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Antimicrobial resistance – causes, threats, solutions

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Abstract

Antimicrobial resistance (AMR) is one of the most serious problems requiring urgent solutions to protect public health, and has a negative impact on healthcare, veterinary medicine, and agricultural systems worldwide [6]. The increase in AMR may endanger the therapeutic effectiveness of antibiotics, increase treatment failures and lead to longer and more severe illness episodes with higher treatment costs and mortality rates. The World Health Organization (WHO) has already declared AMR a high-priority issue to be resolved by collective global action [8].

Keywords: Scope of AMR; AMR Burden globally and in Bulgaria; EU One Health Initiative; AMR and environment; Strategic Antibiotics

1. Introduction

Antimicrobial resistance (AMR) is the ability of microorganisms to resist antimicrobial treatments. This is an extremely worrying fact, both for researchers in this field and for those taking and enforcing legislative measures concerning medicinal products, because resistant microorganisms are a prerequisite for ineffective treatment. According to WHO, AMR is one of the 10 serious threats to public health – methicillin-resistant Staphylococcus aureus (MRSA) which is resistant to several classes of antibiotics is a sad example [4]. AMR causes around 10 million deaths worldwide [7].

Knowledge of the clinical and economic impact of antimicrobial resistance is essential to influence the establishment of AMR programs, including in healthcare facilities, to guide policymakers and AMR funding agencies, to define the prognosis of individual patients, and to stimulate interest in developing new antimicrobial agents and therapies [1].

Existing data show that there is an association between antimicrobial resistance in Staphylococcus aureus, enterococci, and Gram-negative bacilli and increases in mortality, morbidity, length of hospitalization, and cost of healthcare [2]. Patients with infections due to antimicrobial-resistant organisms have higher healthcare costs (USD 6,000-30,000) than do patients with antimicrobial-susceptible infections; the difference in cost is even greater when patients infected with antimicrobial-resistant organisms are compared with patients without infection [2].

Given the limited budgets of healthcare systems, knowledge of the clinical and economic impact of antibiotic-resistant bacterial infections, coupled with the benefits of specific interventions targeted to reduce these infections, will allow for optimal control and improved patient safety [2]. Significant evidence has suggested that the knowledge and attitude trends among the community, pharmacists, and physicians can play a critical role in managing the ever-increasing threat of AMR [5].

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The aim of this review is to discuss various aspects of important issues related to antimicrobial resistance and to look for ways to reduce the impact of this problem on the healthcare system in Bulgaria.

A review of the literature on these issues was performed and the links between antimicrobial resistance of different pathogens and adverse outcomes, including increased mortality, length of hospital stay and healthcare costs were presented.

2. Scope of the problem with AMR

Antimicrobials are the beginning of a new era in the treatment of infections with a huge impact on health, and undoubtedly an achievement of our civilization, which is why the emergence of AMR can have huge negative consequences for public health [9]. The World Health Organization (WHO), the Food and Agriculture Organization (FAO), the World Organization for Animal Health (WOAH), the European Parliament and the European Commission recognize that AMR is becoming an increasingly global human and animal health problem, limiting or minimizing the possibilities for effective treatment. Global studies have shown that the development of AMR leads to a decrease in quality of life and has significant economic consequences in terms of increased healthcare costs and productivity losses [9].

The problem with AMR is not a local one. Globally, antibiotic resistance threatens progress in healthcare, food production, and ultimately life expectancy [11]. Research by the Centers for Disease Control shows that in the United States alone, antibiotic resistance causes more than 2 million infections and 23,000 deaths a year.

Modern communication and movement of people, animals, and goods means that antibiotic resistance can easily spread across borders and continents [11]. There are valid concerns regarding recent studies that have found concentrations of antimicrobial residues in freshwater at levels above environmental thresholds across the world, including in Europe. This can be a worrying cause for the development of antimicrobial resistance by gene transfer mechanisms between microorganisms which can then spread to humans and animals [10].

