Summer Training Report on

Examining Strategies to reduce Antimicrobial Resistance and Online Course

By R Varun Sastry

MBA (Pharmaceutical Management)

2019-21

Acknowledgements

First and foremost, praises and thanks to the God, the Almighty, for His showers of blessings throughout my research work enabling me to complete my project successfully. Next to him are my parents, whom I am greatly indebted to for having brought me up to this stage with love and encouragement.

I would like to express my deep and sincere gratitude to my research supervisor, **Dr. Habib Hasan**, PHFI, senior faculty at Indian Institute of Public Health, Delhi for giving me the opportunity to do research and providing invaluable guidance throughout this research. His dynamism, vision and motivation have deeply inspired me. He has taught me the methodology to carry out the research and to present the research works as clearly as possible. It was a great privilege and honor to work and study under his guidance, especially in these trying times.

I owe a deep sense of gratitude to my teacher of Research Methodology and MS Excel – **Mr Rahul Sharma** (Assistant Professor, School of Pharmaceutical Management, IIHMR University, Jaipur) for guiding me in choosing the appropriate online course for upskilling myself in my area of interest.

I am extremely grateful to **Dr. Sakthivel Selvaraj** for welcoming us into PHFI and for smoothening our transition into learning with working.

I express my thanks to the **Human Resource department at PHFI** for the speedy responses to any queries during our early joining period and later during the end of the internship.

I extend my gratitude to the **Indian Institute of Health Management and Research University, Jaipur** for giving me this opportunity.

I am extremely thankful to all my **friends** who have always been helpful and encouraging me throughout this period.

Any omission in this brief acknowledgement does not mean a lack of gratitude or is intentional, only the absence of valuable words to express my thanks.

Table of Contents

Acronyms/Abbreviations

AMR – Antimicrobial Resistance

ASP – Antimicrobial Stewardship Program

FDA – Food and Drug Administration

CDC – Center for Disease Control

GP – General Practitioner

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PICO - P – Patient, Problem or Population. I – Intervention. C – Comparison, control, or comparator. O – Outcome(s) (e.g. pain, fatigue, nausea, infections, death)

MDR – Multi-drug resistance

MDRO – Multidrug Resistant Organism

TDR – Total Drug Resistance

XDR – Extremely Drug resistant

Part 1: Report on Summer Training

Work from Home (Assignment by the Organization) - Systematic Literature Review

Problem Statement – Examining the strategies to minimize antimicrobial resistance in microbes on humans

Abstract

- **Background:** Implementation of effective and accurate strategies are the need of the hour to combat antimicrobial resistance among humans. As it is a rising global threat to public health, the strategies involved should be efficient in nature in terms of health and cost. It should parameterize cost-effectiveness evaluations of interventions which are specifically aiming to tackle this problem.

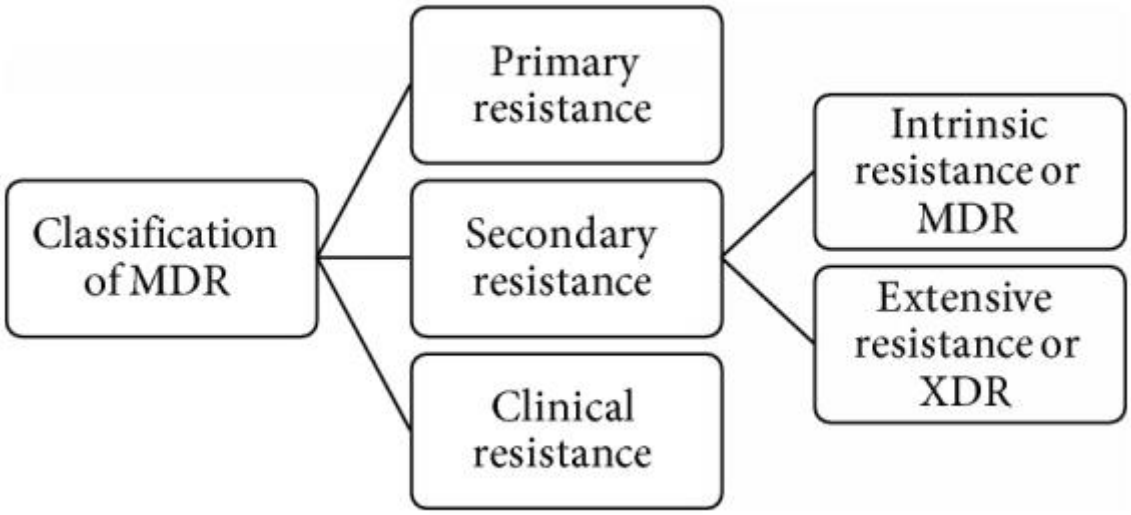
- **Methods:** Google Scholar, PubMed, researchgate.net, hindawi.net are among many of the websites which were used along with the grey literature involved in those research papers. The PRISMA guidelines were followed and a modified version of PICO inclusion/exclusion criteria was followed for screening titles and abstracts, among others.

