JAVNO ZDRAVSTVENI ASPEKTI – ZLOUPOTREBE I NEADEKVATNO KORIŠĆENJE ANTIBIOTIKA

PREGLEDNI RAD

REVIEW ARTICLE

PUBLIC HEALTH ASPECTS – MISUSE AND INAPPROPRIATE USE OF ANTIBIOTICS

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SAŽETAK

Uvod/Cilj: Antibiotici od svog otkrića predstavljaju ključnu odbranu od bakterijskih infekcija, ali sve veći broj sojeva razvija otpornost putem spontanih genetskih mutacija i sticanja gena rezistencije, što se dodatno podstiče njihovom nepravilnom i učestalom upotrebom. Ovaj pregled literature obuhvata radove objavljene od 2010. do 2024. godine i analizira četiri ključne oblasti: zloupotrebu i neadekvatnu primenu antibiotika, razvoj superbakterija, globalne aspekte antimikrobne rezistencije (AMR) i preventivne strategije sa naglaskom na ulogu vitamina. Cilj ovog pregleda je da prikaže dokaze o zloupotrebi antibiotika, razvoju rezistencije i preventivnim strategijama, sa posebnim osvrtom na značaj vitamina u očuvanju imuniteta i unapređenju rada zdravstvenih sistema.

Metode: U pregled literature uključeni su radovi objavljeni u periodu od 2010. do 2024. godine, sa fokusom na analizu nepravilne upotrebe antibiotika, razvoj superbakterija, globalni uticaj AMR-a i ulogu vitamina u preventivnim strategijama.

Rezultati: Rezultati pokazuju da su najčešći uzroci neadekvatne terapije samoinicijativno uzimanje lekova, propisivanje bez mikrobiološke potvrde i loša komunikacija između lekara i pacijenta. AMR je prepoznat kao jedna od najvećih pretnji javnom zdravlju, sa značajnim posledicama po morbiditet, mortalitet i troškove zdravstvenog sistema. Preventivne mere obuhvataju edukaciju zdravstvenih radnika i stanovništva, regulisanje prodaje antibiotika, razvoj novih dijagnostičkih i terapijskih metoda, kao i promociju zdravih navika. Poseban značaj imaju vitamini sa antioksidativnim svojstvima (retinol, tokoferol i L-askorbinska kiselina), koji mogu smanjiti potrebu za antibioticima, posebno uz doprinos vitamina D, za koji je poznato da stimuliše imuni sistem.

Zaključak: Integrisani pristup, u skladu sa konceptom One Health, ključan je za očuvanje efikasnosti postojećih lekova i smanjenje javnozdravstvenog opterećenja uzrokovanog AMR-om.

Ključne reči: antibiotici, antimikrobna rezistencija, racionalna upotreba, crevna mikrobiota, vitamini, javno zdravlje

ABSTRACT

Introduction/Aim: Since their discovery, antibiotics have represented a key defense against bacterial infections, but an increasing number of strains are developing resistance through spontaneous genetic mutations and the acquisition of resistance genes, a process further stimulated by their improper and frequent use. This literature review encompasses studies published between 2010 and 2024 and analyzes four key areas: the misuse and inappropriate application of antibiotics, the development of superbugs, the global aspects of antimicrobial resistance (AMR), and preventive strategies with an emphasis on the role of vitamins. This review aims to present evidence on antibiotic misuse, resistance development, and preventive strategies, with particular attention to the importance of vitamins in maintaining immunity and improving the functioning of healthcare systems.

Methods: This literature review includes studies published from 2010 to 2024, focusing on the analysis of antibiotic misuse, the development of superbugs, the global impact of AMR, and the role of vitamins in prevention strategies.

Results: The results indicate that the most common causes of inadequate therapy are self-medication, prescription without microbiological confirmation, and poor communication between physicians and patients. AMR has been recognized as one of the greatest threats to public health, with significant consequences for morbidity, mortality, and healthcare system costs. Preventive measures include education of healthcare professionals and the general population, regulation of antibiotic sales, the development of new diagnostic and therapeutic methods, and the promotion of healthy lifestyle habits. Of particular importance are vitamins with antioxidant properties (retinol, tocopherol, and L-ascorbic acid), which may reduce the need for antibiotics, especially with the contribution of vitamin D, known to stimulate the immune system.

Conclusion: An integrated approach, in line with the One Health concept, is crucial for preserving the effectiveness of existing drugs and reducing the public health burden caused by AMR.

Keywords: antibiotics, antimicrobial resistance, rational use, intestinal microbiota, vitamins, public health

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UVOD

Nedavni podaci ukazuju na značajan izazov sa kojim se suočavaju zdravstveni sistemi širom sveta. Procene pokazuju da bi antimikrobna rezistencija (AMR) mogla rezultirati sa 10 miliona smrtnih slučajeva godišnje na globalnom nivou i smanjenjem globalnog bruto domaćeg proizvoda za 2% do 3,5%, uz ekonomske posledice koje bi do 2050. godine mogle dostići 100 triliona američkih dolara [1–3]. Rastuća učestalost infekcija i smrtnih slučajeva povezanih sa antimikrobnom rezistencijom (oko 70% infekcija izazvanih bakterijama otpornim na antibiotike javlja se u zdravstvenim ustanovama) primećuje se kod gotovo svih bakterijskih sojeva i srodnih antibiotskih terapija [1–3]. Svetska zdravstvena organizacija je 2019. godine prepoznala AMR kao jednu od deset najvažnijih globalnih opasnosti po javno zdravlje sa kojima se suočava čovečanstvo, dok su Evropska komisija i države članice EU od jula 2022. godine svrstale AMR među tri primarne zdravstvene pretnje [1–3]. Ova zabrinjavajuća situacija ukazuje na potrebu jačanja mera kontrole infekcija, unapređenje svesti i intenziviranje istraživačkih napora [1–3].

Antimikrobna rezistencija (AMR) predstavlja sposobnost mikroorganizama, uključujući bakterije, viruse, gljivice i parazite, da izbegnu dejstvo antimikrobnih lekova koji su ranije bili efikasni u njihovom suzbijanju. Ovaj proces nastaje kao rezultat prirodne selekcije i adaptacije mikroorganizama, uključujući spontane genetske mutacije i horizontalni prenos gena otpornosti, što dovodi do smanjenja ili potpunog gubitka efikasnosti standardnih terapija [1,2].

Antibiotici su biološki važna organska jedinjenja koja su svojim dejstvom spasili mnoge živote širom sveta. Njihovo dejstvo zasniva se na različitim mehanizmima ometanja funkcija bakrerijske ćelije. Neki antibiotici deluju bakteriostatski, a neki bakteriocidno. Bakteriocidne grupe antibiotika dovode do smrti bakterije dok bakteriostatski antibiotici imaju mogućnost da bakterije drže u stazi što znači da ona neće moći da se množi i da obavlja svoje fiziološke potrebe. Ujedno će biti podložna odgovoru antitela i beloj krvnoj lozi koja se nalazi u svakom živom biću i koja će putem bele krvne loze, antitela ali i komponenta komplementa dovesti do smrti bakteriskih ćelija. Dok bakteriocidni antibiotici ometaju direktno bakterisku ćeliju izazivajući njenu smrt na različite načine. Mehanizmi delovanja baktericidnih antibiotika uključuju oštećenje membrane i ćelijskog zida bakterijske ćelije, ometanje metaboličkih procesa, oštećenje RNK molekula i proteina odgovornih za ispravljanje grešaka tokom deobe ćelija, kao i direktno oštećenje DNK. Ovo su samo neki od datih mehanizama.