Researchers from the Malawi-Liverpool-Wellcome Trust Clinical Research Programme have done sentinel surveillance of bacteremia in sub-Saharan Africa and provided evidence for the period from 1998 to 2016, and report long-term trends in bloodstream infection and antimicrobial resistance [3]. Results from this study have shown that 51.1% of 26,174 bacterial isolates were resistant to the Malawian first-line antibiotics amoxicillin or penicillin, chloramphenicol, and co-trimoxazole, including 68.3% of Gram-negative and 6.6% of Gram-positive pathogens. Researchers found a statistically significant increase in resistance to fluoroquinolones from 2003 to 61.9% in 2016 ($p < 0.0001$). Between 2003 and 2016, resistance to extended-spectrum beta-lactamases increased from 0.7 to 30.3% for Escherichia coli, from 11.8 to 90.5% for Klebsiella spp. and from 30.4 to 71.9% for other Enterobacteriaceae. Similarly, resistance to ciprofloxacin rose from 2.5% to 31.1% in E. Coli, from 1.7% to 70.2% in Klebsiella spp, and from 5.9% to 68.8% in other Enterobacteriaceae [3]. Meticillin-resistant Staphylococcus aureus (MRSA) was first reported in 1998 at 7.7% of isolates and represented 18.4% of isolates in 2016. The rapid expansion of extended-spectrum beta-lactamases and fluoroquinolone resistance among common Gram-negative pathogens, and the emergence of meticillin-resistant Staphylococcus aureus, highlight the growing challenge of antimicrobial resistance and development of infections that may become effectively impossible to treat, especially in a resource-limited setting.

Estimating the incidence, complications, and mortality attributable to infections due to antibiotic-resistant bacteria, is challenging.

A. Cassini et al., 2019 [13], assessed the severity of infections due to antibiotic-resistant bacteria of public health concern in countries of the EU and European Economic Area (EEA) in 2015, measured in a number of cases, attributable deaths, and disability-adjusted life-years (DALYs). From EARS-Net (European Antimicrobial Resistance Surveillance Network) data collected between January to December 2015, Cassini et al. estimated 671,689 (95% uncertainty interval [UI] 583,148-763,966) infections with antibiotic-resistant bacteria of which 63.5% (426,277 of 671,689) were associated with healthcare. These infections accounted for an estimated 33,110 (28,480-38,430) attributable deaths and 874,541 (768,837-989,068) DALYs. The burden for the EU and EEA was highest in infants (aged <1 year) and people aged 65 years or older. The team has developed disease outcome models for five types of infections based on systematic literature reviews. Their results present the healthcare burden of these 5 types of infections with antibiotic-resistant bacteria expressed for the first time in DALYs. The approximate severity of infections with antibiotic-resistant bacteria in the EU and the EEA is significant compared to that of other infectious diseases and has increased from 2007 to 2015. Their assessments provide useful information for public health decision-makers prioritizing interventions for infectious diseases [13].

226 carbapenem-insensitive nosocomial Acinetobacter baumannii isolates with multiple drug-resistance identified by gyrB polymerase chain reaction were collected for the period 2014-2016 in a study conducted in four university hospitals in Bulgaria. The aim of the study is to investigate their susceptibility to antimicrobials (according to EUCAST-2016 criteria) and to develop appropriate treatment guidelines. Antibiotic resistance to imipenem (90.7%), meropenem (98.3%), doripenem (100%), amikacin (92.8%), gentamicin (87.2%), tobramycin (55.6%), levofloxacin (98.2%), trimethoprim-sulfamethoxazole (86.2%), tigecycline (22.1%) and ampicillin-sulbactam (41.6%) has been demonstrated (interpreted according to CLSI-2016). A total of 28 of the tested strains (12.4%) have extended resistance to antimicrobials and are only susceptible to colistin. Carbapenems are considered effective for the treatment of infections caused by Acinetobacter baumannii. Resistance to carbapenems, as well as multiple drug resistance, requires the use of other classes of antibiotics and combination therapy. The choice of antimicrobial treatment for multiple drug resistance and XDRAB is usually very limited. The study concluded that there are few effective options including colistin, tigecycline, and ampicillin-sulbactam [12].

