

Strategies for Challenging Development in Antimicrobial Resistance

Rasha A. F. Jasim

Department of Clinical Laboratory Sciences, College of Pharmacy, University of Babylon, Iraq

Abstract

Antimicrobial resistance is a growing problem and a threat to public health. It occurs due to germs developing the ability to drub the antimicrobial agents designed to kill them. The danger comes from the quickly spreading of antimicrobial resistance around the world; therefore, it is recognized as a global public health issue by many international health organizations. Consequently, the reduction of this issue requires major and alternative solutions at the same time. Major solutions involve the ideal use of antimicrobial agents, conduction of antimicrobial and drugs surveillance programs, increased awareness for all categories of society, cleanliness and disinfection, restriction of the use of antibiotics in veterinary medicine and agriculture, and investigation or development of new antimicrobial agents. Whereas, an alternative solution occurs via developing new approaches, and return to the use of ancient drug. Hence, this review comes as an effort to make aware all the categories of society about the possible solutions of this problem.

Keywords: Antimicrobial resistance, resistance emergence, solutions

INTRODUCTION

Antimicrobial agents are chemical compounds designed to inhibit the growth of germs, which allow the host defences to eradicate them.^[1] Although the importance of antimicrobial agents as a second defence line in the world especially after discovering penicillin in 1940,^[2,3] the antimicrobial resistance has been developed to be one of the biggest challenges that threat public health. "Antimicrobial resistance" is a term that describes the ability of germs to avoid the effects of antimicrobial drugs; therefore, they are uninhibited by antimicrobials, which previously inhibited or reduced them.^[4] The scenario of antimicrobial resistance started with the manufacturing of drugs by using chemical substances. For example, at about 350–550 CE, it was observed that the residue of the skeletons of old Sudanese Nubia has traces of tetracycline.^[5,6] Also, in 1940, the use of the Artemisia plant, which contains artemisinin, in traditional Chinese medicine created more exposure to chemical substances. It was discovered that artemisinin is one of the efficient components of an antimalarial drug that was discovered in 1970.^[7] Antibiotic resistance has emerged and spread around the world since the last decade of the twentieth

century.^[1] Currently, antimicrobial resistance is being developed in most important pathogenic microorganisms to a wide spectrum of drugs, causing the failure of antibiotic therapy and the death of more than 100,000 people every year.^[8–11] Examples are the appearance of *Staphylococcus aureus*, which resists methicillin; enterococcus, which resists vancomycin; *Pseudomonas aeruginosa*, which resists multidrugs; *Acinetobacter baumannii*, which resists imipenem; and *Escherichia coli* and *Klebsiella pneumonia*, which resist the third generation of cephalosporin.^[9–11] Moreover, a major threat in future is increasing resistance to the carbapenems and fluoroquinolone by *P. aeruginosa* and *A. baumannii*,^[2,12] *E. coli* and *Salmonella enterica*,^[13,14] and *Mycobacterium tuberculosis*.^[15,16] In fact, the spreading of antimicrobial resistance was observed shortly after the introduction of new antimicrobial compounds.^[17] Therefore, an attempt

Address for correspondence: Dr. Rasha Abdulmahdi Flayyih Jasim,
Department of Clinical Laboratory Sciences, College of Pharmacy,
University of Babylon, Iraq.
E-mail: rasha.197822@gmail.com

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was made to overcome this problem by introducing or developing new antibiotics.^[8,18,19]

To minimize this challenge, both major and alternative solutions are required; therefore, this review attempts to sum up and discuss different routes to minimize this issue.

MAJOR SOLUTIONS

To address the problem of antibiotic resistance, effective strategies are required. This section will summarize and discuss the main strategies to minimize antibiotic resistance.

