

**COMBATTING ANTIMICROBIAL RESISTANCE THROUGH A ONE HEALTH APPROACH:
ACTIONS AND OIE STRATEGY**

Jean-Pierre Orand⁽¹⁾, Gérard Moulin⁽²⁾ & Elisabeth Erlacher Vindel⁽³⁾

¹ Director Anses ANMV, OIE Collaborating Centre For Veterinary Medicinal Products, 8 rue Claude Bourgelat, Parc d'activités de la Grande Marche - Javené - CS 70611- 35306 Fougères – France

² Expert Anses ANMV, OIE Collaborating Centre for Veterinary Medicinal Products, 8 rue Claude Bourgelat, Parc d'activités de la Grande Marche - Javené - CS 70611- 35306 Fougères – France

³ World Organisation for Animal Health, 12 rue de Prony, 75017 Paris – France

Summary: *Antimicrobial resistance poses a threat to disease control throughout the world and is today a primary concern for human and animal health. This issue needs a whole-of-society engagement through a One-Health approach.*

The OIE plays an active part in discussions on this subject in conjunction with other international organisations working in this field, in particular the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) under the tripartite agreement.

The responsible and prudent use of antimicrobials in both people and animals is crucial, not only in the interests of human health but also for animal health and animal welfare.

In this context the Global Action Plan developed by WHO, in collaboration with FAO and OIE, is primordial and Member Countries of the three organisations committed to develop National Action Plans accordingly.

The OIE works on antimicrobial resistance through different actions:

- *Development and harmonisation of standards for legislation, prudent use and surveillance of antimicrobial agents;*
- *Training and education of animal health professionals;*
- *Surveillance of the resistance and data collection on the use of antimicrobial agents;*
- *Availability of good quality antimicrobials for veterinary medicinal products;*
- *Awareness and communication;*
- *And good governance and capacity building.*

The OIE will pursue, develop and reinforce these actions through an OIE strategy for combatting antimicrobial resistance that is in line with the implementation of the Global Action Plan.

1. Introduction

Antimicrobial agents are essential for treating diseases. However, their overuse and misuse can result in the emergence of bacteria resistant to their action. Today, it only takes a few hours for a pathogen to travel across the planet, and a few minutes more to form a colony of thousands bacteria.

With our knowledge that 60% of human pathogens come originally from animals, it is clear that antimicrobial resistance poses a serious threat to the treatment of both animal and human diseases throughout the world.

The “OIE Global Conference on the responsible and prudent use of antimicrobial agents for animals” held in Paris in March 2013 recognised that international solidarity is necessary to fight against antimicrobial resistance. It was concluded that:

- antimicrobial agents are essential tools for protecting animal health and welfare,
- antimicrobial agents also contribute to satisfying the increasing world demand for safe food of animal origin,
- antimicrobial resistance is a global human and animal health concern that is influenced by both human and non-human usages of antimicrobial agents,
- good governance practices, including national legislations and regulatory frameworks for import, marketing authorisation, production, distribution (including transport and storage) and use of quality veterinary medicinal products worldwide are very important.

Resistant bacteria emerging either in humans, animals or in the environment may spread from one compartment to another and from one country to another. Antimicrobial resistance knows no geographical or human/animal frontier.

The Global Action Plan on Antimicrobial Resistance (AMR), published in May 2015, has set the target of ensuring the efficacy of treatments for infectious diseases in the long-term, using effective quality-assured antimicrobials. It proposes a series of key actions to be implemented within the coming 5 to 10 years and requires that countries include a national action plan in the global plan within 2 years. The OIE significantly contributed to its preparation on aspects related to the use of antimicrobials in food-producing animals. The 180 OIE Member Countries also made a commitment to support this Global Action Plan by adopting Resolution 26 at the OIE’s 83rd General Assembly last May.