Antibiotici su, od revolucionarnog otkrića do danas, ostali glavna linija odbrane od bakterija. Međutim,

INTRODUCTION

Recent figures underscore a significant dilemma within healthcare systems worldwide. Estimates suggest that AMR could result in 10 million deaths annually on a global scale and a reduction of the global gross domestic product by 2% to 3.5%, with economic consequences potentially reaching 100 trillion US dollars by 2050 [1–3]. The rising incidence of infections and deaths associated with antimicrobial resistance (with around 70% of infections caused by antibiotic-resistant bacteria taking place in healthcare facilities) has been observed across nearly all bacterial strains and the related antibiotic therapies [1–3]. In 2019, the World Health Organization (WHO) recognized antimicrobial resistance as one of the ten foremost global public health threats confronting humanity, while the European Commission and EU member states identified AMR as one of the three primary health threats as of July 2022 [1–3]. This alarming situation highlights the need to strengthen infection control measures, raise awareness, and intensify research efforts [1–3].

Antimicrobial resistance (AMR) refers to the ability of microorganisms, including bacteria, viruses, fungi, and parasites, to evade the effects of antimicrobial agents that were previously effective in eliminating them. This process occurs as a result of natural selection and adaptation of microorganisms, including spontaneous genetic mutations and horizontal transfer of resistance genes, leading to a reduction or complete loss of effectiveness of standard therapies [1,2].

Antibiotics are biologically important organic compounds that have saved countless lives worldwide. They act in different ways to disrupt the physiological processes and structural integrity of bacterial cells. Some antibiotics act bacteriostatically, while others are bactericidal. Bactericidal groups of antibiotics induce bacterial cell death, whereas bacteriostatic antibiotics halt bacterial growth and reproduction, which means that they will not be able to multiply and perform their physiological needs and will be susceptible to the response of antibodies and white blood cells found in every living being and which, through white blood cells, antibodies and complement components, will lead to the bacterial eradication. Bactericidal antibiotics exert their effects by directly targeting the bacterial cell, leading to cell death through various mechanisms. Some of them damage the bacterial cell membrane and cell wall, while others suppress essential metabolic processes. Certain agents impair RNA molecules and specific proteins involved in the correction of errors during cell division, and some act directly on the bacterial DNA itself. These are just some of the known mechanisms.

From their revolutionary discovery until today, antibiotics have served as the main line of defense against

sve veći broj različitih sojeva bakterija razvija otpornost putem endogenih mehanizama, uključujući spontane genetske mutacije i sticanje ili ekspresiju gena otpornosti. Pored ovih inherentnih puteva, nepotrebno i neopravdano izlaganje bakterija antibioticima može dovesti do ovog fenomena. Bakterije često ne postaju odmah potpuno otporne. U početku razvijaju osetljivost, osetljivost bakterija je označena sa "S" (osetljiva), a zatim ulaze u stanje parcijalne osetljivosti, što je označeno sa "I" (srednja osetljivost). Tek nakon ponovljenog izlaganja datom antibiotiku dolazi do potpune rezistencije, što je na antibiogramu naznačeno sa "R" (otporan). Procenjuje se da će do 2050. godine nivo bakterijske rezistencije na antibiotike dostići veoma visoke razmere [1]. Takođe je važno napomenuti da određene klase antibiotika sintetizuju ljudi i ne mogu se naći u prirodi. Nasuprot tome, određene grupe antibiotika sintetizuju drugi mikroorganizmi, odnosno mogu se naći u prirodi. Čak i kada se pravilno koriste, antibiotici mogu izazvati ozbiljne neželjene efekte ako se ne koriguju na vreme. Ovo uvodi važnu etičku dimenziju, kao i odgovornost kliničara koji propisuje antibiotik [2].

Cilj ovog pregleda literature je da prikaže najnovije naučne dokaze o zloupotrebi i neadekvatnoj upotrebi antibiotika, razvoju superbakterija povezanih sa njihovom prekomernom primenom, globalnim aspektima antimikrobne rezistencije i preventivnim strategijama, sa posebnim naglaskom na ulogu vitamina u očuvanju imunološke funkcije. Svrha rada je da se doprinese boljoj zaštiti ugroženih populacija, unapređenju racionalne primene antibiotika i efikasnijem radu zdravstvenih sistema.

Značaj antimikrobne rezistencije (AMR)

Antimikrobna rezistencija (AMR) predstavlja jedan od najvećih izazova savremene medicine i javnog zdravlja, sa potencijalno katastrofalnim posledicama na globalnom nivou[1–3]. Prema najnovijim procenama, ukoliko se trenutni trend porasta rezistencije nastavi, do 2050. godine AMR bi mogao uzrokovati do 10 miliona smrtnih slučajeva godišnje, uz smanjenje globalnog bruto domaćeg proizvoda za 2–3,5% [1]. Svetska zdravstvena organizacija je 2019. godine svrstala AMR među deset najvećih pretnji po javno zdravlje, dok su institucije Evropske unije 2022. godine prepoznale ovaj problem kao jednu od tri prioritetne zdravstvene pretnje [2,3]. Posebno zabrinjava podatak da se oko 70% infekcija izazvanih bakterijama otpornim na antibiotike javlja u zdravstvenim ustanovama, dok se porast njihove učestalosti beleži se kod gotovo svih značajnih patogenih sojeva [3]. Ovakva situacija zahteva intenziviranje mera kontrole infekcija, povećanje svesti javnosti i zdravstvenih radnika, kao i jačanje istraživačkih aktivnosti usmerenih na pronalaženje novih terapijskih rešenja.

bacteria. However, an increasing number of different strains of bacteria are developing resistance through endogenous mechanisms, including spontaneous genetic mutations and the acquisition or expression of resistance genes. In addition to these inherent pathways, the frequent, unnecessary, and unjustified exposure of bacteria to antibiotics can also lead to this phenomenon. Bacteria often do not immediately become completely resistant. Initially, they develop sensitivity; the sensitivity of bacteria is indicated by "S" (susceptible), then they move into a state of partial sensitivity, which is labeled by "I" (intermediate sensitivity). Only after repeated exposure to a given antibiotic does complete resistance occur, which is indicated on the antibiogram by "R" (resistant). It is estimated that by 2050, there will be very high levels of bacterial resistance to antibiotics [1]. It is also important to note that certain classes of antibiotics are synthesized by humans and cannot be found in nature. In contrast, certain groups of antibiotics are synthesized by other microorganisms, or rather, can be found in nature. Even when used appropriately, antibiotics can cause severe adverse effects if side effects are not promptly managed. This introduces an important ethical dimension, as well as the responsibility of the clinician who prescribes the antibiotic [2].

This literature review aims to present the latest scientific evidence on the misuse and inadequate use of antibiotics, the development of superbugs associated with their overuse, the global aspects of antimicrobial resistance, and preventive strategies, with particular emphasis on the role of vitamins in maintaining immune function. The purpose of the paper is to contribute to better protection of vulnerable populations, the advancement of rational antibiotic use, and the more efficient functioning of healthcare systems.

Significance of Antimicrobial Resistance (AMR)

Antimicrobial resistance (AMR) represents one of the most significant challenges of modern medicine and public health, with potentially catastrophic consequences on a global scale [1–3]. According to the latest estimates, if the current trend of increasing resistance continues, by 2050 AMR could cause up to 10 million deaths annually, accompanied by a 2–3.5% reduction in the global gross domestic product [1]. In 2019, the World Health Organization ranked AMR among the ten greatest threats to public health, while in 2022, European Union institutions recognized this issue as one of the three priority health threats [2,3]. Particularly concerning is the fact that about 70% of infections caused by antibiotic-resistant bacteria occur in healthcare facilities, with an increase in their incidence observed among almost all major pathogenic strains [3].

METOD

Pretraga literature sprovedena je u bazama MEDLINE i PubMed korišćenjem kombinacije ključnih reči na engleskom jeziku, vezanih za antibiotike, antimikrobnu rezistenciju, prevenciju, racionalnu upotrebu i mikrobiotu. U obzir su uzeti radovi objavljeni u periodu od 2010. do 2024. godine. Uključena su originalna istraživanja, sistematski i narativni pregledi, kliničke studije i relevantni izveštaji međunarodnih zdravstvenih organizacija. Isključeni su radovi bez naučne metodologije i oni koji nisu pružali empirijske podatke o prevalenciji i posledicama neadekvatne upotrebe antibiotika. Analiza je sprovedena kvalitativnim pristupom, a nalazi su grupisani u tematske celine koje obuhvataju ključne aspekte problema i mogućnosti prevencije.

