

# Antimicrobial resistance: an overview

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## Summary

Increased antimicrobial resistance in bacteria that are important pathogens of humans, and spread of resistance from the closed environment of hospitals into open communities are increasingly perceived as a threat to public health. Any antimicrobial use, whether in humans, animals, plants or food processing technology, could lead to bacterial resistance. Use of antimicrobials in livestock production is suspected to significantly contribute to this phenomenon in species of bacteria which are common to humans and animals. Further research is required into the specific use conditions that govern the selection and dissemination of resistant bacteria. International travel and trade in animals and food increase the risks of antimicrobial resistance world-wide. Countries are considering import restrictions for products deemed a risk to public health. The Office International des Epizooties, a World Trade Organization reference organisation for the Agreement on the Application of Sanitary and Phytosanitary Measures, develops international standards on antimicrobial resistance which, as is the case for national measures, must be based on risk analysis. The scientific background and problems of resistance in human medicine are reviewed. Current knowledge, missing information and actions to be taken are identified.

## Keywords

Agreement on the Application of Sanitary and Phytosanitary Measures – Antimicrobial resistance – Containment of resistance – Food – International standards – National measures – Office International des Epizooties – Public health – Resistance mechanisms – Risk analysis.

## Introduction

The existence of antimicrobial resistance, the increase in resistance to a number of antibiotics of bacteria that are important human pathogens, and the spread of resistance from the rather closed environment of hospitals into open communities, are increasingly perceived as a threat to public health.

The appearance of new resistance mechanisms, the development of multi-drug resistance or combinations of resistance, and the facility with which genetic material encoding resistance may, in certain cases, spread horizontally between different species of bacteria, all increase the feeling of defencelessness against diseases that were thought to have been controlled when antibiotics were first developed.

Reports referring to apocalyptic visions of the plague depopulating nations and women dying of puerperal fever, are prone to increase public fears rather than helping to appropriately address important matters of public health. Unfortunately, these kind of publications, such as 'World leading killers planning their escape' are rather common and are not only communicated by the kind of media aiming at increasing their sales figures.

Any use of antibiotics, may it be for human, animal, plant or food processing technology, has the potential to lead, at some point in time, to bacterial resistance. Although many publications are beginning to appear, little is known about the different conditions of use under which antibiotics preferably select, or select to a lesser extent, for resistant bacteria. Resistance, once developed, is not bound to borders of different ecological environments or countries. Limited scientific

research on resistance (abandoned for several decades and only recently re-established, pushed by growing concerns) and the consequent lack of scientific data leave society and decision makers in the uncomfortable situation of requesting and deciding upon corrective actions when the underlying causes may not have been appropriately identified.

This situation, coupled with the slowing, and in certain sectors disappearing, discovery and development of new antibiotics with new mechanisms of action, creates an atmosphere of anxiety calling for immediate action, whether efficient or not.

Globalisation, new trade environments and transfer of resistant bacteria through international travel, and trade of animals and food, raise the risk of the spread of resistance world-wide. It also bears the risk of countries closing borders for trade on the basis of inappropriately evaluated risks or perceived risks.

## Antimicrobial resistance – a responsibility of the Office International des Epizooties

### **Why has the Office International des Epizooties taken action on antibiotic resistance?**

Countries must protect animal and human health. This also includes protecting against risks arising from bacteria resistant to antimicrobial treatment.

At the same time, members of the World Trade Organization (WTO) must respect their obligations under the WTO Agreement on the Application of Sanitary and Phytosanitary Measures (SPS), which are to base any sanitary measure on risk assessment and scientific evidence and to restrict measures to the extent necessary to achieve the chosen level of protection. In cases where several potential measures exist, the least trade restrictive measure must be chosen.

The Office International des Epizooties (OIE), the World Organisation for Animal Health, is the organisation recognised by the WTO for the elaboration of international standards, guidelines and recommendations on matters of animal health and zoonoses relevant for the trade of animals and animal products.

Antibiotic resistance, as it relates to zoonotic bacteria and to resistance determinants (which may be transferred between animals and from animals to humans), and the measures to be taken in view of their control are the responsibility and field of competence of the OIE. The OIE is the appropriate organisation to prepare international recommendations on the detection and

control of antimicrobial resistance as they relate to zoonotic bacteria and resistance determinants as they originate from animal bacteria. These standards, when finalised and adopted by the OIE International Committee, will serve as a WTO reference standard, should trade disputes arise.

### **What action has been taken by the Office International des Epizooties?**

A report on existing activities and capacities for the detection and control of antibiotic resistance was made in 1998 to fifty countries of Europe at the OIE Regional Commission for Europe. This report emphasised that additional efforts should be made to develop official antimicrobial resistance surveillance/monitoring programmes, to improve their harmonisation and the harmonisation of laboratory methodologies, which in turn will improve the reliability and comparability of generated resistance data. The report also pointed out that risk analysis was not commonly used when the implementation of sanitary measures was considered by countries.

Based on this report, the OIE Regional Commission for Europe recommended to the OIE International Committee that an international Ad hoc Group of experts be formed to address, using a comprehensive and multidisciplinary approach, human and animal health risks related to antimicrobial resistance originating from the use of antimicrobials in veterinary medicine. The OIE International Committee endorsed this recommendation in May 1999 and the OIE Director General appointed the Ad hoc Group of experts on antimicrobial resistance.

The OIE Ad hoc Group of experts decided to engage in a three pillar strategy:

- immediate measures to contain and reduce antimicrobial resistance (prudent and responsible use of antimicrobials)
- development of tools to assess and manage the risks to animal and human health (risk analysis methodology), and harmonisation of surveillance systems and laboratory methodologies
- improve knowledge on antimicrobial resistance world-wide (information gathering).

### **The achievements of the Ad hoc Group of the Office International des Epizooties**

As a result of the work of the OIE Ad hoc Group, countries are now gaining access to a set of comprehensive methodologies, assuring that the identification of, and decision upon appropriate intervention measures are conducted in an objective, science-based, transparent and defensible way.