Judicious use of medications

The ideal use of antibiotics means the use of the right drug with the correct doses and route for an appropriate period, after an accurate diagnosis.^[20] However, the availability of antibiotics everywhere over the counter, especially in developing countries, makes it easy to procure them; the unwise usage of drugs by specialists and in hospitals as well as the free use of antibiotics in agriculture lead to the developing of antimicrobial resistance to more than one antibiotic.^[21] Various drugs have been irrationally used by many traditional practitioners. It was observed that more drugs were prescribed by practitioners who earn from the selling of medicines than by nonpractitioners. Moreover, the uncontrolled use of drugs for treating animals or people and the ability to purchase antibiotics without a prescription from any stores in many developing countries comprise another reason for irrational drug usage.^[20] Therefore, it is well known now that substantial resistance is followed by antibiotics usage.^[22] There are several key factors behind the irrational use of antibiotics, such as patient and time pressure, inaccurate diagnosis, uncertain treatment, high antibiotics cost causing poor compliance of patients, and overuse of antimicrobial agents to treat animal and plant diseases, which comprise another threat to increasing antimicrobial resistance. The wide use of subtherapeutic doses of antimicrobial agents such as glycopeptides and streptogramins to enhance animals' growth leads to an increase in antimicrobial resistance. It was observed that resistant bacteria such as salmonella and campylobacter emerged among animals due to the uncontrolled use of antimicrobials in farming. Consequently, resistant bacteria will be transmitted to humans via direct contact and food.^[23] To prevent the increase rate of resistance, once required judicious use of existing antibiotics. This occurs through banning the selling of antibiotics without a prescription, the intensive teaching of judicious antibiotic use for patients and practitioners who are responsible for using antibiotics in hospitals.^[24] There is a global system for the monitoring and surveillance of the increase in antimicrobial resistance called the SMART, which considers different aspects such as geographic region and different infectious sites for isolated strain.^[25] The controlled and restricted use of antibiotics in agriculture

is also required. In fact, solving this issue required the efforts of all members of society, from governments to consumers.

In developing countries such as India, the easy availability of a wide range of drugs coupled with inadequate health services result in increased proportions of drugs being used as self-medication compared with prescribed drugs, thus resulting in impending health problems such as irrational use of antimicrobials and antimicrobial resistance, increased load of mortality and morbidity, and economic loss.^[26] The need for promoting appropriate use of drugs in a health-care system is not only because of the financial reasons with which policy makers and managers are usually most concerned, but also for health and medical care of patients and the community. There is a need for authorities to make the existing laws regarding OTC drugs strong to ensure the rational sale and use of antimicrobials.

Antimicrobial surveillance programs

In addition to poor health services and high treatment cost, in many developing countries, a wide range of drugs that are easy available caused an increase in the usage rate of antibiotics as self-medication compared with prescribed medication. The consequences of this phenomenon are irrational use of antimicrobials, a rise in antimicrobial resistance, and, finally, an elevation in the morbidity and mortality rate, in addition to economic loss.^[26] Therefore, to reduce or stabilize antimicrobial resistance, stewardship or surveillance programs (ASPs) are required. ASPs work via optimizing antimicrobial therapy, reducing treatments' costs, and improving health services in clinical foundations.^[25] Hence, such programs were observed to be conducted in many institutions around the world, specifically in the United States. These programs involve a team of experienced specialists in different fields, such as medicine, pharmacy, microbiology, epidemiology, and infectious diseases, which are aimed at restricting the resistance spreading and evolution.^[27,28] Such programs confirm that there is a connection between the use of antibiotics and the emergence of resistance. Recently, it was observed that the vulnerability of *P. aeruginosa* to imipenem or meropenem was improved due to a reduction in ciprofloxacin usage.^[29] In addition to restriction the antimicrobial viability and considering the antimicrobial susceptibility testing (AST) before prescribe the antibiotic, these programs depend primarily on education. Other studies, for reducing the resistance emergence, suggested the sufficient dose to kill sensitive bacterial strain and inhibit resistant strain, whereas other proposed using of mixing antibiotic.^[25]

Therefore, for controlling a developing antimicrobial resistance issue in developing countries, there is a requirement for Stewardship programs and more studies in this field, strong laws regarding OTC drugs, and improving the education of those who are responsible for drug description and selling.

Education

The success of any step or effort to monitor or reduce the resistance issue by microbes was based on the best education for all society members. First of all, the clinicians or practitioners, who are responsible for daily treatment decisions in the hospitals and clinics, as well as the antibiotics sellers.^[30] It was noticed that most antibiotics can be described by clinicians irregularly and without any certification, whereas anticancer medications have to be prescribed and administered exclusively by oncology specialists.^[28] It was observed that inappropriate prescriptions (incorrect dose and wrong duration) form 50% of antibiotics prescribed in the society and hospitals.^[31,32] Moreover, in most primary care settings, the misuse of drugs continues, in spite of the advice to reduce the prescription of antibiotics.^[33,34] It was reported that wrong prescriptions used for treating nephritis and asymptomatic bacteriuria form about 50% and 70%, respectively, of antibiotics prescription, in primary care. To reduce the risks of all that has been cited earlier, general knowledge about medicine, microbiology, immunology, genetics, and antibiotics characterization have to be provided to all prescribers. In addition, continuing education about rational treatment use and dealing with patients who demand overuse of antibiotics have to be sufficient and available for all professionals in health care. Moreover, people belonging to all societies have to be educated about the side effects and the disadvantages of overuse of antibiotics to become more aware. Otherwise, all efforts to minimize antimicrobial resistance will fail.^[35]

