Antimicrobial resistance – a challenge for public health

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"Resistance to antibiotics risks
health 'catastrophe' to rank with terrorism
and climate change…".
Dame Sally Davies
Chief Medical Officer UK, 2013

Abstract

Penicillin, the first antibiotic introduced into clinical practice opened a new era in medicine. The 'golden age' of antibiotic discoveries in the 1950s, 60s and 70s significantly helped our fight against bacterial infections. In parallel with the introduction of new drugs, resistance strains were identified. This was, however, neglected because of the belief that pharmaceutical companies would continuously supply us with new products. In contrary, a pipeline of new antibiotics slowly dried out and in the 1980s we realized that the proportion of resistant bacteria was increasing faster than the supply of new antibiotics. New mechanisms of resistance emerged and multidrug and pandrug resistant bacterial strains started to spread globally. Antimicrobial resistance is recognized now as one of the greatest threats to public health worldwide. The WHO and EU as well as national agencies are calling for actions which should be immediately undertaken if we do not want to lose the battle.

Key words: antimicrobial resistance, call for actions to contain antibiotic resistance, rational antibiotic use

Słowa kluczowe: działania ograniczające oporność na antybiotyki, oporność na antybiotyki, racjonalne stosowanie antybiotyków

Introduction

The introduction of antibiotics into treatment began a new era in medicine. The first antibiotic – penicillin – started to be extensively used in the final phase of World War II. About 15 years had passed since its discovery by Alexander Fleming (1928) to its introduction in the drug form. This indicated that the path from discovery to the inclusion of a new antibiotic in treatment could be very long.

Penicillin, which is a natural product of *Penicillium notatum*, directed scientists to search for antimicrobial compounds in microorganisms living in the environment. This resulted in the discovery of streptomycin, the first antibiotic active against *Mycobacterium tuberculosis*, produced by *Streptomyces griseus*, a type of soil bacteria. The discoverer was Samuel Waksman, who introduced the term antibiotic into medicine (derived from

the Greek ἀντί, anti 'against' and βίος, bios 'life') and said: "From the earth shall come thy deliverance." Indeed – it turned out that the species of the genus *Streptomyces*, living in the soil, are a particularly rich source of antibiotics. And so it was discovered that they produce i.a.: chloromycetin (chloramphenicol, *Streptomyces venezuelae*), neomycin (*Streptomyces fradiae* and *Streptomyces albogriseus*), rifampicin *Streptomyces mediterranei* (now *Amycolatopsis mediterranei*), clavulanic acid (*Streptomyces clavuligerus*), kanamycin (*Streptomyces kanamyceticus*), tetracycline (*Streptomyces aureofaciens*), daptomycin (*Streptomyces roseosporus*), erythromycin (*Streptomyces erythraea* now *Saccharopolyspora*), vancomycin (*Streptomyces orientalis*, now *Amycolatopsis orientalis*). The source of antibiotics turned out to be also the fungi and it was from *Cephalosporium acremonium* that the entire family of

cephalosporins was formed. Antibiotics may also be metabolites of bacteria, e.g. mupirocin is a secondary metabolite of *Pseudomonas fluorescens*.

Subsequent stages of the development of research on antimicrobial drugs resulted in a number of modifications of antibiotics naturally occurring as primary or secondary metabolites of microorganisms. They allowed obtaining drugs with better pharmacokinetic and pharmacodynamic parameters, different formulations and greater stability against the bacterial enzymes that degrade them. For example, the two largest and most important groups of drugs, semisynthetic penicillins and cephalosporins, were developed. Also, carbapenems, until recently regarded as antibiotics of last resort, started to be developed with the natural product *Streptomyces cattleya*, thienamycin. Currently, this group contains a number of drugs, the most commonly used of which are imipenem/cilastatin, meropenem, ertapenem and doripenem. The array of antibacterial drugs was significantly enriched by such synthetic compounds as quinolones and oxazolidinones. The former group is still being improved and includes as many as four generations of drugs with different spectra of activity and clinical indications. Unfortunately, serious side effects after their administration have been recently observed and require their significant reduction and caution in their use. A number of excellent studies refer to both biological, pharmacological and clinical features of antibiotics, which have been applied in the treatment and prevention of human infections [1, 2].