The specific considerations that were given to the different conditions (geographical, use of antimicrobials, resistance

situation) and to the technical capabilities and capacities of countries around the world, open the way for an equal application of these methodologies both to developing and developed countries. The OIE Ad hoc Group emphasises that where animal or human health problems exist throughout the world, without respect to national borders, all countries have an equal need to protect their animal and human populations and their national trade interests.

The tools underlying two of the three pillars of the recommendation of the OIE Ad hoc Group (monitoring the quantities of antimicrobials used in animal husbandry and the immediate measures to contain antimicrobial resistance through the prudent and responsible use of antibiotics) and the tools to assess and manage risks to animals and humans (risk analysis methodology, harmonisation of surveillance systems and laboratory methodologies) became available for implementation by country governments and competent authorities.

The five respective guidelines, prepared by the OIE Ad hoc Group with the participation of the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) compose the body of this document.

The third pillar (to improve knowledge on antimicrobial resistance world-wide) will be constructed as the implementation of the tools constituting the first two pillars proceeds and results are obtained.

### **Future directions of the Office International des Epizooties**

The 69th General Session of the OIE International Committee of May 2001 adopted Resolution No. XXV requesting the OIE Specialist Commissions to develop international standards in the area of antimicrobial resistance. The Specialist Commissions will use the recommendations of the OIE Ad hoc Group to develop these standards. The draft standards proposed by the Specialist Commissions will be circulated for comments to the OIE Member Countries. Revised draft standards will be circulated a second time to the OIE Member Countries and after a second revision, as appropriate, be submitted for adoption to the 70th General Session of the OIE International Committee in May 2002. The standards will be published in the *International Animal Health Code* and the *Manual of Standards for Diagnostic Tests and Vaccines*.

The OIE is taking steps to encourage Member Countries to make use of the new methodologies in order to establish an objective, science-based view on the subject and consequently contain antimicrobial resistance in animal bacteria. The OIE will undertake the necessary steps to provide assistance, as appropriate, to its Member Countries, on aspects related to the implementation of this standard.

The OIE Standards Commission decided during its spring meeting in January 2001 to introduce standards for antimicrobial sensitivity testing into the *OIE Manual of Standards for Diagnostic Tests and Vaccines*. The Standards Commission also recommended the designation of OIE Reference Laboratories for the detection and quantification of antimicrobial resistance in animal bacteria. These laboratories will, among others, assist OIE Member Countries in setting up microbiological laboratories, where appropriate, and in placing the work of these laboratories under quality assurance.

At the 14th Conference of the OIE Regional Commission for Africa, held on 23-26 January 2001, Member Countries decided to actively engage in the promotion of the prudent use of antimicrobials in animals and to undertake efforts to establish national programmes for the management of antimicrobial resistance. The Regional Commission for Africa also recommended that OIE Reference Laboratories assist OIE Member Countries in implementing quality assurance schemes in national microbiological laboratories and in participating in external proficiency testing programmes.

The OIE will continue to insist that sanitary measures are based on risk assessment of sound scientific data, and conducted according to appropriate recommended methodologies.

## **Some scientific facts**

### **The scientific background**

#### **What is antimicrobial resistance?**

Antimicrobial resistance is the capacity of bacteria to survive exposure to a defined concentration of an antimicrobial substance. Antimicrobial resistance has multiple definitions according to the scientific discipline and the goals involved:

- clinical definition: the bacteria survive an adequate treatment with an antibiotic
- pharmacological definition: the bacteria survive a range of concentrations expressing the various amounts of an antibiotic present in the different compartments of the body when the antibiotic is administered at the recommended dose
- microbiological and molecular definition: the bacteria have a mechanism which governs a higher minimum inhibitory concentration (MIC) than the original or wild bacteria
- epidemiological definition: any group of bacterial strains which can be distinguished from the normal (Gauss) distribution of MICs to an antibiotic.

Bacterial resistance to a particular antibiotic can be a natural property of the bacteria or a secondarily acquired mechanism. Surviving the effect of an antibiotic is a normal reaction of a bacterial cell. When successful, such a reaction gives origin to a clone of bacterial cells able to confront the antibiotic. However, according to the mechanism of resistance, the bacterial clone

may confront different amounts of antibiotic, ranging from a small amount, close to the amount formerly able to inhibit the growth (MIC) of the bacterial cell, to a very large quantity of antibiotics (e.g. hydrolysing exoenzyme produced by the bacteria).

It is a very well known fact that bacteria can resist any antibiotic, and this is a global phenomenon which affects all countries. However, characteristics of the resistance phenomenon relate to the affected bacterial species, the set of antibiotics involved, the distribution of the resistant strains in particular settings in which antibiotics are used (hospital, community, animal husbandry, etc.). The resistant strains are classified according to their identification (genus, species) and to their antibiotic resistance phenotype (sometimes referred to as antibiotype or resistance pattern).

The antibiotic resistance phenotype is established by the comparison of the list of antibiotics active on the reference (original, wild) strain of the bacterial species (which may have a natural resistance to some antibiotics) with the list of antibiotics to which the strain tested is resistant. This represents acquired resistance, which is the opposite of natural resistance. It is recommended to group the antibiotics under classes and subclasses according to the mechanism of resistance. This is called cross-resistance (e.g. a  $\beta$ -lactamase Tem type in *Escherichia coli* governs a cross-resistance to all aminopenicillins, all ureidopenicillins and a few first generation cephalosporins. The cross-resistance for six compounds is expressed by ampicillin resistance).

When the sequence of resistance markers concerns different classes of antibiotics, this is referred to as co-resistance.

Bacterial resistance to an antibiotic can be considered according to three aspects described below.

#### *The mechanism by which the bacteria is able to resist*

It is important to note that a bacterial cell often possesses more than one mechanism to resist to an antibiotic. Co-operation between several resistance mechanisms often generates high level resistance. A summary of resistance mechanisms, the affected antibiotics and the resulting level of resistance, is presented in Table I.

#### *The genetic mechanism governing the proteins involved in the resistance and the origin of resistance*

Two genetic mechanisms are involved, namely: mutation in an existing gene (chromosome or plasmid), and the *de novo* acquisition of a gene governing resistance.