Pregled članka zasnivao se na kvalitativnoj analizi sadržaja radova i empirijskih podataka, a potom i komparativnoj interpretaciji nalaza iz istraživanja. Dobijeni rezultati istraživanja su potom tematski kategorisani u četiri teme (Slika 1): zloupotreba i neadekvatna upotreba antibiotika [3–18], razvoj superbakterija povezan sa prekomernom upotrebom antibiotika [18–29], globalni aspekti antimikrobne rezistencija [30–33], i strategije prevencije prekomerne upotrebe antibiotika [34–39].

Zloupotreba i neadekvatna upotreba antibiotika

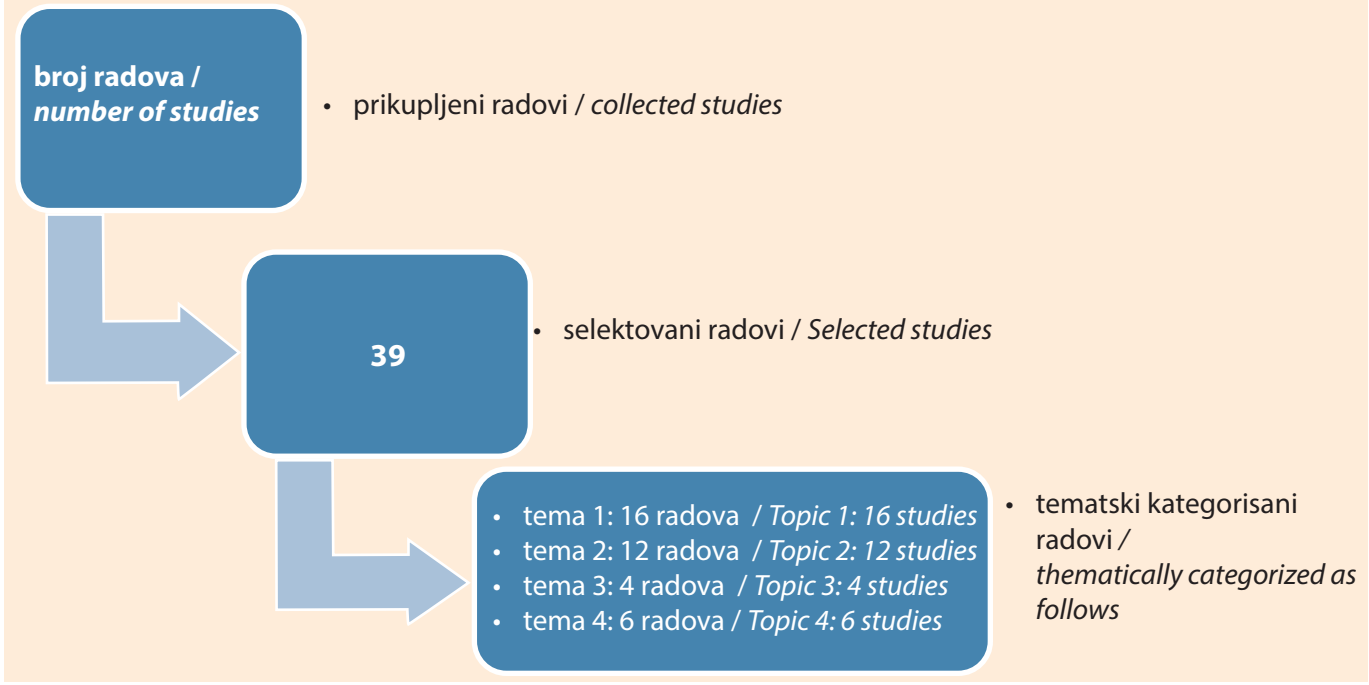
Glavni uzrok trenutne globalne krize jeste prekomerna upotreba i zloupotreba antimikrobnih sredstava, kao što je ranije pomenuto. Značajno je da brojne studije

This situation requires intensifying infection control measures, increasing awareness among the public and healthcare professionals, and strengthening research activities aimed at finding new therapeutic solutions.

METHOD

The literature search was conducted in the MEDLINE and PubMed–databases using a combination of English-language keywords related to antibiotics, antimicrobial resistance, prevention, rational use, and microbiota. The review included studies published between 2010 and 2024. Original research articles, systematic and narrative reviews, clinical studies, and relevant reports from international health organizations were included. Studies without scientific methodology and those that did not provide empirical data on the prevalence and consequences of inappropriate antibiotic use were excluded. The analysis was conducted using a qualitative approach, and the findings were grouped into thematic units covering key aspects of the problem and prevention opportunities.

The review was based on a qualitative analysis of the content of the studies and empirical data, followed by a comparative interpretation of the research findings. The obtained results were then thematically categorized into four topics (Figure 1): misuse and inadequate use of antibiotics [3–18], the development of superbugs associated with the overuse of antibiotics [18–29], global aspects of antimicrobial resistance [30–33], and strategies for preventing antibiotics overuse [34–39].



Slika 1. Proces urađenog pregleda literature o samoupotrebi i zloupotrebi antibiotika za period

Figure 1. Process of the literature review on self-medication and misuse of antibiotics for the period

predviđaju da godišnje na globalnom nivou ima 10 miliona smrtnih slučajeva uzrokovanih infekcijom rezistentnih bakterijskih sojeva. Stoga treba uzeti u obzir činjenicu da većina rezistentnih antibakterijskih sredstava predstavlja problem javnog zdravlja koji zahteva multidisciplinarni pristup i hitnu implementaciju globalnih mera javnog zdravlja [3]. Sve alarmantnija briga za javno zdravlje su bakterije koje su već rezistentne na skoro 99% antibiotika, što je dokumentovano u originalnom istraživanju sprovedenom na Institutu za plućne bolesti Vojvodine, Sremska Kamenica, Srbija [4]. Ova studija pokazuje da je bakterija *Clostridium difficile* do sada bila osetljiva samo na tri antibiotika: vankomicin, teikoplanin i metronidazol. Međutim, tokom vremena bakterija je razvila otpornost na ove agense. Za rešavanje teških bolesti koje su posledica komplikacija *C. difficile*, uvođenje novog makrolidnog antibiotika, fidaksomicina, može ponuditi i terapeutske i profilaktičke koristi. Njegova upotreba može pomoći u sprečavanju recidiva i smanjiti rizik od progresije bolesti povezane sa ovom infekcijom [4]. U randomizovanoj studiji sprovedenoj između 2017. i 2019. godine, u kojoj su kliničari i roditelji dece uzrasta od jedne do pet godina, koja su primila tretman, učestvovali u obrazovnoj intervenciji. Studija je naglasila ključnu ulogu obrazovanja u poboljšanju ishoda lečenja. Otkriveno je da je jedan od glavnih doprinosa neuspešnom lečenju i neodgovarajućem propisivanju antibiotika bila neadekvatna komunikacija između kliničara, roditelja i pacijenata. Unapređena komunikacija dovela je do poboljšanog uspeha lečenja i informisanije upotrebe lekova [5]. U prospektivnim jednostruko slepim kliničkim studijama sprovedenim širom Sjedinjenih Američkih Država, izvučeno je nekoliko važnih zaključaka. Jedan ključni nalaz je istakao da su mnogi kliničari propisali antibiotike isključivo na osnovu kliničke prezentacije. Iako takva odluka može, u određenim slučajevima, biti medicinski i etički opravdana, oslanjanje samo na kliničku procenu – kada postane rutina i zaobilazi mikrobiološku i laboratorijsku potvrdu – predstavlja dvostruku pretnju javnom zdravlju. Prvo, ova praksa može dovesti do neefikasnog lečenja, jer klinička slika može biti tačna ali ne kazuje da li taj antibiotik deluje na datu kultivisanu bakteriju, zbog čega su neophodne pomenute validacije. Drugi javnozdravstveni problem sa ovim načinom lečenja pacijenta je globalan, jer se ogleda u činjenici da pacijent, osim patološkog uzroka koji nije adekvatno tretiran antibioticima, ostaje organizam domaćina, dok je raznovrsna fiziološka mikrobiota značajno poremećena, čime se povećava tendencija razvoja mikrobiote, otpornost na dati lek [6]. Dvostruko slepa, randomizovana studija sprovedena tokom 6 meseci u 2019. godini pokazala je značajne rezultate

