

Factsheet for experts

Nosocomial infections and antimicrobial resistance are two special health issues listed in Annex 1 of Commission Decision 2000/96/EC of 22 December 1999 on the communicable diseases to be progressively covered by the Community network under Decision No 2119/98/EC of the European Parliament and of the Council.

Nosocomial infections correspond to infections acquired in hospitals. The term “Healthcare-associated infections” is now preferred because it includes not only infections acquired in hospitals, but also in other settings where healthcare is provided, e.g. long-term care facilities, nursing homes, home care, etc.

Microorganisms – also called microbes – include bacteria, viruses, fungi and parasites.

Antimicrobials are medicinal products that kill or stop the growth of living microorganisms and include among others:

- Antibacterials (often called antibiotics, active against bacterial infections),
- Antimycobacterial drugs (which are antibacterials specifically active against tuberculosis and other mycobacterial infections)
- Antivirals (active against viral infections, e.g. influenza, HIV, herpes infections),
- Antifungals (active against fungal infections),
- Antiparasital drugs (active against malaria and other infections due to parasites).

Antimicrobial resistance, i.e. being resistant to one or several antimicrobials used for therapy or prophylaxis, is not a disease but a characteristic that may apply, as a matter of principle, to each of the microorganisms responsible for the communicable diseases listed in Commission Decision 2000/96/EC and for nosocomial and other healthcare-associated infections.

Antimicrobial-resistant microorganisms, including multidrug-resistant types, are often responsible for healthcare-associated infections, but they are also responsible for infections in patients outside hospitals and can be found as part of the normal bacterial flora of healthy individuals, in pet animals and in the environment. They are also responsible for infections and isolated from food-producing animals and sometimes isolated from foods.

Conversely, many healthcare-associated infections are caused by microorganisms that are not resistant to antimicrobials. The two concepts are thus really quite separate, but for historical and professional reasons they are often dealt with together.

Antimicrobial resistance

Antimicrobial resistance is the ability of a microorganism (e.g., a bacterium, a virus, or a parasite, such as the malaria parasite) to resist the action of an antimicrobial agent.

- It is an adaptation of the microorganism to its environment.
- Any use of an antimicrobial forces microorganisms to either adapt or die.
- It is the microorganisms that colonise and sometimes infect humans and animals which become resistant to antimicrobials, not the humans or animals themselves. Humans and animals do not become resistant to antimicrobial treatments, but bacteria and other microorganisms can.
- Antimicrobial resistance results in a reduction or elimination of effectiveness of the antimicrobial agent to cure or prevent infection due to this microorganism.

For bacteria, antibiotic resistance is the ability of bacteria to resist to the action of an antibiotic.

- Bacteria have antibiotic resistance when specific antibiotics have lost their ability to kill or stop their growth.
- Some bacteria are naturally resistant to certain antibiotics (intrinsic or inherent resistance).
- A more worrying problem is when some bacteria that are normally susceptible to antibiotics become resistant as a result of adaptation through genetic change (acquired resistance).
- Additionally, within the body of a human being, the genes coding for antibiotic resistance in one species of bacteria can easily spread to other bacterial species through an exchange of genetic material.
- In the continuous fight for “ecological space”, all resistant bacteria are selected as the antibiotic kills the still-susceptible bacteria around them.
- All antibiotic-resistant bacteria survive in the presence of the antibiotic and continue to grow and multiply causing longer illness or even death.
- Infections caused by antibiotic-resistant bacteria may require more care as well as alternative and more expensive antibiotics, which also may have more severe side effects. Treatment of antibiotic-resistant bacteria may also require intravenous antibiotics given in hospitals instead of oral antibiotics that could be taken by patients at home.
- Once established in a person, antibiotic-resistant bacteria can spread to another person and a high antibiotic consumption in a population (hospital or community) strongly favours such spread.

Multidrug resistance corresponds to resistance of a microorganism to multiple antimicrobials.