Hygiene and disinfection

Hospital-acquired infections are one of the biggest public health concerns around the world, and they are often caused by multidrug resistance pathogens (MDR). There are many consequences for this infection, such as a requirement for more expensive antibiotics, further hospitalization, and death. For example, it was recorded that about 100,000 of deaths in the United States were caused due to hospital-acquired infections each year.^[25] It was believed that normal patient flora is the main origin of MDR. However, workers in the health-care industry also constitute an important source.^[36,37] The hands of these workers are considered the main route for the transmission and spreading of health care-associated pathogens.^[38,39] The contamination of their hands could occur directly via contact with patients or indirectly via handling contaminated surfaces.^[40,41] In addition, all instruments that are used by health-care workers, such as gloves, uniforms, and gowns, comprise another source of infection. It was observed that MDR pathogens are colonized on these instruments.^[42-44] Therefore, it was logically that prevention and reduction of this infection require convenient hospital disinfection, and personal healthcare workers cleanness as well as all used tools. Hence, there are guidelines offered by the Centers for

Disease Control and Prevention (CDC) and the Society for Healthcare Epidemiology of America (SHEA) to prevent the transmission of nosocomial MDR bacteria in hospitals.^[25] In the intensive care units (ICUs), it was demonstrated that a significant decrease in methicillin resistant *Staphylococcus aureus* nosocomial infections resulted from increasing handwashing.^[45,46] Hand hygiene guidelines, in health care, were presented by the World Health Organization (WHO) and the CDC.^[47] Further, the importance of improving the cleanliness of the environment in the reduction of MDR transmission among patients has been demonstrated by several studies.^[48-50]

In conclusion, decreasing the transmission of resistant microbes can be achieved by hygiene, cleaning, and disinfection of the workers' hands, patients, hospital environments, and all used tools.

Restriction of using antibiotics in veterinary medicine

Veterinary medicine used antibiotics that used for human treatment since using penicillin.^[51] Moreover, most antibiotics that are used specifically for animal treatment belong to the same class of antibiotics that are used for treating human diseases.^[52,53] Furthermore, it was surprise that using of human antibiotics treatment in agriculture as veterinary medicine and as growth promoter formed approximately 70% of antibiotics that use in animals feeding around the world.^[51,54-58] Although antibiotics are used as growth promoters in low concentrations, using them for a long period is very dangerous as it increases antimicrobial resistance.^[59,60] In 1990, it was mentioned that vancomycin-resistant appeared in *Enterococcus faecium* due to the using of avoparcin, that belongs to the vancomycin family, as growth promoter.^[61] Therefore, the European Union and the United States prohibit the use of this antibiotic as well as all antibiotics as growth promoters.^[52,62] Recently, it was reported that extended spectrum beta-lactam (ESBL) and carbapenemase-positive Enterobacteriaceae strains and methicillin resistant *Staphylococcus aureus* are present in food animals and food products,^[36,59,63,64] in addition to various MDR bacteria.^[65,66] Moreover, it was observed that multidrug resistance human pathogenic *E.coli* plasmids originate from animal pathogens such as *Aeromonas salmonicida*.^[67] Eventhough the using of antibiotics are low in general, the antibiotic spray in opened environment can develop MDR bacteria.^[25] For all of the above, reduction of resistance development and transferring antibiotic resistance via animals food require new ways in management animals diseases such as (a) hygiene improvement, (b) using vaccines in an optimal way, (c) improving health via using of enzymes, probiotics, prebiotics, and acids, (d) using of bacteriocins, antimicrobial peptides, and bacteriophages as growth promoter instead of antibiotics, and (e) formulation

international standard protocol for using antibiotics in animals farming.