We use the term 'antimicrobial drugs' to describe drugs that act on micro-organisms, regardless of how they are obtained, and for simplicity reason we now consider antibiotics to be not only natural products but all antibacterial and sometimes antifungal drugs, also known as antimycotics.

This article focuses on bacterial pathogens because it is against them that the largest number of antibiotics have been developed, incomparable with drugs effective against other microorganisms, such as fungi and parasites. General remarks on the increasing resistance to antibiotics amongst bacteria apply to all groups of microorganisms. This article does not deal with the resistance of *M. tuberculosis*, fungi and parasites. Resistance of *Mycobacterium tuberculosis* to drugs is very high and it belongs to the group of pathogens with the highest public health risk.

Most of the currently used antibiotics were introduced into medicine in the 1960s and 1970s, and so this period could be called the 'golden age' of antibiotic treatment.

It should also be noted that an equally wide range of antimicrobial drugs was introduced to treat infections and prevent them in animals.

The success of the antibiotics was so spectacular that they were given the name 'miracle drugs'. They started to be used broadly, not only in medicine and veterinary medicine but also in animal and even plant production. The belief was born that antibiotics are an excellent remedy 'for everything'. This caused their enormous abuse.

An important feature of antibiotics is their selective toxicity, i.e. they act on the microorganisms in low concentrations, usually not affecting human cells, causing the death of the microorganism or inhibiting its multiplication. The former are called bactericidal antibiotic; the latter – bacteriostatic. However, it is the patient's immune system that plays a key role in combating infection, and antibiotics are an important aid. Selective toxicity, i.e. toxicity directed only at the microorganism, means that the patient is safe to use antibiotics. We know, however, that depending on the drug but also on the patient's characteristics, adverse effects may be observed [1].

As already mentioned, antibiotics are the metabolic products of microorganisms which – when producing them – must be equipped with resistance mechanisms that allow them to survive in the presence of these products. Therefore, resistance genes existed prior to the introduction of antibiotics into treatment. Because of their use, microorganisms have also improved the functions of other genes, which are now responsible for resistance [3]. The development of resistance is a natural evolutionary process supported by the widespread and excessive use of antibiotics in medicine, veterinary medicine and agriculture.

Resistance, in general, means the lack of sufficient activity against a given micro-organism in a concentration that would be safe for the patient. We divide it into a natural, also called intrinsic resistance, and an acquired one [4]. The former is a constant feature of the species and should always be taken into account when deciding on the inclusion of a given antibiotic in the treatment schedule. Here are some illustrative examples. Each antibiotic has its target (point of activity) in the cell and its lack will cause its ineffectiveness.

In *Mycoplasma pneumoniae*, which does not have a cell wall, there is no 'target' for β-lactams, so the microorganism presents a natural resistance to this group of drugs. Pneumonia caused by this bacteria cannot be cured by using any of the β-lactam antibiotics. Another example is the glycopeptide antibiotics, which are too large molecule to reach the target in *Enterobacterales*, so they cannot inhibit the biosynthesis of the cell wall and inhibit the pathogenic process. The non-fermenting Gram-negative rod, *Stenotrophomonas maltophilia* always produces carbapenemase, so infections caused by it cannot be treated with a group of antibiotics called carbapenems. There are also examples of antibiotics that have naturally low penetration through the cell wall, which prevents them from reaching their target in the cell, but the addition of an additional drug (combined therapy) with a different mechanism of action may result in an excellent synergistic effect. The best examples are aminoglycosides, which are not effective in therapy of enterococcal infections but combined with penicillin or ampicillin or glycopeptide result in great synergy and bactericidal effect. This combination is used in the treatment of enterococcal endocarditis.

Acquired resistance is the result of mutations in chromosomal genes or acquisition of foreign DNA encoding resistance by a previously susceptible cell. The latter

type known as horizontal gene transfer of resistance acquisition is observed through conjugation, transformation and transduction. The process of spreading resistance genes is particularly dynamic when antibiotics are overused [5].

The introduction of antibiotics into medicine resulted in a significant decrease in morbidity and mortality caused by infections and infectious diseases. A particularly spectacular effect was seen in the most common infections, which are associated with high or even very high mortality. An excellent example of the effectiveness of penicillin is the significant reduction in mortality in puerperal fever caused by *Streptococcus pyogenes* and in pneumonia caused by *Streptococcus pneumoniae*. The availability of penicillin has helped reduce gonorrhoea and achieve significant success in controlling the most common sexually transmitted bacterial infections. Until now, the nearly always fatal meningitis, as well as severe infections caused by *Staphylococcus aureus*, have been cured. To a large extent, it is penicillin that has led to the reduction of the incidence of rheumatic fever; and there are many more examples.