The location of the altered or the new genes is important (chromosomes, integrons, transposons or plasmids). The most important consequence of the location of the resistance genes concerns the spread of the resistance:

– a chromosomal mutation affects a bacterial cell. The clone issued from this cell will multiply and spread. This mode of spread is often called vertical transmission of resistance

– a resistance gene located on a transposon or a plasmid can be transmitted horizontally, independently from the spread of the resistant clone. Moreover, the horizontal transmission may occur between different bacterial species. Concomitantly or independently to the expansion of the resistant bacteria, plasmid (gene) epidemics can occur. Many of them have been reported affecting six to eight species of Gram-negative bacteria.

Plasmids or transposons are the main systems (genetic material) transferring resistance from bacteria (donor) to bacteria (recipient). They usually carry more than one marker of resistance. Large plasmids may transfer several different mechanisms of resistance against a number of different antibiotics. Their concurrent appearance in the same bacteria explains that one antibiotic may continue to co-select for the whole set of resistance mechanisms (multi-drug resistance).

#### *The medical (or therapeutic) aspect*

Bacterial resistance is recognised in medicine when an antibiotic treatment fails to cure a patient and the bacterial pathogen persists unharmed by the antibiotic prescribed. This is the point in time when human medicine becomes concerned. It is important to note that when a particular resistance emerges

**Table I**  
**Resistance mechanisms, the affected antibiotics and the resulting level of resistance**

Mechanism	Affected antibiotics	Level of resistance
Efflux	Tetracyclines	Low
	Macrolides	
	Quinolones	
	Others in different systems	
Penetration	$\beta$ -lactams	Low
	Chloramphenicol	
	Trimethoprim	
	Tetracyclines	
Target alteration	$\beta$ -lactams	Variable
	Aminoglycosides	
	Macrolides	
	Quinolones	
	Rifampicin	
	Glycopeptides	
By-pass	Sulphonamides	High
	Trimethoprim	
Enzyme detoxification	$\beta$ -lactams	High
	Aminoglycosides	
	Macrolides	
	Chloramphenicol	
	Lincosamide	

in a human bacterial pathogen (except the rapid selection of a chromosomal mutant bacteria), it can be assumed that many bacteria (commensal, environmental and animal) have also acquired the same resistance mechanism. A delay, sometimes very long, elapsed between the emergence of the resistance mechanism and its medical visibility.

**Why and how does resistance develop?**

Resistance develops as an answer to the selection pressure exerted by an antibiotic, or by another compound (e.g. antiseptic), provided that they share at least one similar mechanism of resistance. Two conditions should be met. The selecting substance (selector) must be in prolonged contact with the bacterial population. The selector should be at a concentration which allows the bacteria to survive. This is generally referred to as a sub-inhibitory concentration. However, it should be noted that the lower limit of a sub-inhibitory concentration still acting as a selector has been poorly explored.

An apparent contradiction exists between the statement that there is a positive correlation between high consumption/usage of antibiotics in a country and resistant bacteria, and the fact that low doses of antibiotics in an individual ecosystem (patient, animal or environment) are more selective for resistance. This stems from the fact that two different systems are compared, which are not directly related. One system is the total human or animal population in a country, the other system is the bacterial populations in a patient or group of patients. High consumption of antibiotics is a surrogate measure of the amount of antibiotics **distributed** among humans, animals and the environment. The important criteria is not the high concentration of an antibiotic in an individual patient or animal, but the extent of distribution of the antibiotics in the ecosystem. The larger the distribution of antibiotics, the greater the chance that in some place a large population of bacteria will be in contact with the correct selecting concentration of the antibiotic.

The different events in bacterial life which can lead to the development of resistance are shown in Table II.

In the first case, the resistance trait is generated from a mutation which occurs in the particular clone in contact with the selector.

In the second case, the acquisition of a resistance gene requires the transfer of such a gene from a donor strain to the recipient strain. In that case, two populations of bacteria are required in the presence of the antibiotic, with one resistant (donor) and one susceptible (recipient).

It should be noted that in infectious diseases, there is usually one bacterial population at the site of infection. Resistance due to mutation can be acquired by the patient during treatment (rifampin, fluoroquinolones). Only emergence of resistance due to mutation can be easily and rapidly observed in the patient, whereas resistance due to acquisition of genes is only recognised after a delay of months or even years.

The primary origin of genes governing mechanism of resistance and able to circulate between bacteria of the same or different species remains partly unknown. However, it is accepted that these genes may originate from the antibiotic-producing organism, which uses the mechanism to survive its own antibiotic production (e.g. enzyme modifying aminoglycoside). This is an event that occurs in nature and is independent of the man-made production and use of antibiotics.

There is also evidence that transferable resistance genes can originate from a 'pick up' mechanism which mobilises a gene from the chromosome of a naturally resistant bacteria (e.g. plasmid located cephalosporinase).

Although no strict separation can be made between chromosomal resistance and transferable resistance, it is useful to keep the distinction as an epidemiological tool. It can be of importance to recognise that the spread of quinolone resistant strains is clonal (resistance to quinolone is a chromosomal mutation) compared to that of ceftriaxon resistant *Salmonella*. In that case, plasmid-mediated spread is combined with clonal spread, and can be linked to different *Salmonella* species or other Enterobacteriaceae.

