

Acta Scientifica Naturalis

Former Annual of Konstantin Preslavsky University of Shumen: Chemistry, Physics, Biology, Geography

Journal homepage: <https://content.sciendo.com/view/journals/asn/asn-overview.xml>

Antimicrobial drug resistance against the background of the COVID-19 pandemic in Bulgaria and Europe: A profound review of the available literature sources

Yordanka Mihaylova¹, Sylvia Stamova², Emilia Georgieva¹, Neli Ermenlieva³, Berna Beyti⁴

¹ Medical College of Varna, Medical University of Varna, 55 Marin Drinov Str., 9002 Varna, Bulgaria

² Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Medical University of Varna, 150 Tsar Osvoboditel Blvd., 9002 Varna, Bulgaria

³ Department of Microbiology and Virology, Faculty of Medicine, Medical University of Varna, 55 Marin Drinov Str., 9002 Varna, Bulgaria

⁴ Student of Medical College of Varna, Medical University of Varna, 55 Marin Drinov Str., 9002 Varna, Bulgaria

Abstract: *Improper use of antibiotics is an extremely worrying trend worldwide. This leads to the development of resistance to these drugs. As a result, antibiotics stop working and bacteria continue to grow. The highest levels of resistance, both in our country and worldwide, are to second and third-generation cephalosporins, some aminoglycosides, and others. The reason is that these antibiotics have been used most irrationally over the years. The pandemic of COVID-19 and Antimicrobial drug resistance (AMR) are parallel and interrelated serious health situations, between which there is a causal link, manifested in high mortality among the human population. This review highlights relations between growth rates of antimicrobial resistance and the Covid-19 pandemic situations in Bulgaria and Europe in this fast-growing research area.*

Keywords: COVID-19; SARS-CoV-2; antibiotic resistance; antimicrobial resistance

Introduction

The severe acute infection caused by SARS-CoV-2 was first identified in Wuhan, China [1]. The first proven case in Bulgaria was on March 8, 2020. Human-to-human transmission has led to its worldwide spread and pandemic. The world continues to respond to COVID-19 by adhering to the world's accepted guidelines for the treatment of the disease. In most cases of post-viral complications, antimicrobial therapy remains the primary treatment. Widespread and unnecessary use of antibiotics facilitates the emergence and spread of resistant pathogens [2, 3, 4]. AMR remains a worrying issue as pathogens causing resistant infections thrive in hospitals and medical facilities, putting all patients at risk, regardless of the severity of their medical condition [5]. This may further complicate the response to the COVID-19 pandemic [6, 7]. Unfortunately, this hidden threat from AMR is not receiving the same global attention as the COVID-19 pandemic. An estimate has been made that the AMR could cause up to 10 million deaths worldwide by 2050 [8]. Undoubtedly, COVID-19 posed enormous challenges for all aspects of healthcare from an economic, social, and medical point of view. Health systems have triggered policies to prevent infections through COVID-19 and antimicrobial resistance.

Secondary bacterial infections play a crucial role in COVID-19-related mortality. Studies show that a small proportion of patients with COVID-19 need antibiotics to treat secondary bacterial infections. The present evidence confirms the need not to administer antibiotic therapy or prophylaxis to patients with mild COVID-19 or to patients with suspected or confirmed moderate COVID-19 disease unless otherwise indicated. The pandemic has also highlighted deficiencies in health systems around the world. Despite advances in medicine, we remain vulnerable to infections with limited or non-standard therapies. It is important to look at the situation in the context of AMR as well, as resistant pathogens are evolving and leading us to the era of incurable infections. There is a need for continuous research to detect and control infectious agents, as well as to develop newer functional antimicrobial agents. Of great importance is the need to strengthen, expand and enforce a plan and programs for the use of antimicrobials [1].

Exposure

All types of bacteria can build resistance. It is due to a mutation in the cell that helps the bacterium to survive adverse conditions. This mutation is passed on to offspring and can be transmitted between unrelated bacteria through various mechanisms. The main factor in the selection of resistant bacteria, in this case are antibiotics [9, 10]. In many countries, the level of drug resistance has more than doubled in the last three years [10, 11, 12]. The most common strains are *Streptococcus pneumoniae* – insensitive to penicillin and resistant to erythromycin, *S. aureus* – resistant to ciprofloxacin, strains of *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli* is a normal flora of the gastrointestinal tract, and the most common Gram-

negative bacterium isolated from blood cultures, as well as the most common cause of bacteraemias and urinary tract infections. *Klebsiella pneumoniae* is a normal flora of the gastrointestinal tract and a cause of infections in humans (skin, pharynx, and upper respiratory tract), resistant to third-generation carbapenems and cephalosporins.