Subsequently introduced antibiotics expanded the range of treatment options. They allowed the development of many new branches of medicine, especially neonatology, transplantation and various subspecialties of surgery. They have found application not only in the treatment but also in bacterial prophylaxis, especially perioperative.

Antibiotics disrupt various life processes of bacteria and, as mentioned before, lead to their death or inhibition of growth. β-lactams (penicillins, cephalosporins, monobactams and carbapenems) and glycopeptides inhibit cell wall biosynthesis, while aminoglycosides, macrolides, tetracyclines, lincosamides and oxazolidinones block protein biosynthesis; daptomycin and polymyxin (colistin) interfere with the permeability of the cytoplasmic membrane; and quinolones, rifampicin and metronidazole block the biosynthesis of nucleic acids [1, 2].

Almost parallel with the development of new antibiotics, resistant strains appeared. Resistance to penicillin was described before its mass introduction to treatment. It was already in 1940 when it was shown that *Staphylococcus aureus* can destroy this antibiotic due to the production of penicillinases, i.e. β-lactamases with a narrow spectrum of activity. By the mid-1950s, more than half of the isolates of *Staphylococcus aureus* in England were already producing penicillinases. In 1959, methicillin, the first semisynthetic penicillin against *Staphylococcus aureus* was introduced into the market, followed by oxa-, cloxa- and dicloxacillin and nafcillin. These drugs are effective against staphylococci producing penicillinases and were a milestone in the development of semisynthetic drugs through chemical modification of natural products. It seemed that the fight against bacteria had been won again. Unfortunately, already two years after the introduction of methicillin, the first resistant strains (MRSA – meticillin-resistant *S. aureus*) appeared in England due to acquisition of SCC*mec* gene cassette from coagulase-negative *Staphylococcus* (*S. sciuri*

group) through its horizontal transfer. The *mec*A gene is responsible for the production of a new low-affinity PBP 2a (2') protein. Its presence determines resistance to all β-lactam antibiotics except for the recently introduced ceftaroline and ceftobiprole. Further genes such as *mec*B (on plasmid), *mec*C and recently *mec*D are already known. The last-mentioned one already detected in *Macrococcus caseolyticus* gives resistance to newly introduced V-generation cephalosporins (ceftaroline and ceftobiprole). Resistance to methicillin is accompanied by resistance to several antibiotics, so the methicillin-resistant strain is always multi-drug resistant [6–8].

Simultaneously to the acquisition of resistance by staphylococci, a rapid increase of resistance was observed in the Gram-negative bacteria both *Enterobacterales* and non-fermenting ones (*Pseudomonas aeruginosa* and *Acinetobacter spp.*). The most important mechanism is the production of β-lactamases. Initially, these were enzymes with the so-called broad substrate spectrum, such as TEM-1, TEM-2 or SHV-1, and nowadays the most important role is played by ESBL (Extended Spectrum Beta-lactamases), i.e. β-lactamases with an extended substrate spectrum, which hydrolyses all β-lactams except carbapenems. Unfortunately, carbapenemase-producing strains are increasingly responsible for Gram-negative infections, which usually also produce ESBL and have mechanisms of resistance to other drugs, which makes the therapeutic options very limited and often lacking [9–11].

In addition to the most common resistance mechanisms and examples given above concerning selected species, bacteria have developed various strategies of 'escape' from antibiotics action, often several for one group of antibiotics [12].