This Global Action Plan represents a next step in the collaboration on antimicrobial resistance between the World Health Organization (WHO), the Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (OIE) and clearly outlines the tripartite approach and collective actions to minimize the emergence and spread of AMR.

The aim is to:

- ensure that antimicrobial agents continue to be effective and useful for curing diseases in humans and animals;
- promote prudent and responsible use of antimicrobial agents;
- ensure global access to medicines of good quality.

The OIE fully contributes to this strategy and works actively to promote rational use of antimicrobials in order to overcome common challenges such as:

- lack of veterinary service capacities;
- lack of legislation;
- poor application of legislation and implementation of standards;
- insufficient education for prescribers, dispensers and users;
- need for surveillance and data on resistance and use of antimicrobial agents;
- unavailability of good quality, safe and efficient antimicrobials;

through several kinds of core actions that are described in this report.

2. Harmonisation and intergovernmental standards

To assist its Member Countries in implementing these strategic objectives, the OIE has adopted a number of standards included in the *Terrestrial Animal Health Code* (the *Terrestrial Code*) and *Aquatic Animal Health Code* (the *Aquatic Code*), as well as in the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (*Terrestrial Manual*). The *OIE Codes* also provide recommendations on risk assessment for antimicrobial resistance arising from the use of antimicrobials in animals. These standards are used to define a

harmonised framework for managing veterinary medicinal products and for antimicrobial resistance surveillance and monitoring, which are prerequisites for developing risk analysis and for adopting management measures and recommendations for the prudent use of antimicrobial agents tailored to each country's specific requirements.

In addition, the World Assembly of OIE Delegates has adopted a List of Antimicrobials of Veterinary Importance, which complements the list of critically important antimicrobials in human medicine elaborated by WHO. This list includes recommendations on the use of antimicrobials that are considered to be critically important both for human and animal health (fluoroquinolones and third and fourth generation cephalosporins). It also includes recommendations for antimicrobial classes/subclasses used only in human medicine.

The standard-setting process is and continues to be active. Between 2009 and 2015, the OIE updated and completed its intergovernmental standards and the OIE List of antimicrobial agents of veterinary importance to promote the appropriate use of antimicrobial agents in animals, in close collaboration with its international network of experts and with the participation of FAO and WHO. These standards, which form the foundation of the OIE's considerable contribution to the development of the veterinary component of the WHO Global Action Plan, will continue to be updated in collaboration with FAO and WHO to take into account new knowledge.

Surveillance and monitoring:

- Harmonisation of national antimicrobial resistance surveillance and monitoring programmes (Chapter 6.7 of the *Terrestrial Code*);
- Laboratory methodologies for bacterial antimicrobial susceptibility testing (Chapter 1.1.6 of the *Terrestrial Manual*);
- Monitoring of the quantities and usage patterns of antimicrobials agents used in food-producing animals (Chapter 6.8 of the *Terrestrial Code*);
- Monitoring of the quantities and usage patterns of antimicrobial agents used in aquatic animals (Chapter 6.3 of the *Aquatic Code*);
- Development and harmonisation of national antimicrobial resistance surveillance and monitoring programmes for aquatic animals (Chapter 6.4 of the *Aquatic Code*).

Legislation, use of antimicrobial agents and risk analysis:

- Veterinary legislation (Chapter 3.4. of the *Terrestrial Code*);
- Risk assessment for antimicrobial resistance arising from the use of antimicrobials in animals (Chapter 6.10 of the *Terrestrial Code*);
- Responsible and prudent use of antimicrobial agents in veterinary medicine (Chapter 6.9 of the *Terrestrial Code*);
- Principles for responsible and prudent use of antimicrobial agents in aquatic animals (Chapter 6.2 of the *Aquatic Code*);
- Risk analysis for antimicrobial resistance arising from the use of antimicrobial agents in aquatic animals (Chapter 6.5 of the *Aquatic Code*).