**Table II**  
**Events leading to the development of resistance**

Event	Result	Spread
<b>Chromosomal mutations</b> (one or more) Induction Derepression (pre-existing mechanism not expressed or barely expressed)	Altered target Altered cell wall Efflux system Modifying enzyme	Clonal (not transferable)
<b>Mutation</b> (plasmid)	Modifying enzyme Inducible trait → constitutive	Clonal and transferable
<b>Acquisition of genes</b> Plasmids, transposons, phages	Modifying enzyme Efflux By-passing target	Transferable Needs donor strains and recipient strain

### Where does resistance develop?

Very few studies have demonstrated the favourable niche for resistance development. The selector must be mixed with the bacterial population at the right concentration and time needed for the selection and the multiplication of the resistant population. In a unique bacterial population, emerging resistance is necessarily selected through mutations in the pre-existing genes of the bacterial cells. When the niche comprises mixed populations of different bacteria (resistant and susceptible), the emerging resistance may be due either to mutation or to a *de novo* acquisition of genes from a resistant bacterial cell. An antibiotic entering a niche with several bacterial species will kill the susceptible bacteria while the resistant species will multiply by mere vital advantage. Resistant clones from the susceptible population may be selected provided that:

- a) the antibiotic concentration has declined, allowing the survival of a portion of the susceptible population
- b) a mutant bacterial cell exists in the bacterial population (the frequency of mutation varies greatly between antibiotics)
- c) a transfer of genes (plasmids or transposons) has taken place between the pre-existing resistant bacterial cells and the surviving susceptible bacterial cells.

The most studied location of emergence of resistance is the digestive system of humans and animals. The enormous number of bacteria and species and the obligatory presence of most antibiotics in the gut (oral administration and bile elimination) explain the importance of this essential niche for resistance emergence.

Clearly, mutant bacterial cells are theoretically selectable in any site where bacteria and antibiotic are in contact (e.g. abscess, empyema, urine, etc.).

However, resistance by chromosomal mutation is not the most frequent system of resistance and does not affect a large number of antibiotics. The only antibiotics affected are those for which a high frequency of mutation ( $> 10^{-8}$ ) exists (rifampin, fusidic acid, quinolones and phosphomycin).

In these cases, mutations are readily selected. Resistant clones are often observed during treatment or shortly afterwards. Such emergence of resistant strains is spectacular and easily observed by medical doctors or veterinarians.

In fact, mutations are a small part of the resistance problem. The principal problem is related to the selection and the stabilisation of mechanisms governed by foreign genes acquired by the originally susceptible bacterial cells.

As mentioned earlier, the intense circulation of bacteria can either be gene circulation or bacterial cell circulation. The emergence of multiple-resistant pathogens (with plasmids,

transposons or integrons) takes a long time, during which numerous bacteria (commensal, environmental) are involved; during this period the phenomenon is not clinically visible. In this case, emergence of the resistant pathogen occurs far from the prescriber of the antibiotic and a long time after the original selection.

The second important locations where resistant strains are built and selected are those related to the environment (water, soil, animal litter, sewage, hospital fomites, etc.).

Several antibiotics can be present together in a niche. Those antibiotics will select for resistance separately, but also in a cooperative manner, if bacteria exist which are already resistant to them. The multiple resistant strains are favoured, since they can more easily survive the exposure to multiple antibiotics. Those multiple resistant strains are also more likely to acquire a new resistance.

### What problems are faced?

#### Infectious diseases and resistance in human medicine

The difficulties faced in depicting the current situation of antimicrobial resistance are related to the limited, or in many cases lacking, systematic official disease investigations and reporting in this area. Hard data, such as laboratory confirmed cases, are limited even in developed countries where sophisticated disease investigation and reporting systems exist. Total disease burden, morbidity, mortality and economic impact descriptions are based on estimations, which may inherit errors and uncertainties depending on the validity of the underlying assumptions. The few countries that have, in recent years, started official resistance surveillance are beginning to obtain *in vitro* bacterial susceptibility data. However, systematic reporting of data on clinical outcomes is limited. Therefore, in many instances, *in vitro* data may have to be interpreted without being able to relate back to clinical outcomes.

The reasons for this situation may be related initially to the inherent costs of disease investigation and reporting, but also to political unawareness and the potential negative impact of disease statistics on public opinion.

According to the WHO, the emergence and spread of antimicrobial resistance in human pathogens is considered a global problem which increasingly affects the successful treatment of infectious diseases in humans.

The WHO has identified six diseases (tuberculosis, malaria, pneumonia, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), diarrhoea and measles) which cause 90% of infectious disease deaths world-wide. A proportion of these diseases is caused by bacteria and a relatively larger proportion by parasite and virus infections.

To provide an overview on the resistance situation in medicine, these infections will be briefly reviewed.

### *Tuberculosis*

Tuberculosis, a disease once thought to be controlled, is currently responsible for the deaths of 1.5 million people a year (a further 0.5 million die from a combination of tuberculosis and HIV/AIDS). Nearly two billion people (one-third of the population of the world) have latent tuberculosis infection. This constitutes a huge potential reservoir for the disease. Tuberculosis is one of the biggest infectious killers of adolescents and adults, and a leading cause of death among women. In addition, infection with HIV weakens the immune system and can activate latent tuberculosis. Infection with HIV is also believed to multiply the risk of contracting tuberculosis. Approximately one-third of all AIDS deaths are currently caused by tuberculosis.

Because a patient may have both AIDS and tuberculosis, the reservoir for tuberculosis has increased and threatens more people in the community.

Moreover, tuberculosis is becoming increasingly resistant to anti-tuberculosis drugs. Researchers assess the approximate number of multi-drug resistant tuberculosis cases at between 1% and 2% of current global tuberculosis figures. However, in some parts of the world, the rates of multi-drug resistant tuberculosis are much higher. China (Henan and Zhejiang), India (Tamil Nadu), Iran, Mozambique and Russia (Tomsk) each reported high levels of multi-drug resistant tuberculosis (over 3%) in new cases. Israel, Italy, Mexico (Baja California, Oaxaca and Sinaloa) reported multi-drug resistant tuberculosis in over 6% of both new and previously treated cases.

### *Malaria*

Malaria kills over one million people a year, most of them young children. Most malaria deaths occur in sub-Saharan Africa, where malaria accounts for one in five of all childhood deaths. Women are especially vulnerable during pregnancy, suffering miscarriages or giving birth to premature, low-weight babies, and are more likely to die from the disease. An estimated 300 to 400 million people world-wide are infected by this mosquito-borne parasite each year.

The development of resistance in the malaria parasite shows similarities to bacterial resistance.

### *Acquired immune deficiency syndrome and sexually transmitted infections*

At the end of 1999, an estimated 33.6 million individuals were living with HIV world-wide. There is still no cure on the horizon. In some countries, up to one in four of the adult population is now living with HIV/AIDS. The worst affected region is sub-Saharan Africa.