The most common mechanisms of resistance are:
- enzymatic inactivation of the antibiotic by specific enzymes e.g. β-lactamases hydrolysing β-lactams, or their modification and inactivation (e.g. enzymes modifying aminoglycosides, or chloramphenicol acetyltransferase, or hydrolysing/modifying macrolides, lincosamides and tetracyclines);
- the change in the target of antibiotic action is a widespread mechanism in Gram-positive bacteria (both pneumococci and enterococci), Gram-negative cocci (meningococci and gonococci) and *H. influenzae* rod-shaped bacteria. They concern the changes in penicillin-binding proteins, causing them to decrease the affinity to various groups of β-lactam antibiotics. It is also a common mechanism of resistance to fluoroquinolones as a result of mutations in genes encoding the DNA gyrase and/or topoisomerase IV;
- the reduced permeability of cell wall, which results in diminished antibiotic transport to the cell (e.g. imipenem resistance *P. aeruginosa* and *Enterobacter spp.*);
- active drug removal from the bacterial cell – various types of membrane pumps (especially frequent in non-fermenting Gram-negative bacilli) that can simultaneously provide resistance to many unrelated antibiotic groups;

- the overproduction of antibiotic target molecules concerns mainly sulfonamides and trimethoprim (in the case of resistance to sulfonamides, over-production of p-aminobenzoic acid occurs, and in the case of trimethoprim, an increased amount of dihydrofolate reductase);
- replacement of antibiotic target molecules with alternative structures – glycopeptide resistance of *Enterococcus spp.*;
- making difficult for the antibiotic to reach its target location in the cell – e.g. thickening of the cell wall in staphylococci resulting in reduced susceptibility to glycopeptides (hVISA and VISA *S. aureus* phenotypes).

New antibacterial drugs had been regularly introduced until the 1980s, but only a few were registered between 1985 and 2000, and several companies withdrew from development of new antimicrobials. This situation overlapped with the emergence of new resistance mechanisms and their dynamic spread and thus significantly increased the demand while supply dwindled.

More and more often, disturbing reports were being published, initially mainly coming from both diagnostic and research laboratories, but the problem started appearing in the daily press as a result of increasing number of therapeutic failures in the treatment of infections that used to be efficiently treated. Not only the drugs of first choice, i.e. those with the highest efficacy and safety, were observed to be less effective, but also of further choices. This situation resulted in increased morbidity and mortality, and therefore, not only the health consequences but also the economic aspects of this phenomenon began to be noticed.

The analysis of the situation in EU countries showed that in 2015 at least 671,689 patients were infected with multi-drug resistant strains of bacteria, of which at least 33,110 [13] died. Data recently presented by the Infectious Diseases Society of America (IDSA) in 2018 indicated that 162,044 died in the USA due to infections with multi-resistant bacteria, for which there were no effective therapeutic options [14].

The last decade of the 20th century showed the enormous evolutionary potential of microorganisms allowing them to survive in the antibiotic environment thanks to the development of new resistance mechanisms and the efficient transfer of resistance genes not only within a given species but also between different species. Particularly dynamic is the phenomenon of the so-called horizontal transfer of resistance genes, intensive in environments with high concentrations of antibiotics, such as hospitals or sewers. Multi-drug resistance has become a common phenomenon both in key human and animal pathogens.

The analysis of resistance in individual countries showed slight differences in the species composition of the most resistant pathogens. In Poland, for example, they are referred to in the 2011 Regulation of the Minister of Health concerning alert pathogens due to their resistance. It lists staphylococci (*S. aureus*) resistant to methicillin (MRSA) or glycopeptides (VISA

or VRSA) or oxazolidinones; enterococci (*Enterococcus spp.*) resistant to glycopeptides (VRE) or oxazolidinones; Gram-negative *Enterobacteriaceae spp.* (now *Enterobacterales*) producing β-lactamases with an extended substrate spectrum (e.g. ESBL, AmpC) or resistant to carbapenems or other two groups of drugs or polymyxins; *P. aeruginosa* rods resistant to carbapenems or other two groups of drugs or polymyxins; non-fermenting *Acinetobacter spp.* bacteria resistant to carbapenems or other two groups of drugs or polymyxins; *Streptococcus pneumoniae* resistant to 3rd generation cephalosporins or penicillins [15]. The situation is very similar for the USA, described by the acronym ESKAPE, standing for *Enterococcus faecium, S. aureus, Klebsiella pneumoniae, Acinetobacter baumannii, P. aeruginosa* and *Enterobacter spp.* [16].

