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Mini review article

HUMAN-RELATED FACTORS OF ANTIMICROBIAL RESISTANCE

FAKTORI ANTIMIKROBNE REZISTENCIJE U HUMANOJ POPULACIJI

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Abstract

The global issue of antimicrobial resistance stems from the irrational use of antibiotics in humans, animals, and agriculture, inadequate sanitation, international travel and trade, and challenges within healthcare organizations including financing of healthcare. Recent literature indicates that antimicrobial resistance spreads between countries faster than previously assumed and the COVID-19 pandemic has just exacerbated this issue. Addressing this problem requires globally coordinated and multisectoral interventions.

The interaction between humans, animals, and the environment is complex, providing numerous pathways for the transmission and spread of antimicrobial resistance. The causes of the resistance that are related to the human population could be classified into several categories, such as inappropriate use of antimicrobials in medicine, inadequate sanitation and hygiene, but also the issues of widespread use of cosmetics with antibiotics, detergents, and biocides. Factors contributing to irrational antibiotic use in humans include excessive prescribing in primary healthcare, irrational use in hospitals, and low awareness and knowledge levels regarding rational antibiotic use at the population level. Addressing this necessitates the consideration of numerous factors, including the organization of healthcare systems, population demographics, patterns of antibiotics prescription and usage, among others.

This review underscores the complexity of antimicrobial resistance, stressing the need for comprehensive measures across different levels to control and suppress its development and spread. Since antimicrobial resistance puts number of gains of modern medicine at risk, making infections more complicated to treat and other medical procedures and treatments riskier, urgent attention and action of all public health stakeholders globally is essential.

Keywords:
antimicrobial resistance, antibiotic misuse and overuse, over-prescription of antibiotics

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Sažetak

Globalnom problemu antimikrobne rezistencije doprinose neracionalna upotreba antibiotika kod ljudi, životinja i u poljoprivredi, neadekvatne mere sanitarne zaštite, međunarodna putovanja i trgovina, kao i različiti organizacioni izazovi u sistemu zdravstvene zaštite, uključujući i načine finansiranja zdravstvenih sistema. Noviji radovi sugerišu da se otpornost na antimikrobne lekove širi između zemalja brže nego što se ranije pretpostavljalo, a pandemija COVID-19 pokazala se kao dodatni izazov i potencijal za dalje širenje antimikrobne rezistencije. Rešavanje ovog problema zahteva globalno koordinisane i multisektorske intervencije.

Interakcija između ljudi, životinja i životne sredine je kompleksna, pružajući brojne moguće puteve prenosa i širenja antimikrobne rezistencije. Uzroci antimikrobne rezistencije koji su povezani sa humanom populacijom mogu se klasifikovati u nekoliko kategorija: nepravilna upotreba antimikrobnih sredstava u medicini, nedostatak mera sanitacije i higijene, kao i problemi široke upotrebe kozmetike koja sadrži antibiotike, deterdženata i biocida. Činioci koji doprinose neracionalnoj upotrebi antibiotika kod ljudi uključuju prekomerno propisivanje antibiotika u primarnoj zdravstvenoj zaštiti, njihovu neracionalnu primenu u bolničkim uslovima, kao i nizak nivo svesti i znanja o racionalnoj upotrebi antibiotika na nivou populacije. Rešavanje ovog problema zahteva razmatranje mnogo različitih faktora, uključujući i organizaciju zdravstvenih sistema, demografske karakteristike populacije, obrasce propisivanja i korišćenja antibiotika.

Ovaj mini pregledni rad prikazuje složenost fenomena antimikrobne rezistencije, naglašavajući potrebu za preduzimanjem sveobuhvatnih mera na različitim nivoima, kako bi se kontrolisao i suzbijao njen razvoj i širenje. Budući da antimikrobna rezistencija dovodi u pitanje neka od najvažnijih dostignuća savremene medicine, čineći infekcije sve komplikovanijim za lečenje, a druge medicinske procedure i tretmane rizičnijim, potrebne su veća pažnja i hitna akcija na ovom polju svih relevantnih učesnika i zainteresovanih strana u oblasti javnog zdravlja širom sveta.