A small but growing number of patients are showing primary resistance to zidovudine (AZT), as opposed to 'secondary' resistance where viruses grow increasingly insensitive to antivirals over the course of the illness. This is also true for protease inhibitors which became available only ten years ago.

Gonorrhoea and sexually transmitted infections (STIs) are important co-factors in the transmission and spread of HIV. This is because HIV bonds to white blood cells collecting at inflamed sites around the uro-genital tract. Studies show that those co-infected with gonorrhoea and HIV shed HIV at nine times the rate of individuals affected with HIV alone.

Of the STIs, including chancroid and chlamydial infections, gonorrhoea is the most resilient, with a resistance rate that continues to outstrip new treatment strategies. Gonorrhoea resistance was first reported in American servicemen during the Vietnam war and is now entrenched around the globe, with multi-drug resistant strains appearing in 60% of those infected each year. In most of South-East Asia, resistance to penicillin has been reported in nearly all strains at an overall rate of 98%. Recent, more expensive drugs, notably ciprofloxacin, are likewise showing an increasing failure rate. Owing to resistance, chronic gonorrhoea has become a driving force in the HIV epidemic.

### *Pneumonia*

Acute respiratory infections (ARIs) are responsible for 3.5 million deaths each year. Pneumonia, the most dangerous ARI, kills more children than any other infectious disease. Most of these deaths (99%) occur in developing countries, while in industrialised countries childhood deaths from pneumonia are rare. Pneumonia often affects children with low birth weight or those whose immune systems are weakened by malnutrition or other diseases. Without treatment, pneumonia kills quickly.

The major causes of pneumonia are the influenza virus and *Streptococcus pneumoniae*.

The development of resistance to penicillin G by *S. pneumoniae* is now recognised world-wide. However, the prevalence of resistant strains ranges from 5% to 70% of the investigated laboratory samples. Most of these strains are also resistant to several other antibiotics (macrolides, tetracyclines, trimethoprim), dangerously restricting the choice of first-line therapy.

### *Measles*

Measles is the most contagious disease known to mankind. It is a major childhood killer in developing countries, accounting for approximately 900,000 deaths a year. The measles virus may ultimately be responsible for more child deaths than any other single microbe, due to complications from pneumonia, diarrhoea and malnutrition.

### *Hospital acquired infections*

Methicillin-resistant *Staphylococcus aureus* (MRSA),

vancomycin-resistant Gram-negative rods (VRE) and enterococci and fermentative Gram-negative Enterobacteriaceae are the most frequent multi-drug resistant bacteria isolated in hospitals both in developed and developing countries, and are responsible for the most difficult-to-treat hospital infections.

### *Diarrhoeal diseases*

Diarrhoeal diseases claim nearly two million lives a year among children under five. These diseases are so widespread in developing countries that parents often fail to recognise the danger signs. Children die simply because their bodies are undernourished through lack of food and then are weakened through rapid loss of fluids. Diarrhoeal diseases impose a heavy burden on developing countries, accounting for 1.5 billion cases of illness a year in children under five. The burden is highest in deprived areas where there is poor sanitation, inadequate hygiene and unsafe drinking water. In certain developing countries, epidemics of diarrhoeal diseases such as cholera and dysentery affect both adults and children.

Other diarrhoeal diseases include typhoid fever, rotavirus infection, salmonellosis and campylobacteriosis.

Multi-drug resistance is also occurring in microbes that cause diarrhoeal diseases. One such agent, *Shigella dysenteriae*, is a highly virulent microbe that is resistant to almost every available drug. The results of this growing crisis were illustrated most notably in the wake of the 1994 civil war in Rwanda when the bacterium spread through vulnerable refugee populations already traumatised by war and loss. Left untreated, death can follow within days of infection. Ten years ago, a shigella epidemic could easily be controlled with co-trimoxazole, a drug available in generic form at low cost. Today, nearly all shigella are non-responsive to the drug, while resistance to ciprofloxacin (the only remaining viable medication) appears to be imminent.

The bacteria that cause cholera and typhoid are also revealing the ease with which they acquire resistance. For the treatment of cholera, fluid replacement is paramount, but antibiotics (especially tetracycline) play an important public health role in limiting the spread of epidemics. *Salmonella* serotype Typhi, like shigella, is adept at accumulating cassettes of resistance genes, producing strains that withstand first-line, second-line and now, third-line drugs. Until 1972, chloramphenicol was the treatment of choice for typhoid fever throughout much of the subcontinent of India. By 1992, two-thirds of reported cases were chloramphenicol-resistant, thereby necessitating treatment with expensive quinolones that are themselves losing effectiveness. Without proper treatment, typhoid is a serious and frequently relapsing disease that kills up to 10% of those infected.

### *Food-borne infections*

Food- and water-borne pathogens generally cause diarrhoeal

diseases. Six major bacterial groups (*Salmonella*, *Campylobacter*, *E. coli*, *Yersinia*, *Clostridia* and *Listeria*) are responsible for these infections. In severe cases, systemic forms of disease may develop.

Due to the considerable potential for food and water for human consumption to be contaminated by animal and environmental bacteria, scientists have started to focus attention on this area. Although available scientific data is limited, food and food-borne diseases are considered by many to play a specific role in antimicrobial resistance in humans.

When considering antimicrobial resistance in this context, a number of elements should be taken into account, of which a few are mentioned below.

If food- or water-borne bacteria cause disease in humans (e.g. *Salmonella* and *Campylobacter*), they may directly cause human illnesses, independent of whether they are resistant or susceptible to antibiotics. These food- and water-borne illnesses will, in most cases, result in diarrhoeal diseases. The majority of these diseases are self-limiting, do not require antibiotic treatment and are most appropriately treated by symptomatic treatment. If the illness is caused by a resistant bacteria and does require an antibiotic treatment, the treatment may be prolonged or recourse may have to be taken to another, potentially more expensive, antibiotic. In cases where a bacteria is resistant to all available antibiotics, the infection may become untreatable by antibiotics and eventually a patient may die due to the consequences of a non-controllable infection.