Cause of opportunistic infections in immunocompromised, sepsis, and nosocomial epidemics, *Acinetobacter baumannii* is a typical nosocomial pathogen. It is the cause of VAP, sepsis, SSI, and urinary tract infections [10, 13]. Tends to persist for a very long time in a hospital environment (resistant to drought). When bacteria of a strain become resistant to three or more groups of antibiotics, they are referred to as polyresistant.

Risk factors for infection with resistant bacteria are the hospital stay of more than five days, extreme age, chronic diseases, recurrent infections, treatment in the last 90 days with antibiotics, the appointment of low doses of antibiotics, irrational courses (very short or too long), improper intake, the appointment of an unnecessary antibiotic (for viral infections), travel, etc. Infections caused by such bacteria are treated longer, with a combination of several antibiotics, often these patients are subject to hospitalization. AMR complicates the treatment of infections and increases the risk of spreading the disease, greater severity of disease, and death [11, 14]. Also, many chronic infections are due to bacterial biofilms. Biofilms and their inherent resistance to antibiotics are responsible for different health issues [15]. Patients with severe Covid 19 disease typically require supplemental oxygen and should be monitored closely for worsening respiratory status, because some patients may progress to acute respiratory distress syndrome (ARDS) [16]. The continuous application of oxygen mask could lead to the some major drawbacks. One of these is the possible occurrence of biomaterial-centered infections (BCI). Subsequent surface growth of the microorganisms will lead to a mature biofilm and infection, which is difficult to eradicate by antibiotics [17]. The antibiotic binds to structures only in the bacterial cell that is unique and unparalleled in human and animal cells, so they are effective and relatively low toxic. There are 61 authorized types of antibiotics in Bulgaria, which are sold under 197 trade names and 375 dosage forms [10, 11].

Hospitalized patients are more likely to be prescribed antibiotics (10) and approximately 50% of all antibiotics used in hospitals may be inappropriate [14, 18]. The emergence, spread, and selection of resistant bacteria in Europe is a threat to patient safety in hospitals [13, 19] because:

- Infections with resistant bacteria lead to an increase in morbidity and mortality of patients, as well as to an increase in the length of hospital stay;
- Antibiotic resistance often leads to delays in appropriate antibiotic therapy;

• Inadequate or delayed antibiotic therapy in patients with severe infections has been associated with poorer patient outcomes and sometimes death [20, 21].

Combating AMR is a comprehensive approach that brings together all stakeholders in order to effectively reduce and limit the emergence and spread of resistance by permanently and sustainably reducing the overall volume of antimicrobials used. The use of antibiotics for the EU in the last year has averaged 15.0 DDD per 1000 people per day, ranging from Austria by 7.1 to Greece by 26.4. In Bulgaria, the use of antibiotics increased to 22.7 DDD per 1000 people per day in the hospital system, and in outpatient care, the daily consumption was 20.0 DDD per 1000 people. The use of antibiotics in our country has increased significantly in recent years associated with the COVID-19 pandemic [10,11]. At its lowest levels of use, it was 17.00 per 1000 people per day. There is a decline in consumption in the hospital sector. During the pandemic, we receive information about the illegal and excessive use of antibiotics. According to EARS, in several European countries, 6% to 46% of the population has self-treated with antibiotics. At the same time, 79% to 86% of them were not infected and used antibiotics “for prevention”, i.e. without any benefit. Only 8% – 10% of those taking the antibiotic had a severe COVID-19 infection [18, 22].

AMR levels for Bulgaria are extremely high, with data showing that the relative share of resistance to four antimicrobial groups is the highest in Europe. Table 1 shows comparative data on established antimicrobial resistance between Finland, Italy, and Bulgaria from 2017 to *E. coli*, *K. pneumoniae* and *Acinetobacter species*. The distribution of isolates is as follows: fully sensitive and resistant to one, two, three, and four, and five antimicrobial groups – aminopenicillins, fluoroquinolones, third-generation cephalosporins, aminoglycosides, and carbapenems [23].