The development of novel antibiotics

Because of the ability of bacteria to develop and to improve their resistance to antibiotics between species, there is a requirement for developing new weapons to overcome bacterial infections. Nevertheless, there is a significant reduction in the discovery or development of new antibiotics. Most classes of used antibiotics were discovered during 1930–1960. Moreover, only two new classes of antibiotics were discovered 30 years ago and neither of them is effective against Gram-negative bacteria.^[68-71] Various obstacles have been limited the development of novel drugs. One of them is the emergence of resistance due to the overuse of broad spectrum antibiotics, as opposed to the heart diseases drugs, and as a result these antibiotics became short-term drugs.^[72] Another limitation is that the overuse of cheap antibiotics in the society can affect the selling of novel antimicrobial agents.^[73] Providing financial assistance in different ways or decreasing research and development cost can be effective steps to overcome these challenges.^[74] In conclusion, not only novel antibiotics but also strategies were used for rationally designing approaches as well as alternative solutions, such as using ancient medicine, which could be involved in addressing this issue.

ALTERNATIVE STRATEGIES

In the 1940s–1960s, antibiotics were discovered depending on the microbial secondary metabolites in the soil.^[75] Therefore, that period is considered the gold era due to the activity of antibiotics in eradication of most infectious agents and improving human health.^[76] However, antimicrobial resistance to most antimicrobial agents has developed rapidly around the world. Therefore, considering new approaches, such as those that used all unexploited natural resources, are required. In fact, there are several alternative approaches, such as (1) the using of bacteriophages, phage lysins, antimicrobial peptides, and medicinal nanoparticles^[77,78]; (2) the using of monoclonal bacterial antibodies^[79]; (3) chemical modifying of antimicrobial agents^[80-82]; and (4) the using of DNA sequences in synthetic specific antimicrobials sequenced to be more selective to pathogens.^[83-88] Though these entire alternative approaches, the resistance was emerged quickly. However, classical medicines such as minerals in natural clay, plant derivatives, animal products, and marine or terrestrial minerals were used for a long time in medical and biomedical applications. These are well known by their antimicrobial activity against broad spectrum infectious diseases. These unexploited sources can be used as new weapons in the war against resistant infectious agents.^[89] Recently, minerals in ancient clays that have been used in treating infectious diseases for

a long time before any knowledge had emerged about infectious agents have been receiving more attention.^[90] It was observed that the application of natural clay minerals heals wounds successfully, sedates the irritation, and suppresses the hemorrhage.^[91] Recently, the antimicrobial activities of several ancient clays have been investigated. Moreover, *in vitro*, it was observed that mineral clays have broad spectrum antimicrobial activity.^[92] Therefore, the using of clay minerals could be a good complement solution for addressing resistance emergence.

CONCLUSION

Bacteria can adapt easily to antibiotics when they are exposed. Moreover, they can transfer their developing resistance among the species. More serious problem is unawareness of different society members and even some prescriber and practitioner about the antibiotics overuse consequences in a gradual resistance increase around the world. Although this huge problem comprises a real threat to public health, it can be reduced via several ways, such as developing formal guidelines for appropriate antibiotics usage, educating various community members about rational antibiotics use, making people aware about the hazard of wide or missed antibiotic use, following an effective and accurate diagnosis before any prescription, developing new antibiotics, restricting antibiotics use in agriculture and animal farming, and, finally, using all untapped natural sources in disease treatment.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Levy SB, Marshall B. Antibacterial resistance worldwide: Causes, challenges and responses. *Nat Med* 2004;10:S122-9.
2. Ehrlich P, Hata S. Die experimentelle chemotherapie der spirilosen. Berlin: Julius Springer; 1910.
3. Mahoney J, Arnold R, Harris A. Penicillin treatment of early syphilis. A preliminary report. *Verer Dis Inform* 1943;24: 355-7.
4. Zaman S, Hussain M, Nye R, Mehta V, Mamun KT, Hossain N. A review on antibiotic resistance: Alarm bells are ringing. *Cureus* 2017;9:e1403.
5. Bassett EJ, Keith MS, Armelagos GJ, Martin DL, Villanueva AR. Tetracycline-labeled human bone from ancient Sudanese Nubia (A.D. 350). *Science* 1980;209:1532-4.
6. Nelson ML, Dinardo A, Hochberg J, Armelagos GJ. Brief communication: Mass spectroscopic characterization of tetracycline in the skeletal remains of an ancient population from Sudanese Nubia 350–550 CE. *Am J Phys Anthropol* 2010;143:151-4.
7. Cui L, Su XZ. Discovery, mechanisms of action and combination therapy of artemisinin. *Expert Rev Anti Infect Ther* 2009;7: 999-1013.
8. Palmer AC, Kishony R. Understanding, predicting and manipulating the genotypic evolution of antibiotic resistance. *Nat Rev Genet* 2013;14:243-8.