Misuse and inadequate use of antibiotics

The main cause of the current global crisis is the excessive use and misuse of antimicrobial agents, as previously mentioned. Significantly, numerous studies forecast that infections from resistant bacterial strains cause 10 million annual deaths worldwide. Therefore, it should be taken into account that most resistant antibacterial agents represent a public health issue that requires a multidisciplinary approach and the urgent implementation of global public health measures [3]. An increasingly alarming public health concern is bacteria that are already resistant to almost 99% of antibiotics, as documented in original research conducted at the Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia [4]. This study shows the bacterium *Clostridium difficile* has so far been sensitive to only three antibiotics: vancomycin, teicoplanin, and metronidazole. However, over time, the bacterium has also demonstrated evolving resistance to these agents. To address severe diseases resulting from *C. difficile* complications, the introduction of a novel macrolide antibiotic, fidaxomicin, may offer both therapeutic and prophylactic benefits. Its use may help prevent recurrence and reduce the risk of disease progression associated with this infection [4]. A randomized study conducted between 2017 and 2019, involving clinicians and parents of children aged one to five years who had received treatment, included an educational intervention. The study emphasized the critical role of education in improving treatment outcomes. It revealed that one of the main contributors to unsuccessful treatment and inappropriate antibiotic prescribing was inadequate communication between clinicians, parents, and patients. Improved communication led to greater treatment success and more informed use of medications. [5]. In prospective single-blind clinical studies conducted across the United States of America, several important conclusions were drawn. One key finding highlighted that many clinicians prescribed antibiotics solely based on the clinical presentation. While such decisions may, in certain cases, be medically and ethically justified, reliance on clinical judgment alone -when it becomes routine and bypasses microbiological and laboratory confirmation-poses a dual threat to public health. First, this practice may lead to ineffective treatment, as the clinical presentation may be accurate but does not necessarily indicate whether the given antibiotic is effective against the cultured bacterium, which is why laboratory validations are necessary. The other public health problem with this way of treating the patient is global, as it is reflected in the fact that the patient, apart from the pathological cause that has not been treated adequately with antibiotics, remains the host organism, while a colorful physiological microbiota is significantly disturbed, thereby in-

kada se upoređuje indiferentna supstanca sa lekom iz grupe derivata penicilina. Strogi statistički pokazatelji ukazali su da nije bilo značajnih razlika između ove dve grupe subjekata koji su primili ove supstance nakon operacije. Ovde je veoma važno javno zdravlje koje pokazuje kako nepotvrđena laboratorijska upotreba antibiotika preti na globalnom nivou zbog sve veće pojave rezistencije, kako u derivatima penicilina, tako i u drugim grupama lekova [7]. Randomizovano kontrolisano ispitivanje sprovedeno u Hong Kongu imalo je za cilj da istraži vršnjačko obrazovanje putem društvenih mreža, pokazujući i potvrđujući da je edukacija ključ za sprečavanje razvoja bakterijske rezistencije na antibiotike [8]. Druga randomizovana i dvostruko slepa studija pokazala je važnost komunikacije između lekara i roditelja. S obzirom da je ova komunikacija ključna, posebno ako su pacijenti deca, pravilna heteroanamneza značajno smanjuje prekomernu i neopravdanu upotrebu antibiotika kod dece sa čestim respiratornim infekcijama gde bakterijsko učešće nije potvrđeno kulturama ili antibiogramima [9]. Randomizovana, dvostruko slepa studija sprovedena u osam američkih gradova, kako u ambulantnim uslovima, tako i u hitnim medicinskim centrima, istraživala je decu lečenu od nekomplikovane upale pluća. Ova studija je obuhvatila dve grupe subjekata, od kojih je jedna primila placebo (supstancu bez terapijskog dejstva) i pokazala je veoma značajan rezultat, što ukazuje na statistički značajne razlike između dece koja su lečena od upale pluća pet dana i onih koja su lečena deset dana. Ovo istraživanje je od velikog značaja za javno zdravlje iz preventivne perspektive, jer pokazuje koliko antibiotika se zapravo nepotrebno propisuje za ovu vrstu infekcije, čime se nanosi šteta mikrobioti subjekata i doprinosi globalnom razvoju multi-rezistentnih bakterijskih sojeva [10]. Statistički značajne razlike su primećene kod pacijenata koji su profilaktički primali ceftriakson u poređenju sa onima koji su hospitalizovani zbog pogoršanja bolesti jetre koji su primali placebo. Nije bilo razlike u učestalosti recidiva, infekcija, stope smrtnosti ili brojnih laboratorijskih parametara. Ceftriakson je moćan cefalosporin treće generacije. Iz ove studije možemo zaključiti da se rezistencija može razviti čak i na tako jake antibiotike ako se ne koriste na odgovarajući način [11]. Međutim, određene studije pokazuju sve veći broj pacijenata koji zloupotrebljavaju lekove i preparate za akutnu upalu grla i traže alternativne metode da se izleče bez stručnog saveta [12]. U meta-analizi sprovedenoj u cilju analize podataka u svrhu racionalne antibiotske profilakse kod stomatoloških pacijenata, dobijeni su poražavajući rezultati, što ukazuje na to da je na svakih 19 funkcionalno zdravih subjekata samo jedna osoba zaštićena od potencijalne

creasing the tendency of the microbiota to develop resistance to the given drug [6]. A double-blind, randomized study conducted over 6 months in 2019 showed significant results when comparing an inert substance to a drug from the penicillin derivatives group. Strict statistical indicators showed no significant differences between the two groups of subjects who received these substances after surgery. Here, public health concerns are paramount, as unconfirmed laboratory use of antibiotics poses a global threat due to the increasing prevalence of resistance, both in penicillin derivatives and in other groups of drugs [7]. A randomized controlled trial conducted in Hong Kong aimed to explore peer education through social networks, showing and confirming that education is the key to preventing the development of bacterial resistance to antibiotics [8]. Another randomized, double-blind study underscored the importance of communication between physicians and parents. Given that this communication is crucial, especially if the patients are children, proper heteroanamnesis significantly reduces the excessive and unwarranted use of antibiotics in children with frequent respiratory infections where bacterial involvement has not been confirmed by cultures or antibiograms [9]. A randomized, double-blind study conducted in eight U.S. cities, both in outpatient settings and in emergency care settings, investigated children treated for uncomplicated pneumonia. This study included two groups of subjects, one of which received a placebo (an inactive substance), and revealed highly significant results, showing statistically meaningful differences between children treated for pneumonia for five days and those treated for ten days. This research is of great importance to public health from a preventive perspective, as it highlights how many antibiotics are actually unnecessarily prescribed for this type of infection, thereby harming the subjects' microbiota and contributing to the global development of multi-resistant bacterial strains [10]. Statistically significant differences were observed among patients who received ceftriaxone prophylactically compared to those hospitalized for liver disease deterioration who received a placebo. No differences were noted in recurrence, infection rates, mortality, or numerous laboratory parameters. Ceftriaxone is a potent third-generation cephalosporin. From this study, we can conclude that resistance can develop even to such strong antibiotics if not used appropriately [11]. However, certain studies report an increasing number of patients misusing medications and preparations for acute pharyngitis, seeking alternative treatments without expert advice [12]. A meta-analysis aimed at evaluating data on rational antibiotic prophylaxis in dental patients yielded alarming results, showing that out of every 19 functionally healthy subjects, only one person is protected from potential in-