Evidence from the Organization for Economic Co-operation and Development (ODCE) show that the burden on healthcare systems due to infections caused by AMR bacteria in the EU/EEA population is comparable to that of influenza, tuberculosis and HIV/AIDS combined, and nearly 40% of the health burden of AMR is caused by infections with bacteria resistant to last-line antibiotics, such as carbapenems and colistin [1]. This evidence is worrying because these antibiotics are the last treatment option available and when last-line antibiotics are no longer effective, it is extremely difficult or, in many cases, impossible to treat infected patients. 75% of the health burden of AMR is due to healthcare-associated infections. Adequate infection prevention and control measures, as well as antibiotic stewardship in hospitals and other healthcare settings are therefore essential to reduce the burden of AMR.

Increased consumption of antibiotics is part of the problem with AMR. In the outpatient settings, the mean consumption of antibiotics in EU/EEA in 2017 was 18.9 defined daily doses (DDDs) per 1,000 inhabitants per day, ranging from 8.9 in the Netherlands to 32.1 in Greece. The EU/EEA average consumption of broad-spectrum antibiotics was 10.1 DDDs per 1,000 inhabitants per day, ranging from 0.9 in Norway to 23.3 in Greece.

In acute care hospitals, the mean prevalence of patients receiving at least one antibiotic on a given day in EU/EEA in 2016-2017 was 30.7% and varied from 14.9% in Hungary to 55.1% in Greece. Of these, the EU/EEA mean proportion of patients receiving at least one broadspectrum antibiotic on a given day was 45.9%, ranging from less than 30% in Lithuania, Iceland, and Estonia to 74.7% in Bulgaria [13]. Along the clinical treatment guidelines, as much as possible, the use of narrow-spectrum antibiotics (i.e. those effective against only a specific group of bacteria) should be preferred in medical practice over the use of broadspectrum antibiotics, as the latter is more likely to promote the development of AMR in a broader group of bacteria [1, 13].

Another study on AMR incidence in European acute care hospitals confirmed that antibiotic use is positively associated with AMR. Conversely, antibiotic stewardship activities, such as reviewing and changing prescriptions when necessary, prevent AMR.

In addition, having more resources for hospital infection prevention and control is positively associated with AMR [1]. For example, the percentage of hospital beds with alcohol hand rub dispensers at point of care, the percentage of beds in single rooms (for isolating patients with bacteria with AMR), and the percentage of hospitals with at least 0.4 full-time-equivalent infection prevention and control nurse for 250 beds ($r= -0.35$, $p=0.04$, data not shown) are all negatively associated with AMR.

Of all antibiotic-resistant bacteria studied, a large relative proportion was found in the population, i.e. outside of hospitals. This means that antimicrobial stewardship should not be restricted to hospital settings and that targeting primary care prescribers as well as infection prevention and control interventions in primary care are also necessary to reduce the burden of AMR.

3. EU One Health Initiative in the fight against AMR and the EU Green Deal

United Europe is increasingly aware of the need for coordinated measures to tackle the AMR problem. The first steps in this direction in the WHO European Region date back to September 2011, when all 53 member states adopted the European Strategic Action Plan on Antibiotic Resistance (2011-2020), which a few years later was followed by the Global Action Plan against AMR and the European Commission’s Action Plan against AMR – One Health launched in 2014. These plans form a comprehensive framework for a comprehensive response against AMR in the WHO European Region, and many governments follow this example and develop national action plans.

The Stakeholder Network on Antimicrobial Resistance (AMR) hosted within the EC Health Policy Platform and managed by the European Public Health Alliance (EPHA), is the only civil society-led pan-European stakeholder network on AMR. It comprises over 80 leading organizations and individuals committed to tackling AMR from a “One Health” approach [10] - a term widely used in the EU and in the 2016 UN Political Declaration on AMR [19]. “One Health” is an initiative that recognized the health of people is closely connected to the health of animals and that diseases may transmit from humans to animals and vice versa, and therefore the problem needs to be addressed by those involved in both directions.

In June 2017, the European Commission adopted the EU One Health Action Plan against AMR which builds on the 2016 EU Council conclusions on combating AMR. The main objectives of the plan are structured in terms of 3 aspects:

- Strengthening the EU as a region by implementing best practices;
- Strengthening research and innovation;
- Shaping a global agenda on AMR issues.