In 2014, the World Health Organization produced a comprehensive report based on a detailed analysis of the situation of antibiotic resistance among 114 member states, with very strong, even dramatic conclusions: "The 21st century may become the post-antibiotic era. This means that even mild infections could result in death. It is not apocalyptic fantasy, but a real picture of the 21st century". The report stresses that antibiotic resistance cannot be considered a threat of the future. Such thinking leads to delaying actions and inviting catastrophe. Resistance to antibiotics is already omnipresent, and therefore actions to limit it and prevent its further growth and spread must be taken immediately! [17]. The report focuses on 7 most important pathogens worldwide in regard to resistance and includes: *K. pneumoniae* resistant to 3rd generation cephalosporins and/or producing carbapenemases, *Escherichia coli* resistant to 3rd generation cephalosporins and fluoroquinolones, methicillin-resistant *S. aureus* (MRSA), *Streptococcus pneumoniae* resistant to penicillin, *Salmonella spp.* resistant to fluoroquinolones, *Shigella spp.* resistant to fluoroquinolones and *Neisseria gonnorrheae* resistant to 3rd generation cephalosporins. All these microorganisms belong to the Multi-Drug Resistant Organisms (MDRO) group.

A very important document unifying the resistance definitions has been developed by a team of experts appointed by the ECDC and the CDC. As a result of their work, the following definitions have been proposed, which significantly facilitate the analysis and comparison of the situation between countries [18].

MDR – multidrug-resistance. MDR means insensitivity (resistance) to at least one antibiotic from at least three groups of antibacterial drugs active against a given species, without taking into account the drugs to which the species is naturally resistant. An example is an MLS_B-type resistance in *Streptococcus pyogenes*, which is a condition of insensitivity to macrolides, lincosamides and streptogramins.

XDR – extensively-drug resistant (extremely resistant). A micro-organism is classified as XDR if it is non sensitive to at least one antibiotic in all but two groups of antibiotics active for the species. Examples include *S. pneumoniae* resistant to penicillin, 3rd generation

cephalosporins and macrolides, and *Enterobacterales* producing extended-spectrum β-lactamases (ESBL).

PDR – pan drug-resistance. A microorganism is classified as PDR if it shows *in vitro* resistance to all antibiotics in all classes active against the specific species of the microorganism.

In a subsequent report published in 2017, the WHO presented a classification of multi-drug resistant bacterial pathogens into categories based on the urgency of introducing new, effective drugs [19]. The first critically important category included *P. aeruginosa* and *A. baumannii* resistant to carbapenems, *Enterobacterales* resistant to 3rd generation cephalosporins and carbapenems, and *M. tuberculosis*. The second group included *S. aureus* resistant to methicillin and vancomycin, *E. faecium* resistant to vancomycin, *H. pylori* resistant to clarithromycin, *Campylobacter* resistant to fluoroquinolones, *Salmonella spp.* resistant to fluoroquinolones, *Neisseria gonnorrheae* resistant to 3rd generation cephalosporins and fluoroquinolones.The third one comprised *S. pneumoniae* resistant to penicillin, *H. influenzae* resistant to cephalosporins and *Shigella spp.* resistant to fluoroquinolones. The presence of many species in this category causing exclusively or mainly infections in the community is noteworthy. This shows that the problem of resistance is not restricted to hospitals, but has become a common occurrence in the community.

A rapid increase of resistance was observed in all microorganisms, not only bacteria, on all continents and to all drugs. The scale of this phenomenon is so serious that it poses a threat to public health throughout the world. Numerous countries, especially the EU, the USA, Canada and Australia, have joined the WHO in actions and their governments have signed several declarations and directives.

There have been many studies indicating the need for immediate action. In addition to the WHO documents mentioned above, it is worth noting the enormous activity in this area of the European Union institutions and the individual member states. Particularly noteworthy are the conclusions of the report commissioned by the former British Prime Minister David Cameron to the prominent British economist J. O'Neill on the consequences of antibiotic resistance [20]. The findings are shocking. The report raises the problem of resistance not only in the typical nosocomial and community bacteria, including *M. tuberculosis*, but also refers to the growing number of resistant *Plasmodium* (protozoa) causing malaria. It points out that the main 'culprit' of this phenomenon is the misuse of antimicrobial drugs and points out that between 2000 and 2010, there was a 40% increase in the use of antibiotics in medicine. They are used very widely and inadequately. In many countries, they can be given over-the-counter, 'just in case', or self-administered, contrary to evidence-based medicine (EBM). This problem is much better controlled in developed countries, but there are also many shortcomings. The movement of people and goods contributes to the spread of multi-resistant pathogens to new places, and even countries, with excellent antibiotic resistance control programmes in place, are not safe. Based on current data, the authors of the report predict that if the world does not take immediate actions to reduce the use of antibiotics and introduce effective infection control programmes, 10 million people will become affected by antibiotic resistance in 2050. In economic terms, this will amount to $100 trillion (USD).