9. Meyer E, Schwab F, Schroeren-Boersch B, Gastmeier P. Dramatic increase of third-generation cephalosporin-resistant *E. coli* in German intensive care units: Secular trends in antibiotic drug use and bacterial resistance, 2001 to 2008. *Crit Care* 2010;14:R113.
10. Rossolini GM, Mantengoli E, Docquier JD, Musmanno RA, Coratza G. Epidemiology of infections caused by multiresistant gram-negatives: ESBLs, MBLs, panresistant strains. *New Microbiol* 2007;30:332-9.
11. Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM, *et al.*; Infectious Diseases Society of America. The epidemic of antibiotic-resistant infections: A call to action for the medical community from the Infectious Diseases Society of America. *Clin Infect Dis* 2008;46:155-64.
12. Garau G, Di Guilmi AM, Hall BG. Structure-based phylogeny of the metallo-beta-lactamases. *Antimicrob Agents Chemother* 2005;49:2778-84.
13. Fischer J, Rodriguez I, Schmoger S, Friese A, Roesler U, Helmuth R, *et al.* *Salmonella enterica* subsp. *enterica* producing VIM-1 carbapenemase isolated from livestock farms. *J Antimicrob Chemother* 2013;68:478-80.
14. Fischer J, Rodriguez I, Schmoger S, Friese A, Roesler U, Helmuth R, *et al.* *Escherichia coli* producing VIM-1 carbapenemase isolated on a pig farm. *J Antimicrob Chemother* 2012;67:1793-5.
15. Almeida Da Silva PE, Palomino JC. Molecular basis and mechanisms of drug resistance in *Mycobacterium tuberculosis*: Classical and new drugs. *J Antimicrob Chemother* 2011;66:1417-30.
16. Dye C. Doomsday postponed? Preventing and reversing epidemics of drug-resistant tuberculosis. *Nat Rev Microbiol* 2009;7:81-7.
17. Levy SB. Antibiotic resistance an ecological imbalance. In: Chadwick DJ, Goode J, editors. *Antibiotic Resistance: Origins, Evolution Selection and Spread*. London: Wiley (Ciba Foundation Symposium 207); 1997. p. 1-14.
18. Spellberg B, Powers JH, Brass EP, Miller LG, Edwards JE Jr. Trends in antimicrobial drug development: Implications for the future. *Clin Infect Dis* 2004;38:1279-86.
19. Livermore DM. Minimising antibiotic resistance. *Lancet Infect Dis* 2005;5:450-9.
20. Holloway KA, Rosella L, Henry D. The impact of WHO essential medicines policies on inappropriate use of antibiotics. *PLoS One* 2016;11:e0152020.
21. Sosa Anibal de J, Byarugaba Denis K, Amabile-Cuevas CF, Hsueh PR, Kariuki S, Okeke Iruka N. *Antimicrobial Resistance in Developing Countries*. Berlin: Springer; 2010.
22. Cantas L, Shah SQ, Cavaco LM, Manaia CM, Walsh F, Popowska M, *et al.* A brief multidisciplinary review on antimicrobial resistance in medicine and its linkage to the global environmental microbiota. *Front Microbiol* 2013;4:96.
23. Mitema ES, Kikui GM, Wegener HC, Stohr K. An assessment of antimicrobial consumption in food producing animals in Kenya. *J Vet Pharmacol Ther* 2001;24:385-90.
24. Kim WJ, Park SC. Bacterial resistance to antimicrobial agents: An overview from Korea. *Yonsei Med J* 1998;39:488-94.
25. Lee CR, Cho IH, Jeong BC, Lee SH. Strategies to minimize antibiotic resistance. *Int J Environ Res Public Health* 2013;10:4274-305.
26. Sharma R, Verma U, Sharma CL, Kapoor B. Self medication among urban population of Jammu City. *Ind J Pharmacol* 2005;37:40-3.
27. Bryan J. Developments in antimicrobial resistance and treatment. *Future Microbiol* 2011;6:715-20.
28. Owens RC Jr. Antimicrobial stewardship: Concepts and strategies in the 21st century. *Diagn Microbiol Infect Dis* 2008;61:110-28.
29. Drew RH. Antimicrobial stewardship programs: How to start and steer a successful program. *J Manag Care Pharm* 2009;15: S18-23.
30. Cantón R, Bryan J. Global antimicrobial resistance: From surveillance to stewardship. Part 2: Stewardship initiatives. *Expert Rev Anti Infect Ther* 2012;10:1375-7.
31. Pulcini C, Cua E, Lieutier F, Landraud L, Dellamonica P, Roger PM. Antibiotic misuse: A prospective clinical audit in a French University Hospital. *Eur J Clin Microbiol Infect Dis* 2007;26:277-80.