If food- or water-borne bacteria are non-disease causing in humans (enterococci), they may indirectly lead to human illness in those specific cases where the animal or environmental bacteria has become resistant to antibiotics and where the potential exists for a transfer of the resistance genes of these bacteria to human pathogenic bacteria. As a consequence, a completely different human illness, which may not be food- or water-related, may become more difficult or impossible to treat. The evaluation of the impact of the potential transfer of resistance genes from non-pathogenic animal or environmental bacteria to pathogenic human bacteria is a much more complex and difficult undertaking, which currently still resides in the domain of research. Molecular and epidemiological methods are required to demonstrate the identical composition of the resistant gene in both the animal/environment and the human pathogenic bacteria and to trace the transfer of genes from the animal/environment to the human bacterial populations or vice versa. The tracing of the direction of transfer is particularly difficult in those cases where the incriminated antibiotic has been used both in humans and animals or plants.

To evaluate the impact and the importance for human health of the non-human use of antimicrobials in animals and plants, data should be systematically collected on the contamination of



food and water with resistant bacteria, food-borne infections, the percentage of infections due to resistant bacteria and the clinical outcome of these resistant infections.

#### *Food-borne disease surveillance and resistance*

Although food-borne disease surveillance was launched twenty years ago in some countries (WHO Surveillance Programme for Control of Food-borne Infections and Intoxications in Europe), food-borne disease surveillance appears to be lacking in many countries around the world and requires significant improvement. Where this kind of surveillance does exist, systematic, official collection of information on antimicrobial resistant bacteria in food and water and on human infections due to antimicrobial resistant animal or environmental bacteria appears to be scarce.

Some references to food- and water-borne disease reporting are given below, which may to some extent illustrate the complexity in the evaluation of the role of antimicrobial resistance in food-borne disease, and the role of food- and water-transferred resistance of animal or environmental origin in the human resistance problem.

The 7th report of the WHO Surveillance Programme for Control of Food-borne Infections and Intoxications in Europe states that 'the variety and extent of food-borne diseases are such that no country is able to provide accurate data on their incidence and prevalence and surveillance programmes, where they exist, mostly collect information on only a low number of incidences. It is therefore not possible to give an estimate of the real magnitude of the problem. In some cases, the aetiology is multifactorial in nature and disease becomes manifest only after a long period of exposure. Consequently, many of the health problems resulting from food contaminants do not figure in statistics on food-borne diseases.'

Indicating that there is direct evidence that antimicrobial use in animals selects for antimicrobial resistant non-typhoid *Salmonella* serotypes (referencing resistant *S. Typhimurium* DT 104), and for fluoroquinolone resistant *Campylobacter jejuni* isolated from humans, poultry and poultry meat, the report indicates however that there 'is limited information on the prevalence and spread of resistance in zoonotic bacteria. Monitoring programmes in some countries are in the early stage of development, some of these are in parallel with the strengthening of resistance monitoring in hospitals and community settings. Monitoring of antimicrobial resistance of bacteria from food animals and food of animal origin – whether national or international – is still in its infancy.'

With regard to food-borne illness in the United States of America (USA), summarised quantitative data is readily available and data for 1997 are given below.

In the USA, food-borne diseases are estimated to cause 76 million illnesses, 325,000 hospitalisations and 1,800 deaths.

Among all illnesses attributable to food-borne transmissions, 30% are caused by bacteria, 3% by parasites and 67% by viruses. Six pathogens account for over 90% of the estimated food-related deaths; *Salmonella* (31%), *Listeria* (28%), *Toxoplasma* (21%), Norwalk-like viruses (7%), *Campylobacter* (5%) and *E. coli* O157:H7 (3%).

In 1997, active surveillance by US FoodNet reported 8,576 laboratory-confirmed cases of food-borne illnesses, of which 3,974 were identified as campylobacteriosis, 2,205 as salmonellosis, 1,273 as shigellosis, 468 as cryptosporidiosis, 340 as *E. coli* O157:H7, 139 as yersinellosis, 77 as listeriosis, 51 as *Vibrio* infections and 49 as cyclosporiasis. Overall, 1,270 (15%) of 8,576 patients with laboratory-confirmed infections were hospitalised; the proportion of cases in which people were hospitalised was highest for listeriosis (88%), followed by *E. coli* O157:H7 infections (29%), and salmonellosis (21%). Thirty-six patients with laboratory-confirmed infections died: fifteen with *Listeria*, thirteen with *Salmonella*, four with *E. coli* O157:H7, two with *Cryptosporidium*, one with *Campylobacter*, and one with *Shigella*. In 1997, the catchment area included 16.1 million people, 6.0% of the population of the USA.

Unfortunately, no information is currently available in these publications on the percentage of infections due to resistant micro-organisms.

## **Scientific opinion**

### **Current knowledge**

Antimicrobial resistance is a natural phenomenon. It is the natural response of a bacterium to defend itself against the effects of an antibiotic. The development of antimicrobial resistance is an ecological phenomenon. Any antibiotic use, whether in humans, animals or plants/environment may lead to resistance. In principle, the same molecules and classes of antimicrobials are used in humans, animals and plants. Humans, animals and the environment represent a reservoir in which resistance can develop. As most bacteria can, at least transitionally, contaminate or colonise all possible hosts (humans, animals, plants, environment), there is an exchange between the different hosts and between the hosts and the environment.

There is a problem of antimicrobial resistance in human medicine, increasingly perceived around the world as a threat to public health. The major problems have been described; these generally relate to parasites, viruses and human pathogenic bacterial infections and the use of antimicrobials in human medicine. One of the six major human diseases, diarrhoea, is in part related to zoonotic bacteria. The WHO indicates that cholera, typhoid, shigella and rotavirus infections, coupled with undernourishment, poor sanitation, inadequate hygiene and unsafe drinking water, are the principal causes of the heavy diarrhoeal disease burden in developing countries. In the USA, three pathogens, *Salmonella*, *Listeria* and *Toxoplasma*,

are considered responsible for more than 75% of deaths caused by known pathogens. Of these three, *Salmonella* is a zoonotic bacterial pathogen.