Several important initiatives have been developed within the European Union to combat antibiotic resistance, in close cooperation with partnerships at the international level. The key actions undertaken by the European Commission (EC) initially concerned medicine and were then extended to veterinary medicine and animal production. Several initiatives concerning necessary actions to be taken to slow down antibiotic resistance emergence and its spread have already been developed and the most important are listed below.

A document of the European Parliament and the Council of Europe that laid the foundations for building in the EU countries of epidemiological surveillance of communicable diseases was issued on 24 September 1998 (*Decision 2119/98/EC establishing a network for the epidemiological surveillance and control of communicable diseases in the Community*). One of the main points of this decision was the establishment by the European Commission of the Early Warning and Response System (EWRS). It encompasses the threats related to the spread of bacterial infectious diseases, especially those related to dangerous mechanisms of antimicrobial resistance and rapid and effective response from the EU to these issues.

Another important element of the undertaken actions was the Council Recommendations on the prudent use of antimicrobial agents in human medicine (*Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine*). In this document, the EC presented for the first time a comprehensive approach to the problem through the establishment by member states of the so-called *intersectoral coordinating mechanism* (ICM). In response to this recommendation, a health programme of the Minister of Health was established in Poland in 2004, i.e. before Poland's accession to the EU, called the *National Antibiotic Protection Programme* (Pol. NPOA), which since 2004 has been implemented by a team of specialists from the National Medicines Institute in Warsaw.

ICM recommends several measures, only some of which are included within the NPOA. These are:
- monitoring of the spread of multi-resistant bacterial pathogens in humans;
- monitoring the use of antibiotics;
- education of physicians and other health professionals on diagnosis, treatment and prevention of infections, with a particular focus on the issue of drug resistance;
- development of therapeutic and diagnostic recommendations;
- promoting awareness of the dangers of antibiotic resistance among the general public;
- organising meetings and promoting awareness on antibiotic resistance within the framework of the European Antibiotic Awareness Day;
- national and international cooperation.

The ICM also recommends actions in other areas such as veterinary, agricultural and environmental matters for which the State Veterinary Institute in Puławy is partly responsible, in cooperation with EFSA.

It is recommended that the Member States allocate significant financial resources for the implementation of the above tasks, as well as for research on new antimicrobial drugs and diagnostics. Unfortunately, both the NPOA programme and research on new antimicrobial drugs and diagnostics receive little funding in Poland.

The monitoring of the spread of multi-resistant pathogens in Poland is carried out by the National Reference Centre for Antimicrobial Susceptibility Testing (KORLD, www.korld.edu.pl) and the National Reference Centre for Central Nervous System Infections (KOROUN, www.koroun.edu.pl) for community acquired invasive infections. Data on the susceptibility of (invasive) blood isolates are reported to the European Antibiotic Resistance Surveillance Network (EARS-Net) (see below). These are the most severe infections (bacteremia/sepsis), which often have a fulminant course, and the increasing resistance of their etiologic agents results in increased mortality. Key bacterial pathogens responsible for human infections, i.e. *S. pneumoniae, S. aureus, Enterococcus faecalis, E. faecium, Escherichia coli, K. pneumoniae, P. aeruginosa* and recently *Acinetobacter spp.* are monitored. The results show that Poland belongs to the group of EU countries with the highest percentage of antibiotic-resistant strains and we are constantly observing an upward trend. For example, almost 50% of *K. pneumoniae* isolates in 2017 were resistant to 3 classes of antibiotics (XDR), 20% of *P. aeruginosa* to 4 classes and > 50% of *Acinetobacter spp.* were resistant to 3 classes of drugs. A slight improvement can be seen in the case of *S. aureus*; in 2014 about 20% were MRSA, and in 2017 – 15.2% (www.ecdc.europa.eu). According to the cited data, the treatment of infections in Poland is very difficult and unfortunately, more and more often, we are compelled to use drugs of the last resort and even "rescue" therapy.