32. Harnden A, Perera R, Brueggemann AB, Mayon-White R, Crook DW, Thomson A, *et al.* Respiratory infections for which general practitioners consider prescribing an antibiotic: A prospective study. *Arch Dis Child* 2007;92:594-7.
33. Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, *et al.*; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007;44:159-77.
34. Katsarolis I, Antoniadou A, Poulakou G. Antibiotic prescribing habits in primary care adult respiratory tract infections. *Clin Microbiol Infect* 2002;156:1114-9.
35. Finch RG, Metlay JP, Davey PG, Baker LJ; International Forum on Antibiotic Resistance Colloquium. Educational interventions to improve antibiotic use in the community: Report from the international forum on antibiotic resistance (IFAR) colloquium, 2002. *Lancet Infect Dis* 2004;4:44-53.
36. Caron WP, Mousa SA. Prevention strategies for antimicrobial resistance: A systematic review of the literature. *Infect Drug Resist* 2010;3:25-33.
37. Siegel JD, Rhinehart E, Jackson M, Chiarello L; Healthcare Infection Control Practices Advisory Committee. Management of multidrug-resistant organisms in health care settings, 2006. *Am J Infect Control* 2007;35:S165-93.
38. Allegranzi B, Pittet D. Role of hand hygiene in healthcare-associated infection prevention. *J Hosp Infect* 2009;73:305-15.
39. Sax H, Allegranzi B, Chraïti MN, Boyce J, Larson E, Pittet D. The World Health Organization hand hygiene observation method. *Am J Infect Control* 2009;37:827-34.
40. Weber DJ, Rutala WA, Miller MB, Huslage K, Sickbert-Bennett E. Role of hospital surfaces in the transmission of emerging health care-associated pathogens: Norovirus, *Clostridium difficile*, and *Acinetobacter* species. *Am J Infect Control* 2010;38:S25-33.
41. Kramer A, Schwebke I, Kampf G. How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. *BMC Infect Dis* 2006;6:130.
42. Grabsch EA, Burrell LJ, Padiglione A, O'Keeffe JM, Ballard S, Grayson ML. Risk of environmental and healthcare worker contamination with Vancomycin-resistant *Enterococci* during outpatient procedures and hemodialysis. *Infect Control Hosp Epidemiol* 2006;27:287-93.
43. Perry C, Marshall R, Jones E. Bacterial contamination of uniforms. *J Hosp Infect* 2001;48:238-41.
44. Zachary KC, Bayne PS, Morrison VJ, Ford DS, Silver LC, Hooper DC. Contamination of gowns, gloves, and stethoscopes with Vancomycin-resistant *Enterococci*. *Infect Control Hosp Epidemiol* 2001;22:560-4.
45. Peacock JE Jr, Marsik FJ, Wenzel RP. Methicillin-resistant *Staphylococcus aureus*: Introduction and spread within a hospital. *Ann Intern Med* 1980;93:526-32.
46. Pittet D, Hugonnet S, Harbarth S, Mourouga P, Sauvan V, Touveneau S, *et al.* Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. *Infection control programme*. *Lancet* 2000;356:1307-12.
47. Pittet D, Allegranzi B, Boyce J; World Health Organization World Alliance for Patient Safety First Global Patient Safety Challenge Core Group of Experts. The World Health Organization guidelines on hand hygiene in health care and their consensus recommendations. *Infect Control Hosp Epidemiol* 2009;30:611-22.
48. Dancer SJ, White LF, Lamb J, Girvan EK, Robertson C. Measuring the effect of enhanced cleaning in a UK hospital: A prospective cross-over study. *BMC Med* 2009;7:28.
49. Goodman ER, Platt R, Bass R, Onderdonk AB, Yokoe DS, Huang SS. Impact of an environmental cleaning intervention on the presence of Methicillin-resistant *Staphylococcus aureus* and Vancomycin-resistant *Enterococci* on surfaces in intensive care unit rooms. *Infect Control Hosp Epidemiol* 2008;29:593-9.
50. Hayden MK, Bonten MJ, Blom DW, Lyle EA, van de Vijver DA, Weinstein RA. Reduction in acquisition of Vancomycin-resistant *Enterococcus* after enforcement of routine environmental cleaning measures. *Clin Infect Dis* 2006;42:1552-60.