Concern has increasingly been expressed that, additionally to the resistance existing and emerging in human medicine, the use of antimicrobials in animals and plants will lead to resistance, thereby adding to the existing resistance burden in humans.

Two potential mechanisms of resistance transfer from animals or plants/environment to humans are currently under consideration, as follows:

- a) the transfer of pathogenic bacteria
- b) the transfer of non-pathogenic bacteria or the transfer of their genes encoding resistance.

Infection with resistant zoonotic bacteria may directly lead to human illness. However, the contribution of these bacteria to the overall resistance burden in humans should be carefully evaluated. In view of the very limited existing resistance data in this area, this evaluation might prove to be difficult.

Regarding the transfer of non-pathogenic bacteria, the great fear is that resistance mechanisms encoded in mobile, transferable genetic material may be transferred to already multi-drug resistant human pathogenic bacteria, causing a life-threatening infection, which could be impossible to treat. As a less dramatic scenario, it is thought that the transfer of resistance genes could add to multiple resistance in human pathogens. As the treatment of multiple resistant infections is more difficult and more expensive, such infections would result in an increase in public health costs.

Studies have been published on resistance gene transfer between bacteria. The impact of the potential transfer of resistance genes is a current area of research. Although a very small number of countries performs surveillance of resistance in enterococci (these commensal bacteria are considered as the appropriate indicator bacteria, as they easily develop or pick up transferable resistance), there is no scientific consensus on how surveillance findings should be interpreted.

### Missing information

Where official collection of human infectious disease information exists, information on percentages of resistant infections and clinical outcome data is limited. Food-borne disease surveillance, although present in a number of countries, varies considerably between countries and requires intensification and harmonisation. In other countries, food-borne disease surveillance does not exist. As for zoonotic pathogens, official surveillance of antimicrobial resistance in animal bacteria and food has started only recently in a very small number of countries and in a limited number of bacteria.

Recognising the important efforts made by a number of countries, supported by international organisations such as the WHO and the OIE, additional effort must be made by countries world-wide for the collection of the appropriate data. Countries should attempt to establish their priorities in view of the identified public health problems, the inherent costs and the available resources.

Continued research to increase knowledge of antimicrobial resistance is vital, as is the integration of scientific knowledge in the decision-making processes to the greatest extent possible.

### Future research

All further research in the subject will be valuable and will add to the knowledge and our understanding of the emergence and the appropriate measures for the containment of antimicrobial resistance.

A number of subject areas which urgently require further investigation are presented below:

a) The role of different modes of use of antibiotics in animals and humans. This is critical in the emergence and increased number of resistant strains among pathogens, commensals and environmental bacteria. A number of issues should be considered, namely: dose and duration of treatment, route of administration, pharmacokinetic, pharmacodynamic, number of patients/animals treated, stability in the environment (sewage, litter, land and animal housing), bacterial species and animal species.

b) The innumerable pathways which enable bacteria and genes to spread between animals and humans. From the living animals to the contaminated food on the table of the consumer, there are many opportunities for contamination and transmission. This calls into question the idea that contamination necessarily originates from the animal reservoir and calls for very careful studies to clarify this question. Such studies are particularly difficult to design and conduct in cases where resistance genes, rather than the bacterial strains, are to be tracked down.

c) The colonisation of humans by animal or environmental bacteria. Gram-positive bacteria seem to spread differently to Gram-negative bacteria. The factors in the host specificity of bacteria are to a great extent unknown.

d) The factors to be taken into account when trying to measure human health problems through a risk analysis study, specifically when it is applied to resistance traits (transfer of resistance genes).

e) The information needed to assess and follow the resistance problems. This depends on surveillance systems and records of the antibiotic consumption in humans and animals. Most countries have not yet established any surveillance system. Moreover, the methods of comparison and interpretation of the results are not yet operational.

f) The factors which may explain an increase or a decrease in the prevalence of resistant bacteria. These were recently investigated to determine the strength of their link to the use of a particular antibiotic. Multiple resistance poses a difficult question, since antibiotics other than those immediately concerned can be responsible for co- and cross-selection. Many other questions are raised in accordance with the concern for decreasing or containing antibacterial resistance. Environmental ecosystems, animals and humans are very intimately linked through a bacterial circulation that we are only recently beginning to understand.

Specific studies, basic and applied, coupled with bacterial surveillance systems and more responsible use of antibiotics should generate feedback and deliver clues for new understanding. It must be understood that not all antibiotics behave in the same way, even those belonging to the same class. Such scientific knowledge will be essential in making public health and political decisions and in adapting and updating guidelines for a better protection of the consumer and the global community.

## Actions to be taken

### Immediate actions

The OIE Ad hoc Group of experts invites countries to inform themselves about the problem of antimicrobial resistance.

As an immediate action, the OIE experts urge countries to implement the prudent and responsible use of antimicrobial agents in veterinary medicine, as laid down in their recommendations which are included in *Antimicrobial resistance: responsible and prudent use of antimicrobial agents in veterinary medicine*, later in this volume.

Concurrent with the implementation of the prudent use of antimicrobials, countries are invited to establish the surveillance of importation, distribution and use of antimicrobials in animals. Countries should undertake all necessary efforts to impede the importation, distribution and use of counterfeit antimicrobial products. The recommendations of the OIE Ad hoc Group of experts are included in *Antimicrobial resistance: monitoring the quantities of antimicrobials used in animal husbandry*, later in this volume.

Furthermore, countries should attempt, as a preliminary evaluation, to obtain an overview of the most important public health and antimicrobial resistance problems in their country. To this end, communication between the animal production and the medical field should be established.

Countries should prioritise further medium-term actions, including time frames for their implementation, according to the most important problems identified.

### Requirements for the future

The OIE Ad hoc Group encourages the OIE Member Countries to take ownership of the new methodologies and to make use of them in order to establish an objective, science-based view on the resistance situation in their countries. The OIE urges countries to carry out a risk analysis process when establishing sanitary measures relative to antimicrobial resistance. The respective information and recommendations of the OIE Ad hoc Group of experts are included in *Antimicrobial resistance: risk analysis methodology for the potential impact on public health of antimicrobial resistant bacteria of animal origin*, later in this volume.