infekcije profilaktičkom upotrebom antibiotika. Ovo je alarmantan problem u stomatologiji, jer studija pokazuje da je 18 ljudi ostalo zdravo ali sa sigurno oštećenom mikrobiotom [13]. U indijskoj populaciji, između 5% i preko 30% pojedinaca koristi antibiotike bez lekarskih konsultacija, sa najvećom prevalencijom među korisnicima stomatoloških usluga. Ovo naglašava značajnu ulogu stomatologa i drugih zdravstvenih radnika u propisivanju antibiotika. Međutim, široko rasprostranjeno samoinicijativno uzimanje lekova u zemlji sa populacijom većom od 1 milijarde predstavlja kritičan izazov za kontrolu rezistencije na antibiotike [14]. Samoinicijativna upotreba antibiotika veliki je globalni problem javnog zdravlja, posebno u lečenju dece. Ovaj fenomen varira u zavisnosti od kulturnih, ekonomskih i društvenih faktora. Najčešći razlozi uključuju kupovinu antibiotika bez medicinskog nadzora i upotrebu ostataka lekova iz prethodnih recepata kada se simptomi ponove. Takve prakse pogoršavaju zloupotrebu antibiotika i razvoj rezistencije [15]. Samoinicijativna upotreba antibiotika je veoma česta praksa u Etiopiji. Ova meta-analitička studija naglašava potrebu za ciljanom edukacijom usmerenom na različite ciljne grupe. Takva edukacija prvo treba da se bavi osnovnim znanjem o antibioticima, opasnostima samoinicijativnog lečenja i opasnostima od neadekvatne primene [16]. Određene studije identifikuju apoteke kao primarne izvore antibiotika za samolečenje. Ovo dodaje novu dimenziju krizi javnog zdravlja, jer neki farmaceuti izdaju antibiotike bez receptaa. Iako farmaceuti mogu pružiti informacije o antibioticima, to je nedovoljno bez sveobuhvatne medicinske procene od strane lekara. Pravilan izbor antibiotika zahteva kliničku procenu, analizu bakterijske kulture i druge relevantne dijagnostičke parametre [17]. Štaviše, određene studije pokazuju neopravdano davanje antibiotika deci. Ne samo da ovi tretmani ne olakšavaju oporavak, već doprinose i razvoju rezistencije na primenjene antibiotike, čime se pogoršava širi problem antimikrobne rezistencije [18].

Razvoj superbakterija povezan sa prekomernom upotrebom antibiotika

Da bi se smanjili negativni efekti antibiotika, sve više se istražuju alternativni pristupi, poput probiotika i prebiotika. Autor studije Duan i saradnici su pokazali da suplementacija ovim preparatima može ubrzati oporavak mikrobiote, čime se smanjuje rizik od posledica kao što je disbioza (neravnotežu u sastavu mikrobiote) [18]. Prekomerna upotreba antibiotika postala je značajan globalni problem sa dalekosežnim posledicama po ljudsko zdravlje. Jedan od najvažnijih aspekata ovog problema je poremećaj crevne mikrobiote, koja igra ključnu ulogu u održavanju imunološke funkcije, metabolizma i ho-

fection through prophylactic antibiotic use. This is an alarming problem in dentistry, as the study indicates that while 18 individuals remained healthy, their microbiota was likely harmed [13]. In the Indian population, between 5% and over 30% of individuals use antibiotics without medical consultation, with the highest prevalence among dental care users. This highlights the significant role of dentists and other healthcare professionals in antibiotic prescription. However, the widespread self-medication in a country with a population exceeding 1 billion poses a critical challenge for controlling antibiotic resistance [14]. Self-medication with antibiotics is also a major global public health issue, particularly in pediatric treatment. This phenomenon varies according to cultural, economic, and social factors. The most common reasons include purchasing antibiotics without medical oversight and using leftover medications from prior prescriptions when symptoms recur. These practices exacerbate the misuse of antibiotics and resistance development [15]. Self-initiated use of antibiotics is a widespread practice in Ethiopia. This meta-analytical study highlights the need for targeted education directed at various population groups. Such education should first address basic knowledge about antibiotics, the dangers of self-initiated treatment, and the dangers of inadequate application [16]. Certain studies identify pharmacies as the primary sources of antibiotics for self-medication. This adds a new dimension to the public health crisis, as some pharmacists dispense antibiotics without requiring prescriptions. While pharmacists may provide information about antibiotics, this is insufficient without a comprehensive medical evaluation by a physician. Proper antibiotic selection requires clinical assessment, bacterial culture analysis, and other relevant diagnostic parameters [17]. Furthermore, certain studies show the unjustified administration of antibiotics to children. Not only do these treatments fail to facilitate recovery, but they also contribute to the development of resistance to the administered antibiotics, thereby exacerbating the broader problem of antimicrobial resistance [18].

Development of superbugs associated with the overuse of antibiotics

To reduce the negative effects of antibiotics, alternatives such as probiotics and prebiotics are increasingly being researched. Duan et al. demonstrated that supplementation with these agents can accelerate the recovery of the microbiota, thereby reducing the risk of consequences such as dysbiosis (an imbalance in the composition of microbiota) [18]. The overuse of antibiotics has become a significant global problem with far-reaching consequences for human health. One of the most important aspects of this problem is the disruption of the intesti-

meostaze organizma. Dok antibiotici efikasno eliminišu patogene, njihova neselektivna akcija uništava komensalne bakterije, narušava delikatnu ravnotežu crevne mikrobiote i izaziva potencijalne zdravstvene komplikacije. Istraživanja pokazuju da antibiotska terapija može izazvati značajno smanjenje raznolikosti crevne mikrobiote, što rezultira smanjenom otpornošću na kolonizaciju patogenim mikroorganizmima. Autor Palleja i saradnici su u studiji dokumentovali da, kod odraslih, može potrajati nekoliko meseci da se mikrobiota oporavi nakon antibiotika, a određene bakterijske vrste mogu trajno nestati [19]. Slične nalaze pružaju u svojoj studiji autor Schwartz i saradnici, naglašavajući da poremećaji mikrobiote izazvani antibioticima imaju dugoročne posledice, uključujući povećanu osetljivost na infekcije i upalne procese [20]. Pored akutnih poremećaja, dugoročne posledice uključuju razvoj metaboličkih poremećaja, alergija i autoimunih bolesti. Konstantinidis i saradnici u svom istraživanju su naglasili da antibiotici mogu promijeniti metabolizam kratkolančanih masnih kiselina, koje su ključne za zdravlje crevne sluznice, čime se povećava rizik od inflamatornih bolesti creva [21]. Takođe, lu i saradnici su pokazali u svom istraživanju da disbioza može narušiti integritet crevne barijere, omogućavajući toksinima i bakterijama da uđu u krvotok, što dovodi do sistemske upale [22]. Kod dece, čija se crevna mikrobiota još uvek razvija, antibiotici mogu izazvati trajne promene. McDonnell i autori su u svojoj studiji identifikovali korelaciju između ranog izlaganja antibioticima i povećanog rizika od astme i alergija [23]. Slično tome, istraživanje Patrick i saradnika pokazalo je da je smanjena raznolikost mikrobiota kod dece povezana sa imunološkom disregulacijom [24]. Prekomerna upotreba antibiotika ima značajne štetne efekte na crevnu mikrobiotu i opšte zdravlje. Neophodno je usmeriti napore na racionalizaciju njihove primene, edukaciju stanovništva i promociju upotrebe zaštitnih preparata, kao što su probiotici, kako bi se očuvala ravnoteža mikrobiote i smanjile dugoročne zdravstvene komplikacije. Rešavanje rezistencije na antibiotike zahteva multidisciplinarni pristup, uključujući obrazovanje, razvoj zdravstvenih politika i unapređenje dijagnostičkih metoda. Ključna komponenta prevencije je edukacija zdravstvenih radnika i pacijenata. Studije su pokazale da programi obuke za zdravstvene radnike, zasnovani na principima racionalne upotrebe antibiotika, značajno smanjuju nepravilno propisivanje. Dodatna briga i jedan od najvećih kliničkih izazova širom sveta je porast multirezistentnih infekcija (MDR), sa posebnim naglaskom na MDR tuberkulozu, koja pogađa oko 500.000 novih pacijenata godišnje. Najveće stope MDR-TB zabeležene su u Evropi, dok 87% novih slučajeva dolazi iz 30 zemalja Azije, Afrike i Latinske Amerike. Pored toga, patogeni iz grupe ESKAPE

