AMR in the EU

• To enable the Commission to better identify what new or additional measures should be taken in the medium and long term strategy to combat AMR
Conclusion

- Fight against AMR: top priority for DG SANTE
- Ongoing evaluation: basis to decide on the follow-up
- Availability of data is crucial for success
- Stakeholders' joint responsibility: implement respective actions plans
Questions?