3. Training and education

The veterinary profession, in both its public and private sectors, has a crucial role to play in combatting antimicrobial resistance, particularly with their responsibility in the prescription and delivery of antimicrobial products. For this reason, the OIE has also developed guidelines on veterinary education.

In response to a recommendation adopted at the first OIE Global Conference of Veterinary Education, the OIE convened an *ad hoc* Group on Veterinary Education. The *ad hoc* Group develops OIE guidelines on veterinary education, named "Recommendations on the Competencies of graduating veterinarians to assure National Veterinary Services of quality" and OIE Guidelines on "Veterinary Education Core Curriculum". These guidelines represent a basis on which national needs and circumstances could be added, and are offered primarily to developing and in-transition countries as an initial step to enhance and sustain National Veterinary Services.

The recommendations set out the minimum competencies needed by graduating veterinarians to be adequately prepared to participate in National Veterinary Services.

Concerning veterinary medicinal products containing antimicrobial agents, specific learning objectives are defined in order that the veterinary graduate is able to:

- use common veterinary products in the appropriate manner, including appropriate record keeping;
- understand common mechanisms leading to development of antimicrobial resistance in common pathogens.

To develop these competencies, the Guidelines for a Model Core Veterinary Curriculum define that the microbiology course shall contain education on the different options for a treatment, including the judicious use of antimicrobials and the development of antimicrobial resistance by the pathogen.

In addition, the OIE advocates an appropriate legislative framework to ensure professional ethics and good governance of Veterinary Services within the veterinary profession. With this in mind, the Organisation is developing intergovernmental standards and programmes related to the functioning and constitution of national and regional Statutory Veterinary Bodies, which have the necessary legal powers to oversee degrees, ethics, professional excellence and the exclusion of those whose conduct is inappropriate.

In some countries, para-professionals play an important role in the chain of veterinary medicinal products and may be responsible for the delivery or administration of veterinary medicinal products containing antimicrobial agents to the animal. It is also very important that these professionals are well-educated and well-trained in the prudent use of antimicrobial agents and the OIE should continue and intensify its actions regarding the training and education of animal health professionals including and not limited to veterinarians.

The specific case of the use of veterinary products by Community-based animal health workers should also be taken into consideration.

4. Surveillance of bacterial resistance and collection of data on the use of antimicrobial agents in animals

In many countries today, antimicrobial agents are widely available, directly or indirectly, with virtually no restriction or control. Out of 130 countries assessed by the OIE, more than 110 do not yet have a complete and relevant legislation to ensure appropriate conditions for the import, manufacturing, distribution and use of veterinary medicinal products, including antimicrobial agents. As a result, these products circulate freely, like ordinary goods, and are often adulterated.

Surveillance of resistance of animal pathogens is another important element to assess the level and the evolution of antimicrobial resistance in animals. Currently, very little information is available worldwide on pathogens relevant to animal diseases.

The OIE standard on “Harmonisation of national antimicrobial resistance surveillance and monitoring programmes” and the guideline on “Laboratory methodologies for bacterial antimicrobial susceptibility testing” provide a basis for such testing. Future work will be needed to provide indicator bacteria relevant for the main animal species and to refine recommendations for harmonisation of susceptibility testing in veterinary laboratories.

Collection of data on the use of antimicrobials in animals: data on the use and circulation of antimicrobial agents in animals on a global level are not yet available. Collecting such information will enable countries to better control the quality, safety and efficacy of the products in use and to have better knowledge on the conditions of their use.

In this context, the OIE has been mandated by its Member Countries to collect the missing information and establish a global database to monitor the use of antimicrobial agents in animals. This database, which will be supported by FAO and WHO as part of the Global Action Plan, will allow over time to analyse trends. OIE Member Countries will also improve understanding on the circulation of antimicrobials in their respective countries.