- **Conclusions:** This study highlights the different strategies which are used worldwide and are recommended by WHO to effectively combat the growing incidences of Antimicrobial Resistance.

- **Keywords:** Antimicrobial resistance, Antimicrobial Stewardship, Patient Education, Global Public health Threat.

Introduction and Background

The ability of a disease-causing microbe to successfully resist the effects of medication that could previously treat it is known as *Antimicrobial Resistance (AMR)*. These resistant microbes are more difficult to treat, that is, they require either higher doses of antimicrobials or alternative medications. Often, these approaches tend to be more toxic or expensive or both. Some microbes that are resistant to multiple antimicrobials, these are referred to as *Multidrug-Resistant*. A comparably rare type of microbials also exist, these are considered *Extensively Drug-Resistant (XDR)* or *Totally Drug-Resistant (TDR)* and sometimes also called "*superbugs"*.



During recent decades, antimicrobials have become the cornerstones of clinical medicine. However, during the same period, the incidence of microbial infections has increased dramatically causing the emergence and spread of antimicrobial resistance in pathogens around the world. Among the many factors, high consumption of antimicrobials has been identified as an important driver for increasing AMR. Thus, elevating it as one of the greatest threats to public health globally.

In the current scenario, with many given factors in play, the hope of overcoming this threat by the development of new antimicrobials is diminished. The plummeting fall in the discovery of novel antimicrobials and the growing incidents of pathogens evolving resistance to existing antimicrobials are leading factors. Therefore, to address the problem of AMR, implementation of effective strategies is necessary. Some of which are discussed as follows:

1) **The Development of Novel Antimicrobials**
    a. Antimicrobials have a unique class of drugs known as Antibiotics. These do not directly target the human biochemical processes but instead affect the growth of invading pathogens.
    b. Bacteria in general, are evolving in nature, that is, they can easily adapt to their environmental changes and thus decrease their susceptibility to antibiotics via several mechanisms such as gene transfer between species and mutation. Hence, novel antibiotics are requisite in decreasing the incidence of bacterial infections.
    c. In the last 30 years, only two new systemic classes of antibiotics and two topical classes were introduced in the market. As such, most of the antibiotics being used today were discovered during the mid-20th century.

2) **Adequate Antimicrobial Prescribing and Education of Patients**
    a. The resistance of pathogens against the first commercially available antimicrobial agent was identified in 1948. It was penicillin. Since then, almost all known pathogens have developed resistance to one or more antimicrobials in clinical usage.

    b. Doctors often tend to prescribe the same antimicrobials repeatedly, which sometimes leads to patients self-prescribing medications. This increased usage also helps in increasing the instances of resistant disease-causing microbes.

    c. Some risks that have shown to be associated with overuse of antimicrobials are as follows:
        i. Increase in the length of the duration of the disease
        ii. Increase in the risk of complications
        iii. Increase in mortality rate
        iv. Increase in healthcare costs
        v. Increase in re-attendance into hospitals.