Ključne reči:
antimikrobna rezistencija,
nepravilna i prekomerna upotreba antibiotika,
neadekvatno propisivanje antibiotika

Introduction

During World War II, penicillin was utilized for managing bacterial infections among soldiers. Nonetheless, penicillin-resistant strains of Staphylococcus were identified as early as 1940, predating its widespread therapeutic application (1). Antimicrobial resistance (AMR) is usually defined as a process where microorganisms develop resistance to antimicrobial medications at which they were previously susceptible (2). Alexander Fleming was a visionary who foresaw the development of AMR, saying in 1946: "There is probably no chemotherapeutic drug to which in suitable circumstances the bacteria cannot react by in some way acquiring resistance" (3).

The term often used is "superbug" and it refers to microorganisms that, due to multiple mutations, developed a resistance to different groups of antimicrobials. Therefore, the therapeutic possibilities for these microorganisms are diminished, and the hospital treatment of illness they are causing is prolonged and more expensive (4). In certain instances, resistant bacteria may also exhibit growing virulence and transferability, thereby positioning AMR as a factor contributing to increased virulence (4). Given the widespread use of antimicrobial drugs, particularly in livestock production, some predictions indicate that by 2030, consumption of antimicrobials could nearly double in some countries such as India, China and many others (4). In addition to the importance of the rational use of antibiotics in the human population, the problem of antibiotics usage in domestic animals, which are further used in human nutrition, is often a significant issue (5,6).

Besides the irrational use of antibiotics in human medicine and agricultural production, the determinants of AMR are also the use of illegal antimicrobial drugs in some developing countries, frequent and widely available international trips, challenges in health care financing, climate change, and others (7). Causes of AMR that are related to the human population could be classified into several categories: inappropriate antimicrobial use in human medicine; inadequate sanitation and hygiene in the public settings; using antibiotic-incorporated cosmetics and detergents, and biocides (8). But the challenge of antimicrobial resistance extends beyond a single dimension. Bearing in mind various factors, in recent years, it is more often mentioned in the literature that AMR is spreading from one country to another faster than it was previously assumed (1,7).

The COVID-19 pandemic has underscored the challenge that a global health crisis as pandemic poses to the emergence and dissemination of AMR. Researches indicate increased irrational antibiotic use during the COVID-19 pandemic, which may further increase bacterial antibiotic resistance (9-12). In addition, various and simultaneous infections caused by pathogens which are resistant to antimicrobial medicines have resulted in substantial mortality during previous pandemics (7). These complex and interrelated determinants, crossed with the role of AMR in current and prior pandemics,

strongly indicate the importance and necessity of globally coordinated interventions aimed to cope the practices of irrational use of antibiotics and to act on all these multiple and interdependent factors (1, 6, 7).

Objective of the Review

All of the above indicates the significant, complex, and multifactorial problem of antimicrobial resistance. Therefore, the measures and activities undertaken must be comprehensive and applied at different levels. This review aims to examine some of the important human-related causes influencing the spread of AMR to gain a broad insight into this critical topic and to summarize potential directions for further action in controlling AMR.

Review Methodology

For this mini-review paper, literature was surveyed using the PubMed database to ensure a thorough exploration of relevant studies in the field of antimicrobial resistance and its influencing factors in the human population. Studies and manuscripts were searched using keywords and phrases like antimicrobial resistance (AMR); antibiotic misuse and overuse; over-prescription of antibiotics. Additionally, searches were conducted in Google Scholar by formulating sentences based on specific ideas being explored, and all possible efforts were made to utilize the most relevant information available.

Self-medication and over-prescription of antibiotics

Regulating antibiotic dispensation with a medical prescription is a common practice in developed countries to ensure responsible and appropriate use of antibiotics. However, the possibility of purchasing drugs "online", i.e. via the Internet, is perceived as a problem in both underdeveloped and developed countries (6, 7, 13). Additionally, in some developing countries, access to antimicrobials is not adequately controlled. Therefore, antibiotics can be purchased from street vendors and are sometimes available over the counter without a prescription, encouraging self-medication and inappropriate use of antibiotics (14). Self-medication, which involves patients taking antibiotics without a prescription, is particularly perceived as a global and growing phenomenon (15, 16). It also includes purchasing medications without a prescription, taking or sharing them from or with friends and family, or using leftover medication already present at home (17). Self-procurement and self-administration of antibiotics presents a public health concern attributable to AMR, the potential for adverse drug reactions, interactions between drugs, symptoms concealment, and expanded morbidity (17). A potential reason for self-medication is the general population's lack of knowledge about antibiotic usage. The average value of the Antibiotic Knowledge Score (AKS) in the population of the Republic of Serbia is 2.6 out of 4 (where 4 is the highest knowledge score and 0 is the lowest knowledge score), and it is the same as the average score in the population of the European Union, which shows insufficient general public knowledge about the rational use of antibiotics (16). The **figure 1** shows the share of the respondents from the population of the Republic of Serbia with different levels of AKS and different levels of knowledge about antibiotics.