The first phase of data collection on antimicrobials used in animals was initiated at the end of 2015. 127 answers have been received by the end of April 2016, 70.6% of which provided quantitative data on antimicrobials. This survey shows that a number of countries have started to collect data on antimicrobials. It also shows the need to provide additional support to countries to improve their national data collection systems. Detailed interpretation of the data needs further developments and the future database should allow countries to provide the information through an electronic application on a yearly basis.

The database contributes to the Global Action Plan and will support the work of the three organisations in their fight against bacterial resistance. The information gathered will also make it easier for Member Countries to:

- analyse and control the source of the veterinary medicinal products;
- obtain more reliable information on imports;
- trace their movements, and better evaluate the quality of the products in circulation;
- measure trends in the use of antimicrobial agents in animals over time.

The OIE will also work on the establishment of rules to estimate the biomass of different animal populations as it will be essential to make data on antimicrobial usage comparable over time and between countries. In this respect, the data collected via WAHIS could be useful.

All these data are essential for antimicrobial resistance risk analysis and planning purposes. They can also assist in better understanding and responding to problems of antimicrobial resistance in a precise and targeted way. On country level, these data will also assist in risk management to evaluate the effectiveness of efforts to ensure responsible and prudent use and mitigation strategies (for example, by identifying changes in veterinary prescribing practices) and to indicate where change of antimicrobial usage practices might be appropriate. The publication of these data is important to ensure transparency and to allow all interested parties to perform risk assessments and for risk communication purposes.

5. Availability of good quality veterinary medicinal products: antimicrobials and alternatives

Veterinary medicinal products are key tools for both public and animal health and need therefore to be of high quality, safe and efficient. This objective at international level can be reached if good governance regarding veterinary medicinal products is structured and based on international standards. In order to develop good governance regarding veterinary medicinal products, each country should develop and implement relevant regulations. Public policy must clearly define the scope and the objectives, be transparent and ideally set up an independent competent authority with the necessary resources including an inspectorate. All the activities concerning the veterinary medicinal products must be covered by a national policy, compliant with OIE standards, from the design of the medicines to their final use: design, registration, manufacturing, import, distribution, wholesaling, storage, retailing and use.

5.1. VICH

Guaranteeing veterinary medicinal products that are quality assured and officially authorised through a transparent scientific process is essential. In order to provide a basis for wider international harmonisation of registration requirements, the OIE supports the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) activities.

In 2011 a VICH Outreach Forum was set up with the objective to allow the participation of regulatory authorities from non-VICH countries and regions. The main objective of the VICH Outreach Forum is to provide a basis for wider international harmonisation of registration requirements, improve information exchange and raise awareness on VICH and its guidelines with non-VICH countries/regions.

5.2. Control of the manufacturing, distribution and retailing

The quality of veterinary medicinal products is particularly important in the context of antimicrobial resistance. Indeed, if a product does not contain the required concentration of antimicrobial agents as defined in the registration dossier, this could increase the development of resistance. This is the reason why after the granting of a marketing authorisation, controls should be conducted to ensure:

- the respect of manufacturing process described in the dossier and respect of good manufacturing practices for all forms of veterinary medicinal products including medicated feed,
- the quality of imported veterinary medicines,
- the respect of the conditions of storage (to avoid degradation of the medicines),
- the respect of deliverance rule and conditions of administration.

5.3. Control of quality, falsification and counterfeiting

Some quality controls should be conducted in qualified laboratories to detect quality defects but also falsified or counterfeit medicinal products.

In 2012, the results of a survey showed that among the countries having in place a legislation on medicinal veterinary products, more than 22% of these did not cover the quality control of veterinary medicinal products. The lack of control of the quality of authorised veterinary medicinal products is a concern.

An even more important issue is the circulation of low quality or falsified products but solid data and estimation of the phenomenon are lacking on a global level. Falsified medicinal products may contain no active ingredient, the wrong active ingredient or the wrong amount of the correct active ingredient. Some might even be toxic. Some falsified medicinal products are almost visually identical to the genuine product and very difficult to detect without analysis. Some studies indicate that the percentage of falsified or counterfeit veterinary medicines can be very important in some countries, playing a potential dangerous role in global antimicrobial resistance.