    d. Doctors can also help in ways other than just limiting or differentiating antibiotics while prescribing. Some are as follows:
        i. They can discuss with the patient about antibiotics and inform them that antibiotics do not significantly reduce the duration of

symptoms of self-limiting infections and instead they may cause adverse effects which could also lead to antibiotic resistance.

ii. They should set realistic expectations for symptom duration, including the total average time it will take for the illness to be treated (after seeing the doctor). For example, 1 week for acute sore throat, 1½ weeks for the common cold and 3 weeks for acute cough/bronchitis, among others.

iii. Define the diagnosis of the illness to the patient as a chest cold, or sore throat instead of using medical terms such as 'acute tonsillitis' or 'acute bronchitis'.

iv. Extreme cases or special cases wherein the patient is considerably less informed about their illness, the information could be provided with a leaflet or a brochure highlighting the most important information.

3) Antimicrobial Stewardship Programs (ASP)

a. WHO defines Antimicrobial Stewardship as "the optimal selection, dosage and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance?" To this end, they have segregated the goals of ASP into a 3-fold program which is as follows:

i. The first goal dictates that the healthcare practitioners should work towards helping each patient receive the most appropriate antimicrobial with the correct dosage for the correct duration. In a research paper by Joseph and Rodvold, the "4Ds of optimal antimicrobial therapy" is described, that is, *Right Drug, Right Dose, De-escalation to pathogen-directed therapy, and right Duration of therapy.*

ii. The second goal is to prevent overuse, misuse, and abuse of antimicrobial agents. It is often seen that in a hospital and outpatient setting, physicians use antibiotics even when they are not necessary.

iii. The third goal is to minimize the development of resistance, both at the community level and the individual level.

4) **Disinfection and Hygiene in Hospitals**
    a. Multi-Drug resistant pathogens are one of the major causes of the rising cases of Hospital-Acquired infections. The United States (U.S.A) alone sees 1.7 million new incidents of these infections each year, which causes around a hundred thousand deaths.
    b. The Centers of Disease Control and Prevention (CDC) and the SHEA have specific guidelines in place for prevention of transmission of MDR microbes in hospitals.
    c. Several studies have marked the fact that just an increase in handwashing compliance among patients and healthcare workers severely decreases transmission of MDR microbes.
    d. It should be noted that wearing gloves can prevent hands from becoming contaminated with pathogens, but that if the process of removing gloves while preventing self-contamination is not followed then the incidents will see a dramatic increase regardless of other protocols.

Objectives

1) To examine the different strategies which aid in minimizing the antimicrobial resistance among humans.
2) To build and show the relationship between implementation of different protocols which combat AMR and the decrease in the number of incidences of AMR strains.
3) To make a concise conclusion of different methodologically accurate studies that depict the different protocols by which the governing bodies can effectively combat against AMR.

Methodology

This Systematic Literature Review is in line with PRISMA Guidelines and has followed APA Citation format for all the references.

a) Search Strategy and eligibility criteria

i. Studies which proposed new methods and strategies to raise the public awareness about Antimicrobial Resistance (in humans) were shortlisted. The search was not given a limitation of time-period so that even older strategies could revamped and restructured for usage in the current day.

ii. Google Scholar, PubMed, ASM.org, Researchgate.net and Hindawi.net are among the many online libraries that were searched.

iii. The searches were conducted utilizing a search string and important keywords which employed the following combinations: Antimicrobial Resistance, strategies for AMR, mortality rate, reattendance in hospitals, cost, economic, multi-drug resistance, extensive-drug resistance, global impact, hospital infection rates, susceptible microbes.

iv. The given modified PICO inclusion/exclusion criteria were utilized to screen title/abstracts and subsequently full texts.