Table 1. Distribution of *E. coli*, *K. pneumoniae* and *Acinetobacter species* isolates: fully sensitive and resistant to one, two, three, four, and five antimicrobial groups [23]

Country	Fully Sensitive (%)	Resistant to one antimicrobial group (%)	Resistant to two antimicrobial groups (%)	Resistant to three antimicrobial groups (%)	Resistant to four antimicrobial groups (%)
<i>E. coli</i>					
Bulgaria	26	24	4	13	27
Finland	60	26	10	4	3
Italy	29	27	14	17	15

<i>K. pneumoniae</i>					
Bulgaria	22	8	19	38	13
Finland	88	8	1	3	-
Italy	42	6	10	28	14
<i>Acinetobacter spp.</i>					
Bulgaria	4	7	13	76	-
Finland	100	-	-	-	-
Italy	19	5	6	72	-

Table 2 presents the total number of *P. aeruginosa* and *S. aureus* isolates tested, as well as resistant combinations of invasive isolates tested against at least three antimicrobial groups - piperacillin ± tazobactam, ceftazidime, fluoroquinolones, aminoglycosides, and carbapenems, presented as percentages for countries across Europe in 2017 [23].

Table 2. The total number of tested isolates of *P. aeruginosa* and *S. aureus*, as well as resistant combinations between invasive isolates, tested against at least three antimicrobial groups [23]

Clinical isolate	Fully Sensitive (%)	Resistant to one antimicrobial group (%)	Resistant to two antimicrobial groups (%)	Resistant to three antimicrobial groups (%)	Resistant to four antimicrobial groups (%)	Resistant to five antimicrobial groups (%)
<i>P. aeruginosa</i>	69,2	12,5	7	4	3,4	3,9
<i>S. aureus</i>	81,1	8	10,5	0,4	-	-

These data were purposefully selected to be in the period before the Covid-19 pandemic. They clearly show the link between high mortality from complications of Covid-19 infection and low or high levels of established antimicrobial resistance. For Finland, for example, a study was conducted to compare the early impact of infection and mortality from COVID-19 from February to July 2020 in the Nordic countries, including Finland, using available public data sources and descriptive analysis of potential factors leading to different epidemiological results. The established mortality rates are low – 0.06 deaths per 1000 people [24]. The level is low and correlates with the low levels of antimicrobial resistance in these countries.

Data for Italy in March 2020 identify it as the country with the highest mortality rate of 12% [25]. Again, the relationship between the high levels of antimicrobial resistance is directly proportional to the high mortality rates of Covid-19.

The situation in Bulgaria is slightly different, the first wave of Covid-19 (March – June 2020) did not affect Bulgaria to the same extent as other countries in Europe (Italy, Spain, Belgium, United Kingdom). The severe second wave of the pandemic in Bulgaria was in November – December 2020, and the third wave in March – April 2021, but still Bulgaria, despite the later development and delayed increased incidence of Covid-19, is the second and even first with the highest mortality rate in Europe [26].

The low levels of vaccination and the high levels of antimicrobial resistance define Bulgaria as a risk zone for the spread of Covid-19, as well as are a prerequisite for the reported high mortality.

AMR remains a major challenge for the pharmaceutical and health sectors, despite efforts to reduce antibiotic consumption during the COVID-19 pandemic. This shows the need for adequate measures and global action by public health. Another worrying fact is the lack of new antimicrobials. The latest class of antibiotic was discovered in the 1980s. This necessitates the search for new antimicrobial agents, such as therapeutic peptides, which have enhanced metabolic stability, high selectivity, efficacy, and low toxicity [27, 29]. These characteristics, combined with advances in solid-phase peptide synthesis and purification methods, have led to the increasing penetration of peptide-based drugs in clinical practice [28, 29]. In the human organism, peptides perform various functions - biologically active hormones, neurotransmitters and neuromediators, growth factors, signal molecules and antibiotics [30]. Another investigation has relied on the antimicrobial potential of inulin acetate against seventeen microorganisms (Gram-positive and Gram-negative bacteria, yeasts and fungi). It is worth noting that inulin acetate demonstrated antimicrobial activity at concentration 1 mg/ml against *Listeria monocytogenes* 863, *Escherichia coli* 3398, *Candida albicans* 8673, *Fusarium oxysporum*, and *Aspergillus niger* [31].

EU efforts to mitigate the threat of antimicrobial resistance are linked to the European Commission's single action plan against antibiotic drug resistance. As a result, many Member States are focusing on reducing the use of antibiotics. The European Antimicrobial Resistance Surveillance Network (EARS-Net), formerly known as the European Antimicrobial Resistance Surveillance System (EARSS), provides analyzes of antimicrobial susceptibility trends over time and between all EU Member States and two EEA countries (Iceland and Norway). The data are based on routine results from antimicrobial susceptibility tests collected from a network of clinical laboratories. Currently, the pathogens included in the surveillance network are the following: *Streptococcus pneumoniae*, *S. aureus*, *Enterococcus faecalis*, *E. faecium*, *Escherichia coli*,

Klebsiella pneumoniae, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. EARS-Net is administered and coordinated by the European Center for Disease Prevention and Control (ECDC) [32, 33].