The OIE should intensify its collaboration with appropriate international organisations to provide additional support to OIE countries to produce good quality veterinary medicinal products, control them and fight against falsified and counterfeit products.

5.4. Alternatives to antimicrobials: vaccines

The OIE has initiated work on prioritising diseases for which vaccines could reduce antimicrobial use in animals. Research on other alternatives to the use of antimicrobials should be encouraged.

A first international symposium on ‘Alternatives to Antibiotics’ was held at OIE Headquarters in September 2012. The objectives were to highlight promising research results and new technologies that could potentially lead to alternatives to conventional antibiotics, and assess challenges associated with their commercialisation and provide actionable strategies to support development of alternative antimicrobials.

The OIE will host a 2nd International Symposium on Alternatives to Antibiotics (ATA): Challenges and Solutions in Animal Production organized by USDA in collaboration with OIE, from 13 to 15 December 2016 at OIE Headquarters in Paris (France).

6. Awareness and communication

Antimicrobial resistance is a whole-of-society problem which needs everyone’s involvement. This cannot be achieved without raising awareness and promoting behavioural change, through public communication that target different audiences in human and animal health and agricultural practice, but also reaches consumers. Public information and reporting with accurate and relevant information reinforces key messages.

Key messages need to be adapted to each actor. Specific awareness on the need for good practices is necessary for all sectors including in the food-producing animal sector.

Every year is held a World Antibiotic Awareness week. The goal of this week is to raise awareness of the health risks posed by antibiotic resistance and to promote good practice in this area of concern, to limit the emergence and spread of resistant bacteria throughout the world. OIE develops various background materials on the problem of antimicrobial resistance with free-access to facilitate communication at the country level.

In addition to communication materials, the OIE publishes relevant documents:

- The Terrestrial and Aquatic *Codes*;
- The OIE *Manuals of diagnostic tests and vaccines*: for terrestrial and aquatic animals
- The ‘Antimicrobial resistance in animal and public health’ *Scientific and Technical Review*: the objective of this review is to address the various factors that must be taken into account when trying to understand the antimicrobial resistance problem, with a particular focus on the use of antimicrobials in animals.

International conferences have been organised or hosted by the OIE:

- OIE Global Conference on *the responsible and prudent use of antimicrobial agents for animals* ‘International Solidarity in the Fight against Antimicrobial Resistance’, 13–15 March 2013: more than 300 participants from over 100 countries permitted to elaborate recommendations;
- International symposium on ‘Alternatives to Antibiotics’, 26–28 September 2012, Paris.

7. Good governance and capacity building

The OIE strategy for veterinary medicinal products based on standards and guidelines on veterinary medicinal products includes the strengthening of Veterinary Services.

The OIE provides its Member Countries with a number of tools to help them to implement the antimicrobial resistance standards more effectively. General OIE tools include the Tool for the Evaluation of Performance of Veterinary Services (OIE PVS Tool), which enables countries to make an accurate diagnosis of their ability to manage risk, assess their degree of implementation of OIE guidelines and identify areas for improvement. The OIE has also introduced more specific tools for veterinary medicinal products by designating Collaborating Centres for veterinary medicinal products, establishing networks of national focal points, organising training seminars or conducting twinning projects.

7.1. OIE PVS Pathway

The OIE PVS Pathway is a global programme for the sustainable improvement of the compliance of a country's Veterinary Services with OIE standards on the quality of Veterinary Services.

The OIE international standards and guidelines form the basis for independent external country evaluations of the quality of Veterinary Services and animal health systems. A specific methodology has been developed and the OIE has published the OIE PVS Tool as the basis for evaluating performance against the international standards published in the *Terrestrial Code*.