1) Table for inclusion/exclusion criteria

Criteria	**Inclusion**	**Exclusion**
Population	Humans - All Ages - All Sexes - Infection with Antimicrobial Resistant organism	Animals Plants
Intervention	Not Applicable	Not Applicable
Comparator	Not Applicable	Not Applicable
Outcomes	Associated health burden, to include but restricted to: Mortality and Morbidity. Associated healthcare cost burden, to include but not restricted to: Resource use and Opportunity cost. Economic burden, including loss of productivity. Burden from not being able to use antibiotics in ways	Health-related quality of life only Molecular Biology only Epidemiology only Outcomes associated with the evaluation of an

	previously or currently used in healthcare, including reduced surgery or chemotherapy	intervention such as clinical cure rate only
Study Design	Case–control studies Cohort studies Cross–sectional studies Longitudinal studies Randomized controlled trials Modelling studies Economic Evaluations	Editorials Letters Case series reports Conference reports Evaluations of interventions Reviews
Other	English Language	

b) Data quality assessment

a. Risk of bias in individual studies will be assessed.

b. Risk of bias across studies will be assessed in two groups; studies looking at health burden and studies looking at all other burden and will simply be assessed based on the nature and significance of the outcome. This is due to the expected heterogeneity in studies (outcome, infection, resistance).

c) Data Analysis

a. No meta-analysis was performed due to heterogeneity nature of the study.

b. The following information was extracted: study identifiers, study characteristics, data setting. Study methodology, outcome of interest, results, stated limitations and information used for risk bias assessment.

Overview of Literature

S.No.	Author	Title	Source	Focus	Findings
1)	Lee, C. R., Cho, I. H., Jeong, B. C., & Lee, S. H.	Strategies to minimize antibiotic resistance	*International journal of environmental research and public health*	Antibiotic resistance is growing threat to the global public health. This can be seen by the growing number of antibiotic resistant microbes. Steps need to be taken to combat this effectively.	Antibiotic Resistance can be reduced by using antibiotics prudently based on ASPs and utilizing various data such as PK and PD and properties of antibiotics, among others.

2)	Ancillotti, M., Eriksson, S., Veldwijk, J., Fahlquist, J. N., Andersson, D. I., & Godskesen, T	Public awareness and individual responsibility needed for judicious use of antibiotics: a qualitative study of public beliefs and perceptions.	*BMC Public Health*	To effectively combat the rising threat of antibiotic resistance, simply informing the public about this consequence is insufficient to induce behavioral change. This study explored beliefs and perceptions among Swedes, with the aim of identifying factors promoting and hindering a judicious approach to antibiotics use. The study focused primarily on the medical use of antibiotics, also considering other aspects connected with antibiotic resistance, such as travelling and food consumption.	The severity of the problem was perceived more strongly than the actual likelihood of being affected by it. Metaphors such as climate change were abundantly employed to describe antibiotic resistance as a slowly emerging problem. There was a tension between individual (egoistic) and collective (altruistic) reasons for engaging in judicious behavior. The individual effort needed, and antibiotics overprescribing were considered major barriers to such behavior. In their discussions, participants stressed the need for empowerment, achieved through good health communication from authorities and family physicians.
3)	Lowy, F. D.	Antimicrobial resistance: the example of *Staphylococcus aureus*.	*The Journal of clinical investigation*,	This study focuses on the rising cases of newly discovered microbes being antimicrobial resistant in nature. It tries to define it with an example of *Staphylococcus aureus.*	It was found that there was indeed an emergence of antimicrobial resistant microbes. It was also found that The evolution of increasingly antimicrobial-resistant bacterial species stems from a multitude of factors that includes the widespread and sometimes inappropriate use of antimicrobials, the extensive use of these agents as growth enhancers in animal feed, and, with the increase in regional and international travel, the relative ease with which antimicrobial-resistant bacteria cross geographic barriers.
4)	Tanwar, J., Das, S., Fatima, Z., & Hameed,	Multidrug resistance: an emerging crisis.	*Interdisciplinary perspectives on infectious diseases*	Multi-drug Resistant microbes are growing in number. The research on remedial solutions to combat this is the need of hour and this study rightly shows the different ways with which combat against this growing threat to public health can be done.	It was found that almost all the capable infecting agents (e.g., bacteria, fungi, virus, and parasite) have employed high levels of multidrug resistance (MDR) with enhanced morbidity and mortality; thus, they are referred to as "super bugs." Considering the