OIE Member Countries should assure the use of standardised laboratory methods for the detection and identification of antimicrobial resistance. To generate reliable resistance data, microbiological laboratories should implement quality assurance schemes and participate in external proficiency testing programmes. Proficiency testing programmes would preferably be conducted on a regional or sub-regional level. The recommendations of the OIE Ad hoc Group of experts are included in *Antimicrobial resistance: standardisation and harmonisation of laboratory methodologies for the detection and quantification of antimicrobial resistance*, later in this volume.

After a prioritisation of the most important public health and antimicrobial resistance problems, countries should establish antimicrobial resistance surveillance programmes in human pathogenic bacteria, where necessary, and in animal bacteria and food, as appropriate. The recommendations of the OIE Ad hoc Group on how to address the matter are included in *Antimicrobial resistance: harmonisation of national antimicrobial resistance monitoring and surveillance programmes in animals and in animal-derived food*, later in this volume.

Considering the importance of the issue and to foster consistency in decisions taken, the OIE will continue to co-ordinate its work with other international organisations, such as the FAO and WHO, and will also continue to be available for co-operation with other international or regional organisations, as appropriate.



## Antibiorésistance : une synthèse

J. Acar & B. Röstel

### Résumé

L'augmentation de l'antibiorésistance des bactéries pathogènes pour l'homme et la propagation de cette résistance, de l'environnement confiné des hôpitaux à la collectivité apparaissent, de plus en plus, comme une menace pour la santé publique. Tout traitement antimicrobien appliqué aux humains, aux animaux, aux végétaux ou dans les techniques de transformation des aliments peut entraîner une résistance bactérienne. L'utilisation d'antibiotiques dans les élevages pourrait être en grande partie responsable de ce phénomène dans les espèces bactériennes communes à l'homme et aux animaux. Il est important d'explorer les conditions d'utilisation spécifiques qui président à la sélection et à la dissémination des bactéries résistantes. Le commerce et les échanges internationaux d'animaux et de denrées alimentaires élargissent au monde les risques de la résistance bactérienne. Certains pays envisagent des restrictions à l'importation pour les produits jugés à risque pour la santé publique. L'Office international des épizooties, en tant qu'organisme de référence reconnu par l'Organisation mondiale du commerce aux termes de l'Accord sur l'application des mesures sanitaires et phytosanitaires, élabore des normes internationales sur l'antibiorésistance qui devront s'appuyer sur l'analyse du risque, au même titre que les mesures nationales. Les auteurs examinent les aspects scientifiques de la résistance ainsi que les problèmes qu'elle pose à la médecine humaine. Ils font également le point sur l'état actuel des connaissances, sur les lacunes existantes et sur les mesures qu'il conviendrait de prendre.

### Mots-clés

Accord sur l'application des mesures sanitaires et phytosanitaires – Analyse du risque – Antibiorésistance – Denrées alimentaires – Maîtrise de la résistance – Mécanismes de la résistance – Mesures nationales – Normes internationales – Office international des épizooties – Santé publique.



## Resistencia a los antimicrobianos: síntesis

J. Acar & B. Röstel

### Resumen

El aumento de la resistencia a los antimicrobianos en bacterias que causan importantes afecciones humanas y la salida de esas resistencias del reducto hospitalario al entorno abierto engendran una creciente sensación de amenaza para la salud pública. Cualquier producto antimicrobiano que se utilice en personas, animales, plantas o procesos de transformación de alimentos puede dar lugar a resistencias bacterianas. Hay motivos para pensar que el uso de antimicrobianos en la producción pecuaria contribuye sensiblemente al fenómeno entre especies bacterianas comunes al hombre y a los animales. Será importante investigar acerca de las condiciones específicas de uso que intervienen en la selección y la diseminación de bacterias resistentes. El comercio y movimiento internacional de animales y productos alimentarios confieren una dimensión planetaria a los riesgos de resistencia bacteriana, y no

pocos países están estudiando restricciones a la importación de productos considerados peligrosos para la salud pública. La Oficina Internacional de Epizootias, en cuanto organismo de referencia reconocido por la Organización Mundial del Comercio para el Acuerdo sobre la aplicación de medidas sanitarias y fitosanitarias, elabora normas internacionales sobre la resistencia a los productos antimicrobianos, cuya aplicación, como ocurre con las medidas de ámbito nacional, debe basarse en el análisis de riesgos. Los autores pasan revista a los antecedentes y problemas científicos de las resistencias en el ámbito de la medicina humana y determinan el estado actual de los conocimientos, las lagunas existentes y las acciones que convendría emprender.

#### Palabras clave

Acuerdo sobre la aplicación de medidas sanitarias y fitosanitarias – Alimentos – Análisis de riesgos – Contención de las resistencias – Mecanismos de la resistencia – Medidas nacionales – Normas internacionales – Oficina Internacional de Epizootias – Resistencia a los productos antimicrobianos – Salud pública.



## Appendix A

### Office International des Epizooties Ad hoc Group of experts on antimicrobial resistance

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## Appendix B

### Office International des Epizooties Guidelines on antimicrobial resistance

The following documents constitute the work and the recommendations of the OIE Ad hoc Group of experts on antimicrobial resistance. International experts with recognised expertise in the field composed this group. The group was set up to respect and assure a representation of the different regions of the world. It brought together internationally recognised scientific expertise in medical and veterinary medical sciences, microbiology, laboratory sciences and risk analysis.

- Risk analysis methodology for the potential impact on public health of antimicrobial resistant bacteria of animal origin
- Responsible and prudent use of antimicrobial agents in veterinary medicine
- Monitoring the quantities of antimicrobials used in animal husbandry
- Standardisation and harmonisation of laboratory methodologies for the detection and quantification of antimicrobial resistance
- Harmonisation of national antimicrobial resistance monitoring and surveillance programmes in animals and in animal-derived food

## Appendix C

### Background literature

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