PVS Gap Analysis: the PVS Gap Analysis Tool (a ‘prescription tool’) is a quantitative evaluation of a country's needs and priorities based on the outcome of the independent external evaluation of the country's Veterinary Services using the OIE PVS Tool.

Veterinary legislation: any country that has undergone a PVS evaluation can request a follow-up mission to obtain advice and assistance in modernising their national veterinary legislation.

PVS Pathway Follow-up missions: as a follow-up to a PVS evaluation, and at the request of Members, the OIE conducts missions to help governments wishing to modernise their national veterinary legislation and thereby help Veterinary Services to meet OIE standards.

7.2. Collaborating Centres for veterinary medicinal products

The OIE relies on special structures – Collaborating Centres – to provide specific expertise in a given specialty area. Collaborating Centres help to develop and implement OIE strategic policy. There are four Collaborating Centres particularly involved in the work on antimicrobial resistance: Agence Nationale du Médicament Vétérinaire, Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail (ANMV-Anses), Fougères, France; Center for Veterinary Medicine, Food and Drug Administration (CVM-FDA), Rockville, USA; Center for Veterinary Biologics United States Department of Agriculture, Ames, USA; and National Veterinary Assay Laboratory, Tokyo, Japan. They participate in related *ad hoc* Groups; they support trainings for national focal points and other relevant activities.

7.3. Network of national focal points on veterinary products and capacity-building activities

The OIE has asked each of its Member Countries to appoint national focal points for certain topics that it considered important, including veterinary medicinal products. The permanent Delegate is the official representative of his or her Member Country in dealings with the OIE, while national focal points are specialists in the respective subject. Regarding veterinary medicinal products the Focal Points are responsible for providing expertise to the permanent Delegate, as well as acting as a key contact person for the OIE including for the collection of data on the use of antimicrobial agents in animals.

Training courses for national focal points for veterinary medicinal products have been implemented since 2010. We have reached the 4th cycle of trainings. Good governance of veterinary medicinal products and on antimicrobial resistance was on the agenda of each cycle. VICH is also a recurrent item as the OIE supports the objective to develop a better harmonization of requirement for registration of veterinary medicinal products. During the current cycle, a specific workshop on the collection of data concerning the use of antimicrobial is conducted. It is also the opportunity to discuss a new concern quite similar to antimicrobial resistance: antiparasitic resistance. This could become an important issue in the coming years and approaches similar to the one developed for antimicrobial resistance could be followed.

8. Conclusion

Antimicrobial resistance poses a threat to disease control throughout the world and is today a primary concern for human and animal health. This issue needs a whole-of-society engagement through a One-Health approach.

The numerous stakeholders concerned shall exercise their responsibilities in their respective field of competence in order to safeguard the efficiency of antimicrobials and to guarantee the safety of the food chain.

Good practices shall be developed and implemented by each actor of the veterinary medicinal product chain covering the whole chain from manufacture, distribution to the end use. Antimicrobial agents as pure active ingredients shall not be administered directly to the animals without any registration as a veterinary medicinal product, and without any quality control.

In order to help control the risks, the OIE works on antimicrobial resistance through different actions:

- Development and harmonisation of standards for legislation, prudent use and surveillance of antimicrobial agents;

- Training and education of animal health professionals;
- Surveillance of the resistance and data collection on the use of antimicrobial agents;
- Availability of good quality antimicrobials for veterinary medicinal products;
- Awareness and communication;
- Good governance and capacity building.

However, this subject reaches now a highly political level. The WHO and the OIE General Directors addressed the problem at the G7 health ministers meeting on antimicrobial resistance in Berlin in October 2015 and the preparation of a high-level discussion on antimicrobial resistance at the 2016 United Nations General Assembly has been engaged by FAO, OIE and WHO.

This is why all the actions undertaken by the OIE over the past few years on the different topics mentioned in this report should be gathered together and presented in the framework of a strategy giving the OIE the opportunity to defend its position.

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