- This issue of multidrug resistance is relevant for all microorganisms, including bacteria responsible for healthcare-associated infections, microorganisms responsible for food- and waterborne infections, tuberculosis, and microorganisms responsible for sexually-transmitted diseases, e.g. gonorrhoea and HIV.
- The challenge with multidrug-resistant microorganisms lies in the limited number of remaining options (if any) for therapy of patients infected with these microorganisms.

Examples of common multidrug-resistant bacteria are:

- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Vancomycin-resistant enterococci (VRE)
- Extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* (examples of common *Enterobacteriaceae* are *Escherichia coli* and *Klebsiella pneumoniae*)
- Multidrug-resistant *Pseudomonas aeruginosa*
- *Clostridium difficile*

The two major drivers for antimicrobial resistance are:

- Use of antimicrobials, which exerts an ecological pressure on microorganisms and contributes to emergence and selection of antimicrobial-resistant microorganisms in populations;
- Spread and cross-transmission of antimicrobial-resistant microorganisms between humans, between animals, and between humans and animals and the environment.

The two major areas for management, control and prevention of antimicrobial resistance therefore are:

- Prudent use of antimicrobials (i.e. only when needed, with the correct dose, at correct dose intervals and for a correct duration);
- Hygienic precautions for the control of cross-transmission of antimicrobial-resistant microorganisms (infection control), including hand hygiene, screening, isolation, etc.

Part of the burden of antimicrobial resistance in the EU is due to antimicrobials used in food-producing animals.

- Antibiotics used to treat and prevent infections in animals belong to the same chemical groups as those used in human medicine, therefore animals may carry bacteria that are resistant to antibiotics also used to treat infections in humans;
- Certain bacteria, e.g. *Salmonella* and *Campylobacter* are associated with consumption of contaminated foods and cause diarrhoea;
- Because of exposure to antibiotics, animals may carry antimicrobial-resistant *Salmonella* and *Campylobacter* that are transferred from animals to humans through food;
- Humans may also acquire antimicrobial-resistant bacteria from direct contact with animals as this is the case with certain MRSA strains sometimes isolated from livestock, in particular from pigs.

However, the major cause of antimicrobial resistance in microorganisms from humans remains the use of antimicrobials in human medicine, in the community and in hospitals and other healthcare settings.

At individual/patient level:

- Taking antibiotics always modifies the human normal bacterial flora which often results in side effects, e.g. diarrhoea, as well as emergence and/or selection of antibiotic-resistant bacteria;
- These resistant bacteria may persist, generally without causing infection, up to six months and sometimes longer;
- Patients colonised by/carrying resistant bacteria are generally more likely to develop an infection with these resistant bacteria rather than with susceptible variants of the same bacteria;
- Antibiotics should not be used when they are not needed, e.g. for viral infections such as common colds or influenza;
- When antibiotics are needed (this decision is made by a medical doctor who writes a prescription), they should then be used appropriately, i.e. at the correct dose, at correct intervals and for the prescribed duration, to optimise effectiveness to cure the infection and minimise emergence of resistance;
- Even when antibiotics are used appropriately, antibiotic resistance sometimes develops as a natural adaptive reaction of bacteria. Whenever antibiotic-resistant bacteria emerge and develop, infection control precautions are essential to prevent spread from carriers of infected patients to other patients or persons.

At population level:

- There are large intercountry variations in the proportions of resistant bacteria in the EU and these variations, often showing a North-to-South gradient, can be observed for most antimicrobial-resistant bacteria surveyed by the European Antimicrobial Resistance Surveillance System (EARSS);
- There are also large variations in antibiotic use among EU Member States, as shown by data from the European Surveillance of Antimicrobial Consumption (ESAC) project;
- Once controlled for size of population, the Member States that use the most antibiotics for outpatients, i.e. Greece and Cyprus, use approximately three times more per inhabitant and per year than the Member State that uses the least, i.e. the Netherlands;
- Levels of antibiotic consumption consistently correlate with levels of antibiotic resistance, i.e. the more antibiotics are being used in a population, the more resistance to antibiotics there will be in bacteria responsible for infections in this population.