nal microbiota, which plays a key role in maintaining the immune function, metabolism, and homeostasis of the organism. While antibiotics effectively eliminate pathogens, their indiscriminate action destroys commensal bacteria, disrupting the delicate balance of gut microbiota and causing potential health complications. Research shows that antibiotic therapy can cause a significant reduction in the diversity of intestinal microbiota, resulting in decreased resistance to colonization by pathogenic microorganisms. Palleja et al. documented in their study that, in adults, it may take several months for the microbiota to recover after antibiotics, and certain bacterial species may disappear permanently [19]. Similar findings were reported by Schwartz et al., emphasizing that antibiotic-induced disturbances of the microbiota have long-term consequences, including increased susceptibility to infections and inflammatory processes [20]. In addition to acute disorders, long-term consequences include the development of metabolic disorders, allergies, and autoimmune diseases. Konstantinidis et al. highlighted in their study that antibiotics can alter the metabolism of short-chain fatty acids, which are crucial for the health of the intestinal mucosa, thereby increasing the risk of inflammatory bowel diseases [21]. Also, Lu et al. showed that dysbiosis can impair the integrity of the intestinal barrier, allowing toxins and bacteria to enter the bloodstream, leading to systemic inflammation [22]. In children, whose gut microbiota is still developing, antibiotics can cause permanent changes. McDonnell et al. identified a correlation between early exposure to antibiotics and an increased risk of asthma and allergies [23]. Similarly, research by Patrick et al. demonstrated that reduced microbiota diversity in children is associated with immune dysregulation [24]. The excessive use of antibiotics has significant detrimental effects on gut microbiota and general health. Efforts must be directed towards rationalizing their use, educating the population, and promoting protective interventions, such as probiotics, to preserve the balance of microbiota and reduce long-term health complications. Addressing antibiotic resistance requires a multidisciplinary approach, including education, the development of health policies, and the improvement of diagnostic methods. A key component of prevention is the education of healthcare workers and patients. Studies have shown that training programs for healthcare workers on principles of rational antibiotic use significantly reduce improper prescribing. An additional concern and one of the biggest clinical challenges worldwide is the rise of multidrug-resistant infections (MDR), with a special emphasis on MDR tuberculosis, which affects about 500,000 new patients annually. The highest rates of MDR-TB are recorded in Europe, while 87% of new cases come from 30 countries in Asia,

(*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* i *Enterobacter* vrste) značajno doprinose globalnom teretu rezistencije na antibiotike [25]. Edukacija pacijenata o rizicima povezanim sa samopropisanom upotrebom antibiotika i njihovom neadekvatnom upotrebom može imati dugoročni uticaj na smanjenje rezistencije [26]. Uvođenje naprednih dijagnostičkih alata, kao što su brzi testovi za identifikaciju bakterijskih infekcija i određivanje osetljivosti na antibiotike, može doprineti preciznijem propisivanju lekova i smanjenju nepotrebne primene [27]. Pored toga, globalne inicijative, kao što su regulacija dostupnosti antibiotika bez recepta, kontrolisana distribucija i razvoj novih antimikrobnih lekova, od suštinskog su značaja za borbu protiv ovog sve ozbiljnog problema javnog zdravlja [28]. Preventivne mere, kao što su vakcinacija i poboljšana higijena, takođe mogu doprineti smanjenju potrebe za antibioticima i sprečavanju razvoja rezistencije. Konačno, u razmatranju antimikrobne rezistencije (AMR) važno je prepoznati da ona predstavlja složen i hitan globalni izazov, dodatno pogoršan promenama koje je izazvala pandemija COVID-19. Pored kliničkih okruženja, faktori životne sredine kao što su nekontrolisano ispuštanje otpada, agrohemijska upotreba i migracija divljih životinja takođe doprinose širenju AMR-a, što naglašava potrebu za integrisanim pristupom rešavanju ovog problema [29].

Antimikrobna rezistencija: globalna zdravstvena kriza

Mikroorganizmi, uključujući različite bakterijske populacije u gastrointenstinalnom traktu čoveka, igraju ključnu ulogu u održavanju opšteg zdravlja. Kada se antibiotici prekomerno koriste, oni uništavaju ne samo patogene bakterije, već i korisne mikroorganizme, stvarajući uslove za razvoj "superbakterija" – bakterija koje su otporne na više antibiotika. Ove bakterije mogu izazvati teže infekcije koje je znatno teže izlečiti, čime se ugrožava zdravlje pacijenata. Antimikrobna rezistencija postala je globalna zdravstvena kriza pojavom bakterija rezistentnih na više lekova koje se ne mogu lečiti standardnim antibioticima. Na primer, novi sojevi *Neisseria gonorrhoeae* otporni na karbapeneme treće generacije izazvali su neizlečive infekcije gonoreje u Velikoj Britaniji. Iako su uložena značajna sredstva, razvoj novih antibiotika koji mogu prevazići ovu otpornost napreduje presporo [30]. Studije su pokazale da su pacijenti koji su preterano koristili antibiotike podložniji infekcijama izazvanim sojevima rezistentnim na više lekova, kao što je *Clostridioides difficile* (*C. difficile*), koji je obično prisutan u bolnicama, ali postaje smrtonosna pretnja u okruženju disbioze izazvane antibioticima. Upotreba antibiotika može imati nekoliko negativnih

Africa, and Latin America. Additionally, pathogens from the ESKAPE group (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa,* and *Enterobacter* species) contribute significantly to the global burden of antibiotic resistance [25]. Educating patients about the risks associated with self-prescribed antibiotic use and their inadequate use can have a long-term impact on reducing resistance [26]. The introduction of advanced diagnostic tools, such as rapid tests for the identification of bacterial infections and determination of sensitivity to antibiotics, can contribute to more accurate prescribing of drugs and reduction of unnecessary administration [27]. In addition, global initiatives, such as regulation of over-the-counter antibiotic availability, controlled distribution, and development of new antimicrobial drugs, are essential to combat this increasingly serious public health problem [28]. Preventive measures, such as vaccination and improved hygiene, can also contribute to reducing the need for antibiotics and preventing the development of resistance. Finally, in considering antimicrobial resistance (AMR), it is important to recognize that it represents a complex and urgent global challenge, further exacerbated by the changes brought about by the COVID-19 pandemic. In addition to clinical settings, environmental factors such as uncontrolled waste discharge, agrochemical use, and wildlife migration also contribute to the spread of AMR, which highlights the need for an integrated approach to addressing this problem [29].