					significance of MDR, this paper, emphasizes the problems associated with MDR and the need to understand its significance and mechanisms to combat microbial infections.
5)	Nikaido, H	Multidrug resistance in bacteria	*Annual review of biochemistry*	In this study, the author focused on the different mechanisms by which bacteria generate resistance to antibiotics.	He found that first, these bacteria may accumulate multiple genes, each coding for resistance to a single drug, within a single cell. This accumulation occurs typically on resistance (R) plasmids. Second, multidrug resistance may also occur by the increased expression of genes that code for multidrug efflux pumps, extruding a wide range of drugs.
6)	Cortez, K. J., & Maldarelli, F.	Clinical management of HIV drug resistance	*Viruses*	This study focuses on the abnormalities that occur when therapy for HIV is not clinically managed.	The study found that management of clinical drug resistance requires in depth evaluation, and includes extensive history, physical examination, and laboratory studies. Appropriate use of resistance testing provides valuable information useful in constructing regimens for treatment-experienced individuals with viremia during therapy. This review outlines the emergence of drug resistance *in vivo* and describes clinical evaluation and therapeutic options of the individual with rebound viremia during therapy.
7)	Hurt, A. C.	The epidemiology and spread of drug resistant human influenza viruses.	*Current opinion in virology*	To chart the spread of newly found antibiotic resistant microbes.	It was found that resistance to the newer class of drugs, the neuraminidase inhibitors, is typically associated with poorer viral replication and transmission. But 'permissive' mutations, that compensated for impairment of viral function in A(H1N1) viruses during 2007/2008, enabled them to acquire the H275Y NA resistance

					mutation without fitness loss, resulting in their rapid global spread. Permissive mutations now appear to be present in A(H1N1)pdm09 viruses thereby increasing the risk that oseltamivir-resistant A(H1N1)pdm09 viruses may also spread globally, a concerning scenario given that oseltamivir is the most widely used influenza antiviral.
8)	Llor, C., & Bjerrum, L.	Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem.	*Therapeutic advances in drug safety*	This study focuses on the fact that over-prescribing antibiotics does tend to decrease its effectiveness in the short run. It tries to describe different methods/ways that General Practitioners (GP) can use to avoid this problem cropping up from their end in future.	It was found that there was no reason to explain why the antibiotic prescribing in respiratory tract infections (the most frequent primary care) is so great. Moreover, we know that antibiotics can stop being effective in the short and medium term. The use of the strategies discussed in this paper will help GPs to reduce prescribing of antibiotics. Our duty is to prescribe antibiotics only when they are necessary, i.e. in less than 20% of the infectious seen in primary care.
9)	Akram, M., Shahid, M., & Khan, A. U.	Etiology and antibiotic resistance patterns of community-acquired urinary tract infections in JNMC Hospital Aligarh, India	*Annals of clinical microbiology and antimicrobials*	The aim of this study was to determine the distribution and antibiotic susceptibility patterns of bacterial strains isolated from patients with community acquired urinary tract infections (UTIs) at Aligarh hospital in India as well as identification of ESBL producers in the population of different uropathogens.	This study revealed that *E. coli* was the predominant bacterial pathogen of community acquired UTIs in Aligarh, India. It also demonstrated an increasing resistance to Co-trimoxazole and production of extended spectrum β-lactamase among UTI pathogens in the community. This study is useful for clinician to improve the empiric treatment.
10)	Biswas, D., Gupta, P., Prasad, R., Singh, V., Arya, M., & Kumar, A.	Choice of antibiotic for empirical therapy of acute cystitis in a setting of high antimicrobial resistance.	*Indian Journal of Medical Sciences*	To identify the most appropriate antibiotic for empirical treatment of community-acquired acute cystitis based on local antimicrobial sensitivity profile.	The best in vitro susceptibility profile in our study has been shown by Nitrofurantoin and a significantly high proportion of the urinary E. coli isolates have already developed resistance to the currently prescribed empirical antibiotics, viz. the fluoroquinolones. In view of these in vitro