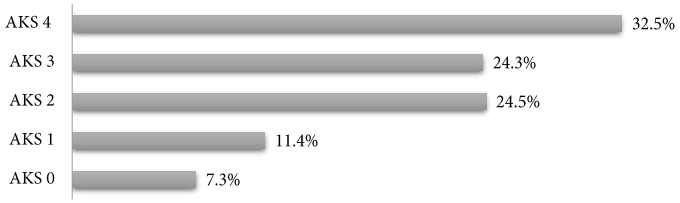

Figure 1. Knowledge about antibiotic use - Antibiotic knowledge score (AKS) from Belamaric et al. (16)

A study from Serbia showed the importance of considering various factors in the process of conducting activities and interventions regarding antibiotic usage. These factors may include demographic characteristics of the population, such as educational level or health status but also the depth of understanding and knowledge regarding antibiotics (16).

The most frequently cited factors contributing to the irrational use of antibiotics in healthcare institutions are excessive prescribing in primary healthcare and the unnecessary use of antibiotics in hospitals (18, 19). A study in primary care in Great Britain revealed that the most common conditions for which antibiotics are inappropriately prescribed are sore throat, cough, sinusitis, and acute otitis media (18). Furthermore, a study conducted from 2007 to 2015 in emergency departments in the USA indicated that a quarter of all patients received antibiotics, even though seven out of ten had no proven bacterial infection (19). However, it is indicated that doctors with more years of experience tend to adhere more thoroughly to patterns of rational antibiotic use compared to younger doctors (20). Additionally, doctors with more experience are less likely to prescribe antibiotics for uncomplicated bronchitis and gastroenteritis (20). Another study investigated how doctors would respond when test results show an isolate sensitive to a narrow-spectrum antibiotic. In this scenario, almost half of all doctors (46%) would switch to narrow-spectrum therapy, 31% would continue with the same antibiotic regimen, and 22% would first consult the infectious disease team (21). Despite physicians being key stakeholders in preventing and controlling antimicrobial resistance (AMR), the lack of adequate training during their undergraduate and postgraduate years may contribute to their hesitancy in assuming these tasks confidently (21, 22). To standardize treatment for various cases requiring antimicrobial drug administration, protocols should be developed and continuously improved. Therefore, doctors should receive support through ongoing education focused on antimicrobial prescribing and through the implementation of developed protocols to avoid negative outcomes resulting from inappropriate antimicrobial use

and prescription. There is also potential for widely used technologies, such as internet-based training, interventions with digital support, and distance learning programs, to reduce outpatient antibiotic prescribing (22). Separate studies have revealed that internet-based communication skills training can reduce antibiotic prescribing rates for adults and childhood acute respiratory tract infections (22, 23). These results indicate the potential broader use of digital tools to enhance awareness and promote responsible antibiotic use among medical practitioners and the general population. Furthermore, it is crucial to underscore the significance of public awareness and health literacy among the general population as integral components of both global and local action plans (24).

Inadequate sanitation and hygiene, infection control and development of new antibiotics

Infection prevention and control measures include hand hygiene, proper use of personal protective equipment, isolation precautions, and disinfection of healthcare environments, including surfaces and medical equipment. In an effort to optimize antibiotic use, the World Health Organization (WHO) in 2017 produced a classification system wherein antibacterial medications are categorized into three groups - "Access, Watch, and Reserve (AWaRe)" - taking into account their spectrum, anticipated risk of resistance development, toxicity risks, and clinical usefulness (25). This categorization has undergone two revisions. While the implementation of the "AWaRe classification" is essential to ensure the responsible use of antibacterials and to help preserve their effectiveness, more work needs to be done to ensure that new and needed reserve antibiotics remain on the market once registered and are held in reserve to be available when resistance levels rise (26).