Based on Directive 2001/83/EC and national legislations in Member States, antimicrobials to be used systemically (i.e. not locally) should only be dispensed at pharmacies upon presentation of a prescription, usually from a medical doctor. Despite this, dispensation of antimicrobials without a prescription still occurs at pharmacies in several Member States.

Since October 2008, it is possible for patients in the UK who are asymptomatic but who have a diagnosed genital infection with *Chlamydia* to obtain from pharmacists (without a prescription) a single dose of the antibiotic azithromycin, representing a complete treatment course. This is the only exception where systemic antibiotics can be dispensed without a prescription.

In a few countries, decreasing trends are being observed for antibiotic use in outpatients and for antibiotic resistance in bacteria commonly responsible for infections in outpatients.

- Six Member States (i.e. France, Belgium, Slovakia, Czech Republic, Slovenia and Sweden) recently reported decreasing trends in antibiotic use in outpatients;
- In France and Belgium, the decrease was attributed to national action including a yearly, nationwide public campaign on the prudent use of antibiotics;
- The EARSS Annual Report 2007, as well as national data, indicated decreasing resistance trends in *Streptococcus pneumoniae*, a bacteria commonly responsible for infections in outpatients, in particular children;
- These positive experiences from some EU Member States are the background for the European Antibiotic Awareness Day, a campaign to reduce use of antibiotics in situations where they are not necessary, for example for viral infections such as colds and influenza.

In a few countries, decreasing trends in resistance are also being observed for one microorganism responsible for healthcare-associated infections, namely MRSA.

The EARSS Annual Report 2007 indicated that seven Member States now report significantly decreasing percentages of MRSA among *Staphylococcus aureus* from bloodstream infections.

This is likely due to increased efforts on infection control, hand hygiene and antibiotic policy in hospitals in these countries as demonstrated by national data from, e.g. Slovenia, France and UK.

Despite these encouraging experiences, antimicrobial resistance still is high or increasing in a majority of Member States, in particular for common bacteria such as *Staphylococcus aureus* (MRSA), *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.

Additionally, cases of infections due to bacteria totally or almost totally resistant to antibiotics are currently emerging in the EU. Examples of such bacteria are carbapenemase (KPC)-producing *Enterobacteriaceae* (often *Klebsiella pneumoniae*), and multidrug-resistant *Acinetobacter*. There is no rational choice of antibiotic therapy for treating such patients and treatment often relies on old and toxic antibiotics such as colistin.

This new trend is worrying since there are very few compounds in the research and development pipeline that would potentially have an activity against these bacteria and could be marketed within the next 5-10 years.

Modern medicine relies on availability of effective antibiotics in the case an infectious complication occurs or for prophylaxis of infection. Without effective antibiotics, intensive care, organ transplants, cancer chemotherapy, care of preterm babies, or even common surgical procedures, such as hip or knee replacement, would not be possible.

Because antimicrobial-resistant microorganisms fail to respond to therapy, infections due to these microorganisms result in greater risk of death, prolonged illness and

stay in hospitals and greater risk of death. The total burden of antimicrobial resistance across all the communicable diseases listed in Commission Decision 2000/96/EC (including nosocomial infections) is currently unknown. Preliminary estimates of the number of deaths directly attributable to hospital-acquired infections due to the most common major multidrug-resistant bacteria are 1/3 to 1/2 of that for hospital-acquired infections overall (see below) (ECDC, preliminary data).

Antimicrobial resistance is a worldwide problem.

- While people die in developing countries because they lack access to the correct antimicrobial treatment, antimicrobial resistance resulting from inappropriate use is causing concern in every continent;
- The World Health Organization (WHO) has issued a global strategy and guidelines to help countries in setting up systems to monitor antimicrobial resistance and implement interventions, e.g. to ensure that antibiotics can only be purchased with a medical prescription.

Travellers that require hospital care while visiting a country with high prevalence of antimicrobial resistance, within or outside of the EU, and who are subsequently repatriated to their home country, may return being colonised or even infected by multidrug-resistant bacteria. Even without having been in contact with healthcare, people who travel in a country with high prevalence of antimicrobial resistance may return being colonised by multidrug-resistant bacteria.