					susceptibility patterns, a transition in empirical therapy appears imminent.
11)	Vromen, M., Van der Ven, A. J. A. M., Knols, A., & Stobbering h, M. E. E.	Antimicrobial resistance patterns in urinary isolates from nursing home residents. Fifteen years of data reviewed.	*Journal of Antimicrobial Chemothera py*	In this study the antibiotic resistance patterns of gram-negative bacteria isolated from nursing home patients between 1983 and 1997 were analyzed.	It was found that Escherichia coli was the most prevalent isolate (48%) followed by Proteus spp. (26%) and other Enterobacteriaceae (20%). During the study period, the susceptibility of E. coli decreased for co-trimoxazole (79% to 62%), increased for nitrofurantoin (79% to 91%) and remained unchanged for amoxycillin (41%). Susceptibility to norfloxacin, available from 1990, decreased from 87% to 71%. Similar trends were observed when the susceptibilities of all gram-negative urinary pathogens were combined. The changes in susceptibility can probably be attributed to the empirical prescribing practices in the nursing homes studied.
12)	Hillier, S. L., Magee, J. T., Howard, A. J., & Palmer, S. R.	How strong is the evidence that antibiotic use is a risk factor for antibiotic-resistant, community-acquired urinary tract infection?	*Journal of antimicrobial chemotherap y*	This systematic review evaluates the published evidence on the relationship between antibiotic prescribing and antibiotic resistance of organisms causing community-acquired urinary tract infection.	This study concluded that fourteen papers met the inclusion criteria, and these reported on five ecological studies and ten studies of individuals. Only one ecological study provided good evidence of a link with prescribing rates. The remaining studies had no control for population differences in demographics and/or no comparison population. Studies at the individual level lacked clear case definitions and statistical power. Until the epidemiology of antibiotic resistance is better defined the design of effective interventions will not be possible.
13)	Mathai, D., Rhomberg , P. R., Biedenbac h, D. J.,	Evaluation of the in vitro activity of six broad-spectrum β-lactam	*Diagnostic microbiology and infectious disease*	This study focused on the fact that the widespread use of beta-lactam antimicrobial agents as first-line therapy for the	The study found that in certain countries, the lack of local or national surveillance programs limits the ability to detect

	Jones, R. N., & India Antimicrobial Resistance Study Group	antimicrobial agents tested against recent clinical isolates from India: a survey of ten medical center laboratories		treatment of serious infections has led to the development of various resistances that have compromised the use of some agents.	these resistant strains and prevent their dissemination. A 10 medical center study in India was initiated to benchmark prevailing resistance rates for a range of bacterial pathogens to beta-lactams, and it found high rates of beta-lactamase-mediated resistance in Escherichia coli and Klebsiella spp.
14)	Palmer, A. C., & Kishony, R.	Understanding, predicting, and manipulating the genotypic evolution of antibiotic resistance.	*Nature Reviews Genetics*	To study the evolution of antibiotic resistance which can now be rapidly tracked with high-throughput technologies for bacterial genotyping and phenotyping.	In this study they found that on combining these new technologies with new approaches the resistance can be evolved in labs and characterized to predict future evolution among pathogens. These methods are revealing the molecular basis and rate of evolution of antibiotic resistance under treatment regimens of single drugs or drug combinations.
15)	Rossolini, G. M., Mantengoli, E., Docquier, J., Musmanno, R. A., & Coratza, G.	Epidemiology of infections caused by multiresistant gram-negatives: ESBLs, MBLs, pan resistant strains	*MICROBIOLOGICA-BOLOGNA*	As Microbial drug resistance is a growing problem of global magnitude, this study focuses on the resistant strains of Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter	It found that an increase in the trends was observed for all major anti-gram-negative agents. A major matter of concern was found to be the emergence of new beta-lactamases capable of degrading the expanded-spectrum cephalosporins and/or carbapenems, such as the extended-spectrum beta-lactamases (ESBLs) and the carbapenemases. These beta-lactamase genes are often associated with resistance determinants to non-beta-lactam agents (e.g. aminoglycosides and fluoroquinolones), and strains producing ESBLs or carbapenemases often exhibit complex multidrug resistant phenotypes and sometimes are pan resistant. The problem is worsened by the dearth of new agents active on multidrug-resistant Gram-negatives in the pipeline.