In hospitals and other healthcare facilities, infection control practices need to be improved in order to reduce the spread of resistant bacteria. In outpatient care, infections can be prevented or reduced through vaccination, physical distance, and good hygiene.

Conclusion

Antimicrobial resistance continues to increase, causing significant morbidity and mortality. Pharmaceutical companies are constantly being challenged to engage with new pharmaceutical forms in the fight against antimicrobial resistance. New (but also old) antimicrobials must be used wisely so that they can be used longer in practice.

References

- [1]. Adebisi, Y. A.; Alaran, A. J.; Okereke, M.; Oke, G. I.; Amos, O. A.; Olaoye, O. C.; Oladunjoye, I.; Olanrewaju, A. Y.; Ukor, N. A.; Lucero-Prisno, D. E., 3rd COVID-19 and Antimicrobial Resistance: A Review. *Infectious Diseases*, **2021**, *14*, <https://doi.org/10.1177/11786337211033870>.
- [2]. Vidovic, N.; Vidovic, S., Antimicrobial resistance and food animals: influence of livestock environment on the emergence and dissemination of antimicrobial resistance. *Antibiotics*. **2020**, *9*, 52.
- [3]. Beović, B.; Doušak, M.; Ferreira-Coimbra, J. et al. Antibiotic use in patients with COVID-19: a ‘snapshot’ Infectious Diseases International Research Initiative (ID-IRI) Survey. *Journal of Antimicrobial Chemotherapy*. **2020**, *75*, 3386-3390.
- [4]. Rezasoltani S, Yadegar A, Hatami B, Asadzadeh Aghdaei H, Zali MR. Antimicrobial resistance as a hidden menace lurking behind the COVID-19 outbreak: the global impacts of too much hygiene on AMR. *Frontiers in Microbiology*. **2020**, *11*, 590683.
- [5]. Weiner-Lastinger, LM; Abner, S; Edwards, JR; et al. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: summary of data reported to the National Healthcare Safety Network, 2015-2017. *Infection Control & Hospital Epidemiology*. **2020**, *41*, 1-18.
- [6]. Del Rio, C; Malani, PN., COVID-19-new insights on a rapidly changing epidemic. *JAMA*. **2020**, *323*, 1339.
- [7]. Rawson, TM; Ming, D; Ahmad, R; Moore, LSP; Holmes, AH, Antimicrobial use, drug-resistant infections and COVID-19. *Nature Reviews Microbiology*. **2020**, *18*, 409-410.

- [8]. Akpan, MR; Isemin, NU; Udoh, AE; Ashiru-Oredope, D, Implementation of antimicrobial stewardship programmes in African countries: a systematic literature review. *Journal of Global Antimicrobial Resistance*. **2020**, 22, 317-324.
- [9]. www.mh.government.bg/bg/informaciya-za-grazhdani/zdravosloven-nachin-na-zhivot/zarazni-zabolyavaniya/informaciya-za-antibiotici/
- [10]. <https://clinica.bg/18976-15--po-malko-antibiotici-v-ES>.
- [11]. Stoeva, T.; Bojkova, K.; Savov, E.; Mihaylova, S.; Sredkova, M., Antimicrobial resistance of clinical isolates *Acinetobacter baumannii*, Union of Bulgarian Medical Specialists, **2007**, 58(5).
- [12]. Ruiz, J., Enhanced antibiotic resistance as a collateral COVID-19 pandemic effect? *Journal of Hospital Infection*. **2021**, 107, 114–115. doi: 10.1016/j.jhin.2020.11.010.
- [13]. Sharifipour, E.; Shams, S.; Esmkhani, M.; Khodadadi, J.; Fotouhi-Ardakani, R.; Koohpaei, A., Evaluation of bacterial co-infections of the respiratory tract in COVID-19 patients admitted to ICU. *BMC Infectious Diseases*. **2020**, 20, 646. doi: 10.1186/s12879-020-05374-z.
- [14]. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. **2020**, 395, 497–506. doi: 10.1016/S0140-6736(20)30183-5.
- [15]. Ignatova-Ivanova, Ts.; Ibrjmov, S.; Andreeva, A., Ivanov, R., Study of Biofilm Formation from *Lactobacillus Fermentum* S Cultivated on Different Carbohydrates. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*. **2017**, 8(6), 282-289.
- [16]. <https://www.covid19treatmentguidelines.nih.gov/management/critical-care/oxygenation-and-ventilation/>.
- [17]. Ignatova-Ivanova, Ts.; Ibrjmov, S.; Ismailov, I.; Christov, V.; Ivanov, R., Adhesion and surface growth of *Staphylococcus aureus* and *Lactobacillus plantarum* on various metals. *Journal of IMAB*, **2015**, Vol. 21, Issue 2. doi: <http://dx.doi.org/10.5272/jimab.2015212.793>.
- [18]. Zavala-Flores, E.; Salcedo-Matienzo, J., Medicación prehospitalaria en pacientes hospitalizados por COVID-19 en un hospital público de Lima-Perú. *Acta Medica Peruana*. **2020**, 37. doi: 10.35663/amp.2020.373.1277.
- [19]. Shi, H.; Han, X.; Jiang, N.; Cao, Y.; Alwalid, O.; Gu, J., Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infectious Diseases*. **2020**, 20, 425–434. doi: 10.1016/S1473-3099(20)30086-4.
- [20]. Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Liu, Z., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. **2020**, 395, 10.