The NPOA monitoring of antibiotic use indicates that as far as non-hospital practices are concerned, in 2017 we consumed 25.7 DDD of antibiotics/1000 inhabitants per day, which places us in 5th last position among the EU countries with the highest consumption, while the Netherlands recorded only 10.6/DDD/1000/per day. As you can see, Poland has a lot of work to do to get closer to the Dutch level. This requires intensive education of family doctors to limit the prescription of antibiotics only to those patients who really need them. The above results emphasize that Poland needs to take immediate actions to reduce the prescribing of this group of drugs because – as mentioned above – the high consumption of antibiotics is the primary cause of the rise and spread of resistance. The data on resistance is transmitted to the ECDC as part of our participation in ESAC-Net (European Surveillance of Antibiotic Consumption-Network).

One of the most serious problems in the area of resistance in Poland is the emergence and dynamic spread of *K. pneumoniae* producing carbapenemases (CPE, carbapenemase-producing *Enterobacterales*), followed by other *Enterobacterales*. Since the appearance in 2008 of the first patient infected with carbapenemase producing *K. pneumoniae* (KPC, class A), we have observed its dynamic spread, and since 2011 also carbapenemase of the NewDelhi type (NDM, metalobetalactamase class B) detected initially in *E. coli* and then in *K. pneumoniae*. In the following years, the KORLD confirmed the occurrence of infections also caused by carbapenemases type OXA-48 (class D) and some other types such as VIM or GES. Initially, these were almost exclusively isolates of *K. pneumoniae* species, especially in the case of KPC and NDM, but now we have been observing their acquisition by other *Enterobacterales*. Carbapenemase producing strains have been mainly isolated from urinary tract infections but also from blood, respiratory tract, skin and soft tissue. They represent extreme resistance to antibiotics, often presenting XDR and even PDR phenotypes. The strains producing carbapenemases are spreading epidemically in Poland, and at the end of 2018 the KORLD identified more than 10,000 isolates from both infections and carriers. These are not complete data because strains are sent to the KORLD on voluntary basis. Due to the wide reservoir of *Enterobacterales* (gastrointestinal tract) and their extreme resistance to antibiotics, the spread of carbapenemase-positive strains is the most important threat to the future of effective treatment of infections. The recently published meta-analysis indicates that mortality in infections caused by carbapenemase-producing *Enterobacterales* is very high and exceeds 50% [21]. CPE is the most serious epidemiological and therapeutic challenge in hospitals along with *Clostridioides difficile*, causing the so-called post-antibiotic diarrhoea, which results often from overuse of antibiotic and poor infection control practices [22].

Antibiotic resistance is a global problem and must be solved at the global level. Initiatives taking place in different countries and continents involving not only medicine but also animals and the environment are of great importance.

Noteworthy is the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) (www.cdc.gpv/drugresistance/tatfar), i.e. bilateral cooperation in the fight against antimicrobial resistance. It was established in 2009 at the European Union-United States summit. It aims to deepen cooperation between the United States of America and the European Union by creating programmes to prevent the rise of antimicrobial resistance. It aimed at providing opportunities for mutual learning, as well as promoting information, exchange, coordination and cooperation.

In 2011, TATFAR published 17 key recommendations for cooperation in the three areas, which are consistent with those made by WHO and the EU:
1. Appropriate use of therapeutic antimicrobials in human and veterinary medicine.
2. Prevention of infections caused by drug-resistant micro-organisms.
3. Strategies to strengthen the development of new antibiotics.

In 2012, under the agreement signed between WHO/Europe and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the Dutch National Institute for Public Health and the Environment (RIVM) an initiative was started to establish a microbial resistance monitoring network for Central Asia and Eastern Europe (http://www.euro.who.int/en/home) titled CAESAR (Central Asian and Eastern European Surveillance on Antimicrobial Resistance). The project aimed to create a network of national AMR-Net surveillance systems in all countries of the region, following the example of EARS-Net. CAESAR is an important element of the implementation of the European Strategic Plan on Antibiotic Resistance (WHO EURO) adopted by the Regional Committee in Baku, Azerbaijan, in September 2011.

Proposing effective measures, for reducing the dynamics of resistance and its spread, requires answering the question about which of our actions have had a particularly significant impact on the current situation.