Antimicrobial resistance: A global health crisis

Microorganisms, including the diverse bacterial populations within the human gut, play a key role in maintaining overall health. When antibiotics are overused, they destroy not only pathogenic bacteria but also beneficial microorganisms, creating conditions for the development of "superbugs" - bacteria that are resistant to multiple antibiotics. These bacteria can cause more severe infections that are much more difficult to treat, thereby endangering patient outcomes. Antimicrobial resistance has become a global health crisis with the emergence of multidrug-resistant bacteria that cannot be treated with standard antibiotics. For example, new strains of *Neisseria gonorrhoeae* resistant to third-generation carbapenems have caused untreatable gonorrhea infections in the United Kingdom. Although considerable resources have been invested, the development of new antibiotics that can overcome this resistance is progressing too slowly [30]. Studies have shown that patients who have overused antibiotics are more susceptible to infections caused by multidrug-resistant strains, such as *Clostridioides difficile* (*C. difficile*), which is commonly present in hospitals but becomes a deadly

efekata na crevnu mikrobiotu, uključujući smanjenu raznolikost vrsta, izmenjenu metaboličku aktivnost i selekciju organizama otpornih na antibiotike, što zauzvrat može dovesti do dijareje povezane sa antibioticima i rekurentnih infekcija *Clostridioides difficile*. Rano izlaganje antibioticima tokom detinjstva takođe je povezano sa gastrointestinalnim poremećajima, imunološkom disregulacijom i neurokognitivnim oštećenjima. Rastući trend potrošnje antibiotika u poslednjih nekoliko godina sugeriše da će se ovi izazovi verovatno intenzivirati u budućnosti [31]. Novi antibiotici su ključni za borbu protiv društvenih izazova koje predstavlja *Staphylococcus aureus* (MRSA) rezistentna na meticilin, gram-pozitivna bakterija odgovorna za ozbiljne infekcije širom sveta. Studija grupe istraživača iz Amerike i Egipta otkrila je novi derivat tetracena - Mersahinone, izolovan iz kulture morskog aktinomiceta *Streptomyces* sp. EG1, pronađenog u sedimentima severne obale Sredozemnog mora u Egiptu. Ovi nalazi potvrđuju potencijal morskih aktinomiceta kao izvora novih bioaktivnih jedinjenja, posebno u relativno neistraženim područjima kao što je Sredozemno more. Buduće studije mogu dodatno iskoristiti biodiverzitet ovog regiona za razvoj obećavajućih antimikrobnih sredstava [32]. Antimikrobna rezistencija, posebno kod bakterija, predstavlja jedan od najvažnijih izazova savremene medicine. Uprkos hitnoj potrebi za novim antibioticima, napredak u njihovom razvoju je spor, dok otpornost na postojeće lekove nastavlja da raste. Potrebna su značajna ulaganja u istraživanje i razvoj kako bi se što pre pronašle efikasne strategije za borbu protiv ove globalne pretnje javnom zdravlju. Važno je napomenuti da je razvoj bakterija otpornih na antibiotike globalni problem koji zahteva koordinirane napore u kontroli upotrebe antibiotika, kao i u istraživanju novih terapijskih opcija i strategija, ne samo za pojedinca, već i za životnu sredinu u celini [33]. Edukacija zdravstvenih radnika i pacijenata o pravilnoj upotrebi antibiotika je od ključnog značaja za smanjenje rizika od razvoja rezistentnih sojeva i očuvanje efikasnosti postojećih terapija. Prekomerna i nepotrebna upotreba antibiotika ima značajan uticaj na mikrobiotu ljudskog organizma i doprinosi razvoju superbakterija. Ove bakterije predstavljaju ozbiljan izazov za javno zdravlje i neophodno je preduzeti odgovarajuće mere za kontrolu njihove pojave i širenja [30,33].

Strategije prevencije prekomerne upotrebe antibiotika

Antimikrobna rezistencija predstavlja kritičan globalni izazov javnog zdravlja. Aktuelne preventivne zdravstvene strategije su sve više usredsređene na strogu regulaciju prakse propisivanja antibiotika, ne samo među lekarima, već i u stomatološkoj praksi [25,26]. Štaviše, primena

threat in the setting of antibiotic-induced dysbiosis. Antibiotic use can have several adverse effects on the gut microbiota, including reduced species diversity, altered metabolic activity, and selection of antibiotic-resistant organisms, which in turn can lead to antibiotic-associated diarrhea and recurrent *Clostridioides difficile* infections. Early exposure to antibiotics during childhood has also been linked to gastrointestinal disorders, immune dysregulation, and neurocognitive impairments. The increasing trend in antibiotic consumption in recent years suggests that these challenges will likely intensify in the future [31]. New antibiotics are key to combating the societal challenges posed by methicillin-resistant *Staphylococcus aureus* (MRSA), a gram-positive bacterium responsible for severe infections worldwide. A study by a group of researchers from America and Egypt discovered a new tetracene derivative, Mersahinone, isolated from a culture of the marine actinomycete *Streptomyces* sp. EG1, found in the sediments of the northern coast of the Mediterranean Sea in Egypt. These findings confirm the potential of marine actinomycetes as a source of new bioactive compounds, especially in relatively unexplored areas such as the Mediterranean Sea. Future studies may further exploit the biodiversity of this region to develop promising antimicrobial agents [32]. Antimicrobial resistance, especially in bacteria, represents one of the most important challenges of modern medicine. Despite the urgent need for new antibiotics, progress in their development is slow, while resistance to existing drugs continues to increase. Significant investment in research and development is needed to find effective strategies to combat this global threat to public health as soon as possible. It is important to note that the development of antibiotic-resistant bacteria is a global problem that requires coordinated efforts in controlling the use of antibiotics, as well as in the research of new therapeutic options and strategies, not only for the individual but also for the environment as a whole [33]. Educating healthcare workers and patients about the proper use of antibiotics is crucial to reducing the risk of developing resistant strains and preserving the efficacy of existing therapies. Excessive and unnecessary use of antibiotics has a significant impact on the microbiota of the human body and contributes to the development of superbugs. These bacteria represent a serious challenge to public health, and it is necessary to take appropriate measures to control their occurrence and spread [30,33].

Strategies for Preventing the Overuse of Antibiotics

Antimicrobial resistance represents a critical global public health challenge. Current preventive health strategies are increasingly focused on strict regulation

strožih zakonskih mera za suzbijanje neovlašćene prodaje i kupovine antibiotika mogla bi značajno smanjiti zloupotrebu antimikrobnih sredstava i napredovanje bakterijske rezistencije [25,26]. Kampanje javnog zdravlja igraju vitalnu ulogu u smanjenju osetljivosti na infekciju različitim bakterijskim sojevima [33]. Ove inicijative, uz promociju pravilne higijene ruku i tela, podstiču zdrave životne prakse kao što su uravnotežena ishrana i adekvatan unos esencijalnih mikronutrijenata [34–38].

Poseban naglasak treba staviti na antioksidativne vitamine, uključujući retinol, tokoferol i L-askorbinsku kiselinu, koji bi mogli smanjiti potrebu za antibioticima, posebno uz doprinos vitamina D, za koji se zna da stimuliše imuni sistem. Vitamini su biološki esencijalna organska jedinjenja široko klasifikovana u dve glavne grupe: vitamini rastvorljivi u mastima i vitamini rastvorljivi u vodi. Oni igraju ključnu ulogu u rastu, razvoju i ukupnoj psihološkoj funkciji organizma. Primarna funkcija određenih vitamina je njihova antioksidativna aktivnost, koja pomaže u sprečavanju endogene supresije imunih odgovora [34]. Vitamin A je snažan antioksidans koji štiti ćelijske membrane od oštećenja uzrokovanih slobodnim radikalima i sprečava međustanična oštećenja. Zbog svoje sposobnosti vezivanja proteina, vitamin A ostaje aktivan u citoplazmi, gde ovi povezani proteini olakšavaju njegov antioksidativni efekat čak i u vodenoj sredini [35]. Još jedan antioksidant rastvorljiv u mastima, poznat kao "vitamin mladosti", je vitamin E. Ovaj vitamin se integriše u ćelijske membrane, pružajući značajnu zaštitu od oštećenja izazvanih slobodnim radikalima. Značajno smanjuje broj slobodnih radikala koji dolaze u kontakt sa ćelijskim membranama [36]. Među vitaminima rastvorljivim u vodi, vitamin C, u svom aktivnom obliku L-askorbinska kiselina, pokazuje snažnu sposobnost da neutrališe slobodne radikale. Pored toga, igra ključnu ulogu u regeneraciji vitamina A i E nazad u njihove aktivne oblike [37]. Vitamin D, još jedan vitamin rastvorljiv u mastima, jedinstveno poseduje antikancerogena svojstva među vitaminima. Bitno je naglasiti da vitamin D nije antioksidant, međutim, njegov klinički značaj leži u njegovoj sposobnosti da poremeti funkciju membrane određenih malignih ćelija. Vitamin D stupa u interakciju sa receptorima smrti u jezgru ćelija raka, čime se indukuje apoptoza. Pored toga, vitamin D učestvuje u prevenciji citokinskih oluja, pojačava ćelijski imuni odgovor i podržava sazrevanje T-limfocita [38]. Pored toga, važno je naglasiti da, iako su određeni vitamini klasifikovani i regulisani kao lekovi, većina je dostupna u obliku suplemenata. Naime, nedostatak vitamina D povezan je sa značajnom imunološkom disregulacijom, pored prethodno pomenutih efekata [39]. Obogaćivanje određene hrane i pića vitaminima takođe može dovesti do smanjenog imunološkog odgovora na

of antibiotic prescribing practices, not only among physicians but also in dental practice [25,26]. Moreover, the implementation of more stringent legal measures to curb the unauthorized sale and purchase of antibiotics could significantly reduce the misuse of antimicrobial agents and the progression of bacterial resistance [25,26]. Public health campaigns play a vital role in reducing susceptibility to infections caused by various bacterial strains [33]. These initiatives, along with the promotion of proper hand and body hygiene, encourage healthy lifestyle practices such as a balanced diet and adequate intake of essential micronutrients [34–38].