51. Anthony F, Acar J, Franklin A, Gupta R, Nicholls T, Tamura Y, *et al.*; Office International des Epizooties Ad hoc Group. Antimicrobial resistance: Responsible and prudent use of antimicrobial agents in veterinary medicine. *Rev Sci Tech* 2001;20:829-39.
52. Cantas L, Shah SQ, Cavaco LM, Manaia CM, Walsh F, Popowska M, *et al.* A brief multi-disciplinary review on antimicrobial resistance in medicine and its linkage to the global environmental microbiota. *Front Microbiol* 2013;4:96.
53. Heuer OE, Kruse H, Grave K, Collignon P, Karunasagar I, Angulo FJ. Human health consequences of use of antimicrobial agents in aquaculture. *Clin Infect Dis* 2009;49:1248-53.
54. Roura E, Homedes J, Klasing KC. Prevention of immunologic stress contributes to the growth-permitting ability of dietary antibiotics in chicks. *J Nutr* 1992;122:2383-90.
55. Silbergeld EK, Graham J, Price LB. Industrial food animal production, antimicrobial resistance, and human health. *Annu Rev Public Health* 2008;29:151-69.
56. Anderson AD, Nelson JM, Rossiter S, Angulo FJ. Public health consequences of use of antimicrobial agents in food animals in the United States. *Microb Drug Resist* 2003;9:373-9.
57. Cabello FC. Heavy use of prophylactic antibiotics in aquaculture: A growing problem for human and animal health and for the environment. *Environ Microbiol* 2006;8:1137-44.
58. Roe MT, Pillai SD. Monitoring and identifying antibiotic resistance mechanisms in bacteria. *Poult Sci* 2003;82:622-6.
59. Gullberg E, Cao S, Berg OG, Ilbäck C, Sandegren L, Hughes D, *et al.* Selection of resistant bacteria at very low antibiotic concentrations. *Plos Pathog* 2011;7:e1002158.
60. Alexander TW, Yanke JL, Reuter T, Topp E, Read RR, Selinger BL, *et al.* Longitudinal characterization of antimicrobial resistance genes in feces shed from cattle fed different subtherapeutic antibiotics. *BMC Microbiol* 2011;11:19.
61. Capita R, Alonso-Calleja C. Antibiotic-resistant bacteria: A challenge for the food industry. *Crit Rev Food Sci Nutr* 2013;53:11-48.
62. Casewell M, Friis C, Marco E, McMullin P, Phillips I. The European ban on growth-promoting antibiotics and emerging consequences for human and animal health. *J Antimicrob Chemother* 2003;52:159-61.
63. Stamey TA, Bragonje J. Resistance to nalidixic acid. A misconception due to underdosage. *JAMA* 1976;236:1857-60.
64. Cantón R, Morosini MI. Emergence and spread of antibiotic resistance following exposure to antibiotics. *FEMS Microbiol Rev* 2011;35:977-91.
65. Colquhoun DJ, Aarflot L, Melvold CF. *gyrA* and *parC* mutations and associated quinolone resistance in *Vibrio anguillarum* serotype O2B strains isolated from farmed Atlantic cod (*Gadus morhua*) in Norway. *Antimicrob Agents Chemother* 2007;51:2597-9.
66. Shah SQ, Colquhoun DJ, Nikuli HL, Sørum H. Prevalence of antibiotic resistance genes in the bacterial flora of integrated fish farming environments of Pakistan and Tanzania. *Environ Sci Technol* 2012;46:8672-9.
67. Rhodes G, Huys G, Swings J, McGann P, Hiney M, Smith P, *et al.* Distribution of oxytetracycline resistance plasmids between aeromonads in hospital and aquaculture environments: Implication of Tn1721 in dissemination of the tetracycline resistance determinant tetA. *Appl Environ Microbiol* 2000;66:3883-90.
68. Lee JH, Jeong SH, Cha SS, Lee SH. New disturbing trend in antimicrobial resistance of Gram-negative pathogens. *PLoS Pathog* 2009;5:e1000221.
69. Lee JH, Bae IK, Lee SH. New definitions of extended-spectrum β -lactamase conferring worldwide emerging antibiotic resistance. *Med Res Rev* 2012;32:216-32.