Even though resistance is an evolutionary feature of microorganisms, the rate of its emergence and spread can be significantly reduced through the rational use of antibiotics and this way gain time to develop new drugs and therapeutic strategies. However, misuse and abuse of antibiotics significantly accelerate this process. In the field of medicine, this inappropriate prescribing occurs in cases of viral infections and bacterial infections that would clear without antibiotics, e.g. self-limiting diarrhoea or furuncle requiring simple surgical intervention. The consumption of antibiotics in Poland significantly increases during the so-called influenza season, which proves that their prescription is not following the recommendations [23]. It is also a common mistake to use an antibiotic with a wider spectrum of activity than is recommended and necessary. An example taken from every day medical practice is the prescribing of antibiotics with β-lactamase inhibitor to treat infections caused by bacteria that do not produce β-lactamases such as *S. pyogenes* or *S. pneumoniae*. This is inappropriate and not only exposes the patient to the undesirable effects of the drug but also increases the reservoir of resistant microorganisms. Another example of misuse of antibiotics is the treatment of carriers, especially among children, which not only does not prevent the disease but also promotes the acquisition of resistance by natural flora and increasing the pool of resistant strains in the patients' body. The development of resistance is also due to the prolonged duration of therapy and the administration of insufficient doses. All these examples demonstrate that physicians do not have adequate knowledge about infections, their epidemiology and therapy. Important causes of the current situation include insufficient use of microbiological diagnostics, which allows targeted treatment and selection of the most appropriate drug, as well as the construction of the "microbiological map" of the hospital, region and even country, facilitating the optimal choice of empirical therapy. According to the recommendations of many leading European institutions and expert groups, all antimicrobial agents should be available by prescription only. Unfortunately, in Poland, furagin (furazydyna) is available without a prescription (OTC)

and anyone can buy it without needing an appointment with a physician. This is inconsistent with modern knowledge and standards. Despite the criticism by medical authorities, this medication is still available over the counter. This situation resembles more the image of developing countries where antibiotics are available over the counter.

Another area of the abuse and misuse of antimicrobials is veterinary medicine and agriculture. Although EU has introduced many regulations restricting the use of antibiotics in veterinary medicine and animal husbandry and has completely prohibited the use of these compounds in animal feed, many countries, including highly developed countries, have only recently withdrawn from such a procedure, e.g. the USA only in 2017. We should welcome the recent decision of the Indian government to ban the use of colistin in agriculture, a drug now recognized as an antibiotic of last resort in the treatment of infections caused by carbapenemase producing *Enterobacterales*. This antibiotic was used on a massive scale in poultry breeding in Asian countries (e.g. China), which resulted in the emergence and rapid spread of plasmid based resistance to colistin. In Poland, the first case of *Escherichia coli* urinary tract infection resistant to colistin in this mechanism occurred in a poultry breeder [24].

For years, the EU has been promoting, also through numerous directives, an approach to the problem of antibiotic resistance as a One Health strategy, i.e. covering both medicine and veterinary medicine. The principles of the use of antibiotics and the measures to reduce resistance in veterinary medicine and breeding are similar to those developed for medicine. It is noted that the most important element is hygiene in the broad sense of the term, and therefore the minimisation of the use of antibiotics that should not replace it.

Many countries have developed national programmes to combat antibiotic resistance. Poland, together with the other EU Member States, committed itself to introduce a national strategy two years ago. A national strategy is urgently needed, which will also fill many of the legislative gaps. The leaders of the Ministry of Health are not determined enough to implement a coherent plan covering all areas of our life and to build awareness, not only among the public and professionals but also among decision-makers, since only multi-level actions can end the crisis of antibiotic resistance.

According to WHO recommendations, as well as those developed by the EU and TAFTAR, all countries that have implemented measures to reduce antibiotic resistance, should monitor the results achieved [25].

Despite the many actions taken in many countries, we are not seeing significant progress because the problem is multi-sectoral and complex, and the process of introducing changes in action and thinking takes time. However, success is possible, as demonstrated by the results of long-term work at various levels of action in Sweden. After 20 years of efforts, the prescribing of antibiotics in paediatrics has been reduced by 70%! and it is a change that has taken place in a country known for its rational approach to antibiotic therapy and low consumption [26].

It cannot be overestimated how important it is to change the awareness of antibiotics prescribers, patients, the general public and decision-makers by showing that this valuable weapon slowly reduces its effectiveness. Can we imagine a world without antibiotics?

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