Infection control, while important overall, is particularly crucial for managing "in-hospital care-associated infections" (HCAIs). This significance is underscored by data from the Antibiotic Resistance Surveillance of Germany database, revealing significantly higher proportions of antibiotic resistance in all major pathogens isolated from inpatients compared to outpatients (27). This challenge is further complicated by the emergence of some highly virulent and dangerous bacterial strains which are particularly prevalent within intensive care units (ICUs), and which typically accommodate high-risk and immunocompromised patients (28). Furthermore, it should be emphasized that focusing on implementing known infection prevention measures is even more important than attempting to solve the problem solely through observation and description (29). Infection control should attract the global attention of all countries because, in today's world, there are few phenomena that can remain localized. While some countries allocate the necessary attention to research and actions to curb the spread of antimicrobial resistance, if this is not the case in other countries, and if there is no global action, it is difficult to anticipate the desired effects, given today's means of communication, travel, and exchange of people and goods.

According to the "World Health Organization's annual pipeline report" (26), the development of new antibacterial treatments is insufficient to effectively combat the escalating threat posed by AMR. The development stages of new antibacterial agents are falling significantly short of addressing global requirements (26). Efforts to discover new antibiotics were a primary focus of research and development in the pharmaceutical field in the past and many efficient antimicrobials were introduced (3). In spite of that, there are currently a large number of microbes that have developed mechanisms to resist different drugs, rendering them largely or entirely ineffective in therapy (3). The mechanisms employed by microorganisms to evade antibiotics undoubtedly existed prior to and outnumbered the therapeutic interventions available. In a collection of soil-dwelling Streptomyces, which are known for producing many clinical therapeutic agents, every organism exhibited multidrug resistance, some even to 21 different drugs (30). In addition to reducing total and inappropriate broad-spectrum antibiotic use in humans, it is crucial to expedite and broaden the development of antibiotic pipelines (26). Therefore, countries should act united in global efforts to discover sustainable solutions and establish incentives for research, development, and innovation in the area of new antimicrobial drugs (26). At the same time, research and development of new vaccines are also steps forward on this pathway since there is evidence that vaccines can reduce demand for antimicrobials and slow the spread of AMR (31).

Antibiotic transmission in the environment and "One Health" approach

The transmission of AMR can occur through diverse routes involving humans, animals, and the environment (32). "One Health" is an approach that seeks to achieve sustainable balance and optimal health outcomes for people, animals, and ecosystems (33). It acknowledges the interdependence of human health, the health of domestic and wild animals, plants, and the broader environment, including ecosystems. This is of the utmost importance for spreading the AMR. For instance, everyday grooming and hygiene products, containing disinfectant additives, are entering ecosystems and contributing to antibiotic resistance (8). Active substances such as triclocarban and triclosan, commonly found in household detergents and cosmetics, exacerbate contamination due to their low solubility and promote the dissemination of resistant genes within bacterial communities (8).

Almost two thirds of emerging infectious diseases originate from wild or domestic animals, and three quarters of all new human pathogens in the past three decades originated from animals (34). Therefore, besides all aspects of antibiotic inappropriate use in human medicine, there is also an issue of excessive and inappropriate use

of antibiotics in agriculture and veterinary practices. The utilization of antimicrobials as growth promoters and therapeutics to meet the increasing demand for meat for human consumption is leading to the evolution of resistant strains of bacteria (35). The interaction between humans, animals, and the environment is complex, and many possible pathways exist to transmit resistant bacteria further. Throughout evolution, commensal microbes and soil bacteria have developed the capacity to produce compounds with antimicrobial potential, and it is believed that the biosynthetic pathway for erythromycin could have originated as far back as 800 million years (36).

Antimicrobial medicines are widely used to maintain health and productivity of the farm animals (37). The overuse of antibiotics in agriculture has been identified as a factor of AMR, posing risks to both animal and human health. The environment serves as a reservoir where genetic elements "move, interact, and disseminate" to various human and animal hosts (37). Each year, more countries outlaw the usage of some important antimicrobials as animal growth promoters. Europe is now one of the regions with the lowest use and authorization of antimicrobial growth promoters, while the Americas have the highest proportion of countries using antimicrobials as growth promoters (37). European countries have been addressing this issue for years, as reflected in their responses and policies.

In the Republic of Serbia, country-specific information about drugs used in veterinary medicine is available online in the publication "Trade in Veterinary Drugs 2019 - 2020". This publication presents data on the trade in veterinary drugs delivered by the holder of the license for the drug, whether it is the manufacturer, representative, or agent. This publication is the third in a series, alongside "Trade in Veterinary Drugs 2014 - 2016" and "Trade in Veterinary Drugs 2017 - 2018", which together provide a comprehensive overview of the seven-year turnover of drugs for use in veterinary medicine (37). Essentially, the availability of this information contributes to a regulated veterinary drug sector in Serbia, fostering responsible practices in the agricultural and veterinary industries within the Republic of Serbia.