70. Lee JH, Jeong SH, Cha S-S, Lee SH. A lack of drugs for antibiotic-resistant Gram-negative bacteria. *Nat Rev Drug Discov* 2007;6. DOI: 10.1038/nrd2201-c1031.
71. Giamarellou H, Poulakou G. Multidrug-resistant gram-negative infections: What are the treatment options? *Drugs* 2009;69:1879-901.
72. Projan SJ. Why is big pharma getting out of antibacterial drug discovery? *Curr Opin Microbiol* 2003;6:427-30.
73. Butler MS, Cooper MA. Screening strategies to identify new antibiotics. *Curr Drug Targets* 2012;13:373-87.
74. Höglberg LD, Heddini A, Cars O. The global need for effective antibiotics: Challenges and recent advances. *Trends Pharmacol Sci* 2010;31:509-15.
75. Davies J, Davies D. Origin and evolution of antibiotic resistance. *Microbiol Mol Biol Rev* 2010;74:417-33.
76. Kardos N, Demain AL. Penicillin: The medicine with the greatest impact on therapeutic outcomes. *Appl Microbiol Biotechnol* 2011;92:677-87.
77. Beyth N, Hourri-Haddad Y, Domb A, Khan W, Hazan R. Alternative antimicrobial approach: Nano-antimicrobial materials. *Evid Based Complement Alternat Med* 2015;2015:246012.
78. Ghosh C, Sarkar P, Issa R, Haldar J. Alternatives to conventional antibiotics in the era of antimicrobial resistance. *Trends Microbiol* 2019;27:323-38.
79. Rios AC, Moutinho CG, Pinto FC, Del Fiol FS, Jozala A, Chaud MV, *et al.* Alternatives to overcoming bacterial resistances: State-of-the-art. *Microbiol Res* 2016;191:51-80.
80. Wright GD. Antibiotic adjuvants: Rescuing antibiotics from resistance. (*Trends in microbiology* 24, 862-871; October 17, 2016). *Trends Microbiol* 2016;24:928.
81. Domalaon R, Idowu T, Zhanel GG, Schweizer F. Antibiotic hybrids: The next generation of agents and adjuvants against gram-negative pathogens? *Clin Microbiol Rev* 2018;31:e00077-17.
82. Gupta V, Datta P. Next-generation strategy for treating drug resistant bacteria: Antibiotic hybrids. *Indian J Med Res* 2019;149:97-106.
83. Bikard D, Euler CW, Jiang W, Nussenzweig PM, Goldberg GW, Duportet X, *et al.* Exploiting CRISPR-cas nucleases to produce sequence-specific antimicrobials. *Nat Biotechnol* 2014;32:1146-50.
84. Citorik RJ, Mimee M, Lu TK. Sequence-specific antimicrobials using efficiently delivered RNA-guided nucleases. *Nat Biotechnol* 2014;32:1141-5.
85. Sully EK, Geller BL. Antisense antimicrobial therapeutics. *Curr Opin Microbiol* 2016;33:47-55.
86. Jayaraman P, Holowko MB, Yeoh JW, Lim S, Poh CL. Repurposing a two-component system-based biosensor for the killing of *Vibrio cholerae*. *ACS Synth Biol* 2017;6:1403-15.
87. Bober JR, Beisel CL, Nair NU. Synthetic biology approaches to engineer probiotics and members of the human microbiota for biomedical applications. *Annu Rev Biomed Eng* 2018;20:277-300.
88. López-Igual R, Bernal-Bayard J, Rodríguez-Patón A, Ghigo JM, Mazel D. Engineered toxin-intein antimicrobials can selectively target and kill antibiotic-resistant bacteria in mixed populations. *Nat Biotechnol* 2019;37:755-60.
89. Davies JE, Behroozian S. An ancient solution to a modern problem. *Mol Microbiol* 2020;113:546-9.
90. Dias DA, Urban S, Roessner U. A historical overview of natural products in drug discovery. *Metabolites* 2012;2:303-36.
91. Gomes CSF. Healing and edible clays: A review of basic concepts, benefits and risks. *Environ Geochem Health* 2018;40:1739-65.
92. Williams LB, Metge DW, Eberl DD, Harvey RW, Turner AG, Prapaipong P, *et al.* What makes a natural clay antibacterial? *Environ Sci Technol* 2011;45:3768-73.