Tackling the environmental dimensions of antimicrobial resistance has also become part of the European Green Deal, which means taking any necessary measures to protect the environment in pharmaceutical production, as pharmaceuticals can enter the environment at all stages of their life cycle [10].

As a result of the widespread use of broad-spectrum antibiotics without an antibiogram, the release of antimicrobial ingredients from these antibiotics into the environment can cause the development of antimicrobial-resistant organisms by gene transfer mechanisms. These genetically transformed microorganisms can then spread to humans and animals [10]. Resistance develops and spreads at high concentration levels, but even low levels of antimicrobial residues from widely used antibiotics without specific indications, as well as the use of antibiotics at inappropriate doses, are a threat to the development of AMR [10].

The European Commission’s ***zero-pollution*** ambitions and ideas mean that the European Green Deal should specify the role of various stakeholders in tackling pharmaceutical pollution [10]. Under the program, the following should apply to actions identified in the national action plans of each member state by 2021: multidisciplinary antimicrobial stewardship programs, measures to improve health literacy and the public understanding of the challenge of tackling AMR; the principles of prudent use of antimicrobials in humans and animals, and the rationale behind the use of diagnostics, vaccination, and infection prevention actions, including better sanitation and hygiene - a set of practical infection prevention measures at national, regional and local level in human and veterinary practice and in wider care and community settings, aimed at reducing healthcare-associated infections (HAIs) and AMR; with the support of the EU and in line with the OECD evidence, EU Guidelines for the prudent use of antimicrobials in human health and the Guidelines for the prudent use of antimicrobials in veterinary medicine.

According to these plans, binding measures to mitigate the impact of pharmaceuticals in the environment further to the EU Strategic Approach to Pharmaceuticals in the Environment must have been adopted:

- to introduce continuous monitoring of AMR in the environment in current environmental monitoring frameworks;
- to set environmental quality standards and concentration limits for pharmaceuticals in water;
- to address the risk of AMR in the Environmental Risk Assessment for all medicinal products [15].

4. The way forward – the need for new strategic antibiotics

Next-generation antibiotics are vital for humanity. Given the nature of resistance, we will always need new antibiotics [14]. However, drug-resistant bacteria are developing faster than new antibiotics can reach the market. According to an assessment by the Pew Charitable Trusts, there are too few antibiotics in clinical development to meet current and anticipated needs today [14]. Most of these compounds are being developed by small biotechnology companies.

More than 99% of the EU budget for AMR is directed at research. EU Funding of AMR-related research since 2004 has exceeded €1.5 billion. One of the flagship initiatives is the New Drugs for Bad Bugs Programme (ND4BB) launched in 2012, funded by FP7 and managed by the JU IMI. This aims to forge a public-private partnership for the discovery, development, and market entry of new antimicrobial treatments. The Commission also funds actions to coordinate and set an AMR strategic research agenda, particularly through the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) [20].

The AMR Action Fund initiative was established In July 2020 – an innovative partnership of more than 20 leading biopharmaceutical companies that aims to bring 2-4 new antibiotics to patients by 2030 to overcome the growing antimicrobial resistance [14].

In view of the long-term health and economic consequences of AMR, at the end of 2021, the G7 finance ministers declared that they commit to accelerating the implementation of their strategies described in their national AMR action plans and to take further and appropriate steps to create the right economic conditions for the implementation of innovative, strategic antibiotics prescribed under strict control for the treatment of specific indications, including by creating regulatory prerequisites for access to such antibiotics [16]. The principles for combating antimicrobial resistance adopted by the finance ministers have also been reaffirmed by G7 health ministers at the end of 2021 [17].

It is assumed that rising levels of AMR will cause increased mortality and morbidity worldwide, which will inevitably also affect global economies. However, higher levels of AMR have a different degree of negative impact on local healthcare budgets and economies, i.e. countries with low and medium levels of GDP are likely to pay a higher price than developed economies, with low-income countries suffering the greatest loss of population and economic output [18]. Therefore, the potential loss from failing to address the AMR challenge cannot be viewed solely as potential health or economic loss, and any future decisions must also consider the negative impact on national social systems with the increase in AMR.