- [21]. Elske Sieswerda, Mark G J de Boer, Marc M J Bonten, Wim G Boersma, René E Jonkers, Roel M Aleva, Bart-Jan Kullberg, Jeroen A Schouten, Ewoudt M W van de Garde, Theo J Verheij, Menno M van der Eerden, Jan M Prins, W Joost Wiersinga, Recommendations for antibacterial therapy in adults with COVID-19 - an evidence based guideline. *Clinical Microbiology and Infection*. **2021**, 27(1), 61–66. doi: 10.1016/j.cmi.2020.09.041.
- [22]. Zafer, M.M.; El-Mahallawy, H.A.; Ashour, H.M., Severe COVID-19 and sepsis: immune pathogenesis and laboratory markers. *Microorganisms*. **2021**, 9, 159. doi: 10.3390/microorganisms9010159.
- [23]. <https://www.ecdc.europa.eu/sites/default/files/documents/AMR-surveillance-EARS-Net-2017.pdf>.
- [24]. Yarmol-Matusiak, E.A.; Cipriano, L.E.; Stranges, S. A comparison of COVID-19 epidemiological indicators in Sweden, Norway, Denmark, and Finland. *Scandinavian Journal of Public Health*, **2021**, 49(1), 69–78. <https://doi.org/10.1177/1403494820980264>.
- [25]. <https://www.europeanreview.org/wp/wp-content/uploads/4066-4067.pdf>.
- [26]. Tosheva, E.; Yordanova, G.; Markova, E.L., Before and during the outbreak: prerequisites for the high Covid-19 mortality rate in Bulgaria. Empirical insights from share data. **2021**, Vol. 8, Num Esp.
- [27]. Ivanova, S.; Mihaylova, S.; Tsvetkova, A., Methods to enhance the metabolic stability of peptide drugs. *Varna Medical Forum*. **2021**, 10(2), 371-379.
- [28]. Mihaylova, S.; Tsvetkova, A.; Arnaoudova, M.; Todorova, A.; Petkova, V.; Dimitrov, M.; Manova, M.; Savova, Al., Current issues regarding approved peptide and protein drugs in Bulgaria. *World Journal of Pharmacy and Pharmaceutical Sciences*. **2020**, 7(4), 708-717.
- [29]. Dimitrova, D., Lambev, M.; Hristova, A.; Mihaylova, S.; Valcheva-Kuzmanova, S.; Pajpanova, T., Antimicrobial peptides (amps) - a potential solution against microbial resistance. *Varna Medical Forum*. **2018**, 7(3), 195-202.
- [30]. Mihaylova, S. Solid-phase peptide synthesis (SPPS). *Varna Medical Forum*. **2017**, Vol. 6.
- [31]. Petkova, N.; Arabadzhieva, R.; Vassilev, D.; Gencheva, G.; Tumbarski, Y.; Ignatova-Ivanova, Ts.; Ibryamova, S.; Todorova, M.; Koleva, M.; Denev, P., Physicochemical Characterization and Antimicrobial Properties of Inulin Acetate Obtained by Microwave-Assisted Synthesis. *Journal of Renewable Materials*, **2020**, 8(4), 365-381.
- [32]. Baron, S.A.; Devaux, C.; Colson, P.; Raoult, D.; Rolain, J.-M., Teicoplanin: an alternative drug for the treatment of COVID-19? *International Journal of Antimicrobial Agents*. **2020**, 55. doi: 10.1016/j.ijantimicag.2020.105944.
- [33]. European Antimicrobial Resistance Surveillance Network (EARS-Net) An agency of the European Union. www.ecdc.europa.eu/en.