Particular emphasis should be placed on antioxidant vitamins, including retinol, tocopherol, and L-ascorbic acid, which may reduce the need for antibiotics, especially with the contribution of vitamin D, known to stimulate the immune system. Vitamins are biologically essential organic compounds broadly classified into two major groups: fat-soluble and water-soluble vitamins. They play a crucial role in the growth, development, and overall psychological function of the organism. The primary function of certain vitamins is their antioxidant activity, which helps prevent endogenous suppression of immune responses [34]. Vitamin A is a potent antioxidant that protects cellular membranes from damage caused by free radicals and prevents intercellular damage. Due to its protein-binding capacity, vitamin A remains active within the cytoplasm, where these associated proteins facilitate its antioxidant effect even in an aqueous environment [35]. Another fat-soluble antioxidant, known as the "youth vitamin", is vitamin E. This vitamin integrates into the cell membranes, providing substantial protection against free radical-induced damage. It significantly reduces the number of free radicals that come into contact with cellular membranes [36]. Among the water-soluble vitamins, vitamin C, in its active form, L-ascorbic acid, exhibits a powerful capacity to neutralize free radicals. Additionally, it plays a crucial role in regenerating vitamins A and E back to their active forms [37]. Vitamin D, another fat-soluble vitamin, uniquely possesses anti-cancer properties among vitamins. It is essential to highlight that vitamin D is not an antioxidant; however, its clinical significance lies in its ability to disrupt the membrane function of specific malignant cells. Vitamin D interacts with death receptors within the nucleus of cancer cells, thereby inducing apoptosis. Additionally, vitamin D participates in the prevention of cytokine storms, enhances cellular immune responses, and supports the maturation of T-lymphocytes [38]. Additionally, it is essential to emphasize that while specific vitamins are classified and regulated as medicine, the

bakterijske patogene, čime se smanjuje potreba za antibiotskom terapijom. Nova antimikrobna sredstva, kao što je fidaksomicin, član klase makrolida, su od posebnog značaja u lečenju infekcija *Clostridium difficile*. Ovaj patogen reaguje na samo tri antibiotika a otpornost na te agense se povećava. Stoga, uključivanje fidaksomicina u terapijske režime igra ključnu ulogu u lečenju ove infekcije [21]. Sve ove mere sa preventivnim javnozdravstvenim strategijama mogu značajno smanjiti bakterijske infekcije, a samim tim i upotrebu antibiotika.

Preporuke Saveta Evropske unije u borbi protiv antimikrobne rezistencije

Savet Evropske unije je 2023. godine usvojio preporuke za unapređenje borbe protiv antimikrobne rezistencije (AMR), zasnovane na konceptu *One Health*, koji integriše zdravlje ljudi, životinja i životne sredine. Preporuke uključuju izradu ili ažuriranje nacionalnih akcionih planova, jačanje sistema nadzora nad potrošnjom antibiotika i praćenjem rezistencije, unapređenje mera prevencije i kontrole infekcija, te sprovođenje programa racionalne upotrebe antibiotika u svim sektorima.

Posebni ciljevi do 2030. godine obuhvataju smanjenje ukupne potrošnje antibiotika za 20% u odnosu na 2019. godinu, povećanje udela antibiotika iz WHO kategorije „Access" na najmanje 65%, smanjenje učestalosti bakterijskih infekcija rezistentnih na antibiotike, te smanjenje prodaje antimikrobnih sredstava za životinje i akvakulturu za 50%. Preporuke naglašavaju i značaj kontinuirane edukacije zdravstvenih radnika i javnosti, ulaganje u istraživanje i razvoj novih terapijskih pristupa, dijagnostičkih metoda i vakcina, kao i jačanje međunarodne saradnje [40].

ZAKLJUČAK

AMR predstavlja značajan izazov za javno zdravlje, koji svake godine čini više od 35.000 smrtnih slučajeva u Evropskoj uniji i Evropskom ekonomskom prostoru (EU / EEA). Hitnu potrebu za efikasnim merama za borbu protiv AMR-a nameće značajan finansijski pritisak zdravstvenim sistemima. Ekonomske implikacije uključuju veće troškove zbog produženog boravka u bolnici, upotreba skupljih lekova i potreba za dodatnim medicinskim procedurama. Kako stope otpornosti eskaliraju, efikasnost standardnih tretmana opada, komplikuje upravljanje pacijentima i povećava učestalost infekcija otpornih na lečenje. Još mnogo treba uraditi na polju rešavanja AMR-za poboljšanje zdravstvenih ishoda, i za očuvanje održivosti zdravstvenih resursa širom Evrope.

Sukob interesa: Nije prijavljen.

majority are available as supplements. Notably, vitamin D deficiency is associated with significant immune dysregulation, in addition to the previously mentioned effects [39]. Enriching certain foods and beverages with vitamins may also lead to a reduced immune response to bacterial pathogens, thereby lowering the need for antibiotic therapy. New antimicrobial agents, such as fidaxomicin, a member of the macrolide class, are of particular importance in the treatment of *Clostridium difficile* infections. This pathogen responds to only three antibiotics, and resistance to these agents is increasing. Therefore, the inclusion of fidaxomicin in therapeutic regimens plays a key role in treating this infection [21]. All these measures, combined with preventive public health strategies, can significantly reduce bacterial infections and, consequently, the use of antibiotics.

Recommendations of the Council of the European Union on Combating Antimicrobial Resistance

In 2023, the Council of the European Union adopted recommendations to strengthen the fight against antimicrobial resistance (AMR), based on the One Health concept, which integrates human, animal, and environmental health. The recommendations include developing or updating national action plans, strengthening surveillance systems for antibiotic consumption and resistance monitoring, improving infection prevention and control measures, and implementing antibiotic stewardship programs across all sectors.

Specific targets for 2030 include reducing overall antibiotic consumption by 20% compared to 2019, increasing the proportion of antibiotics from the WHO "Access" category to at least 65%, reducing the incidence of antibiotic-resistant bacterial infections, and reducing antimicrobial sales for animals and aquaculture by 50%. The recommendations also emphasize the importance of continuous education for healthcare professionals and the public, investment in research and development of new therapeutic approaches, diagnostic methods, and vaccines, as well as strengthening international cooperation [40].

CONCLUSION

AMR represents a significant public health challenge, causing more than 35,000 deaths annually in the European Union and the European Economic Area (EU/EEA). The urgent need for effective measures to combat AMR is underscored by the significant financial burden it places on healthcare systems. Economic implications include higher costs due to prolonged hospital stays, the use of more expensive medicines, and the need for additional medical procedures. As resistance rates

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escalate, the effectiveness of standard treatments declines, complicating patient management and increasing the incidence of hard-to-treat infections. Much more needs to be done to address AMR to improve health outcomes and to preserve the sustainability of healthcare resources across Europe.

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