Based on all information above, it can be concluded that there is an urgent need to promote the development of new antibiotics, as well as to step up efforts to ensure that the future social and economic impacts of AMR will be minimized.

5. The Solution

In order to address negative health and economic trends, all necessary measures should be taken to tackle the problem.

The main tools for the management of the appropriate human use of medicines, including antibiotics, are: 1. marketing authorization procedures which determine for which indication the antibiotic is to be used and how to label medicines available on the market; 2. evidence-based treatment guidelines [19].

WHO AWaRe Classification of Antibiotics provides information on responsible and reasonable use at national, healthcare facility, and physician levels [19]. Globally, there are certain treatment guidelines for specific infections – such as HIV and malaria – and for the treatment of children, the Pocket Book of Hospital Care for Children: WHO guidelines for the management of common childhood illnesses (2nd edition, 2010) which covers infectious diseases such as sepsis, neonatal infections, pneumonia, diarrhea, ear infections. However, there are no global treatment guidelines for the majority of bacterial infections (with the exception of tuberculosis and WHO Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children, 2014). The existing guidelines are also not always up-to-date and do not take sufficient account of AMR [19].

An OECD report from 2018 shows that 3 out of 4 deaths could be averted by spending just USD 2 per person a year on measures as simple as handwashing and more prudent prescription of antibiotics [20, 21]. Up to 1.6 million lives could be saved by 2050 across the 33 countries included in the OECD analysis, if the following measures are implemented: improved hygiene in healthcare facilities, reduced prescription of antibiotics, improved antimicrobial management programs; media campaigns; use of rapid diagnostic tests to detect whether an infection is bacterial or viral. According to the OECD investment in these measures could pay for themselves within just one year and produce savings of about USD 1.5 for every dollar invested thereafter. Combining these measures in a consistent manner would lead to even greater benefits and savings [20, 21].

Only a small number of EU/EEA countries have identified specific funding sources to implement in their national action plans on AMR and have identified a monitoring and evaluation process.

As for the decision to combat AMR in Bulgaria, a number of Bulgarian scientists and professional medical associations consider the problem that not a few clinical pathways, including pediatric pathways, are still underfunded, and at the current level of funding, they cover antibiotic treatment, if needed. In the fight against AMR, strategic narrow-spectrum antibiotics are life-saving, but their inclusion in the cost of the clinical pathway poses a financial barrier to rational and effective treatment. Examples of indications for strategic use of narrow-spectrum antibiotics are septic conditions in children accompanied by polyorgan failure, which are associated with high mortality. An increasingly serious problem with these rarer but high-risk infections is the growing antibiotic resistance. The cost of strategic antibiotics cannot be covered by current clinical pathways. Access to modern strategic antibiotics is only possible when an alternative model of reimbursement of antibiotics for hospital use is established [22]

6. Conclusion

AMR is a global health and development threat and requires urgent multisectoral action in order to achieve the Sustainable Development Goals. It is no accident that WHO has declared AMR one of the top ten global threats to human health. Misuse and overuse of antimicrobials are the main drivers in the development of drug-resistant pathogens. Inadequate infection prevention and control promotes the spread of microbes, some of which can be resistant to antimicrobial treatment. The cost of AMR to the economy is significant. In addition to death and disability, prolonged illness results in longer hospital stay, the need for more expensive medicines, and financial challenges for those impacted. Without effective antimicrobials, the success of modern medicine in treating infections, including during major surgery and cancer chemotherapy, would be at increased risk.

To combat AMR, a comprehensive approach is required that brings together all stakeholders in order to effectively reduce and limit the occurrence and spread of resistance by permanently and sustainably reducing the total use of antimicrobials in stock-breeding and preserving the effectiveness of antibiotics for the treatment of human infections [9]. In other words, only joint, coordinated efforts will help slow down the development and spread of antibiotic resistance and protect people.

Investing in antimicrobial resistance policies will save thousands of lives and significant savings for healthcare systems can be generated in the long term. A new strategy on AMR is needed, aimed at improving awareness and understanding of antimicrobial resistance; strengthening surveillance and research; reducing the frequency of infections; optimal use of antimicrobials and ensuring the resilience of investments in counteracting antimicrobial resistance.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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