Conclusion

For the effective management of AMR, several elements are crucial. These include the rational utilization of antibiotics, surveillance of antibiotic usage through the "One Health Approach", advancements and development within healthcare systems, formulation of comprehensive health insurance policies, restriction of the promotion of drugs, implementation of cohesive disease control strategies, and the establishment of community-driven stewardship initiatives (8, 33). Today, AMR is addressed through multifaceted approaches, aiming to combat the spread of drug-resistant infections and preserve the effectiveness of existing antibiotics. Countries are encouraged to develop and implement national action plans to address AMR, tailored to their specific contexts and needs. The WHO has developed a Global Action Plan, endorsed by member states in 2015, to tackle AMR, providing a framework for countries to produce and implement action plans for AMR. Sharing information, best practices, and coordinating efforts between countries enables collective action.

The movement of people and goods across borders facilitates the spread of drug-resistant pathogens that travelers could carry or transmit via imported and exported food products. Regulation concerning antibiotic dispensing mechanisms varies globally. Therefore, a share of the population can acquire antibiotics without a medical prescription, although a prescription is obligatory to obtain antibiotic therapy. The issue of online antibiotic purchases is a concern in many countries, and inadequate control in some areas allows over-the-counter sales, fostering self-medication and inappropriate antibiotic use. This global phenomenon poses public health risks, including antibiotic resistance, adverse reactions, and increased morbidity. Excessive antibiotic use in hospitals and over-prescription in primary healthcare are identified as contributors to the spreading of AMR. Standardized treatment protocols, continuous education, and optimal utilization of technology, such as internet-based training, are essential to promote responsible antibiotic use among medical practitioners and the general population.

Strengthening regulatory measures to improve the appropriate use of antimicrobials involves obligatory prescription requirements, regulating the sale of antibiotics, and continuous implementation of policies to prevent overuse. Addressing the multifaceted challenges of antibiotic use requires an effort from healthcare systems, regulatory and control bodies, and educational institutions worldwide. Systemized groups of the recommendations for tackling AMR in the human population are listed in **table 1**.

Ensuring the availability of new reserve antibiotics remains a challenge and a task. Infection control is vital, particularly in hospital care, due to higher antibiotic resistance proportions in clinical isolates from inpatients. While global attention is given to antimicrobial resistance in some countries, a collective global effort is crucial given

Table 1. Recommendations for tackling antimicrobial resistance in the human population

	Proposals for future actions on combating antimicrobial resistance
1.	Monitoring the implementation of measures within National Action Plans on antimicrobial resistance
2.	Strengthening regulatory and control mechanisms for the appropriate antibiotic utilization
3.	Emphasize infection control, particularly in healthcare settings
4.	Global cooperation for approaching public insight and consciousness about the rational antibiotic utilization
5.	Research and development on antimicrobial resistance

our interconnected global world. The inadequacy in developing new antibacterial treatments, highlighted in the WHO's 2021 pipeline report, underscores the urgent need for united international efforts and research to address the growing threat. Additionally, evidence suggests that vaccines can be important in reducing antimicrobial demand.

While the spread of antimicrobial resistance occurs through diverse routes involving humans, animals, and the environment, excessive and inappropriate use in agriculture and veterinary practices should be addressed to prevent the evolution of resistant strains. Some regions, like Europe, are making strides in regulating antimicrobial use in all segments.

In summary, addressing antimicrobial resistance requires a multifaceted approach that includes comprehensive action for appropriate antibiotic use, improving infection control, fostering responsible practices in agriculture and healthcare, research and development of new antibiotics, and global cooperation. Efforts to combat AMR should involve all public health stakeholders globally, nationally, and locally - governments, healthcare providers, the pharmaceutical industry, and the whole population raising public awareness and health literacy of lay audiences to reduce the impact of antimicrobial resistance on health in general.

Abbreviations

AMR - Antimicrobial Resistance
AKS - Antibiotic Knowledge Score
AWaRe - Access, Watch, and Reserve (classification in which antibacterial medicines were stratified into three groups)
HCAIs - in hospital care-associated infections
ESKAPE pathogens - Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species
ICUs - Intensive care units
WHO - World Health Organization

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