					The importance to develop better strategies to control resistance is underscored.
16)	Spellberg, B., Guidos, R., Gilbert, D., Bradley, J., Boucher, H. W., Scheld, W. M., ... & 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.	*Clinical infectious diseases*	The ongoing explosion of antibiotic-resistant infections continues to plague global and US health care. Meanwhile, an equally alarming decline has occurred in the research and development of new antibiotics to deal with the threat. This study aims to focus on the policies in America which affect the research and development of new antimicrobials.	The study found that despite intensive public relations and lobbying efforts, it remains unclear whether sufficiently robust legislation will be enacted. In the meantime, microbes continue to become more resistant, the antibiotic pipeline continues to diminish, and most of the public remains unaware of this critical situation. The result of insufficient federal funding; insufficient surveillance, prevention, and control; insufficient research and development activities; misguided regulation of antibiotics in agriculture and, in particular, for food animals; and insufficient overall coordination of US (and international) efforts could mean a literal return to the pre-antibiotic era for many types of infections. If we are to address the antimicrobial resistance crisis, a concerted, grassroots effort led by the medical community will be required.
17)	Lee, J. H., Jeong, S. H., Cha, S. S., & Lee, S. H.	New disturbing trends in antimicrobial resistance of gram-negative pathogens	*PLoS Pathog*	The study focused on the emergence of new fifteen class-C extended-spectrum β-lactamases (ESBLs) produced by Gram-negative pathogens.	They found that the difficulty in type identification of ESBLs hinders hospital infection control and the ability of the physician to prescribe the most appropriate antibiotic, thus increasing the selective pressure and generating antibiotic resistance. It is necessary for health-care professionals to recognize the presence of emerging cESBLs as a new and disturbing trend in antimicrobial resistance of Gram-negative pathogens. Furthermore, there is currently no drug development in progress against cESBL-producing Gram-negative

					pathogens. Therefore, there is a tremendous need for the development of new β-lactams or β-lactamase inhibitors by the structure-based drug-design method using the similar structural mechanism (the significant widening of the R2 active site) of the extended substrate spectrum shown in most cESBLs.
18)	Lee, J. H., Jeong, S. H., Cha, S. S., & Lee, S. H	A lack of drugs for antibiotic-resistant Gram-negative bacteria	*Nature Reviews Drug Discovery*	This study focuses on the various presentations, subsequent discussions, and an appraisal of current literature on the increased incidence of MDR Gram-negative bacteria in all parts of the world.	Following a global, One Health approach and based on the evaluation of the existing knowledge about these pathogens, this paper gives recommendations for prevention and infection control measures as well as proposals for various target groups to tackle the threats posed by Gram-negative bacteria and prevent the spread and emergence of new antibiotic resistances.
19)	Spellberg, B., Powers, J. H., Brass, E. P., Miller, L. G., & Edwards Jr, J. E.	Trends in antimicrobial drug development: implications for the future	*Clinical infectious diseases*	Following the trend of some pharmaceutical companies indicating that they are curtailing anti-infective research programs, this study focuses and evaluates the US FDA databases and R&D programs of some of world's largest pharma and biotech companies.	The study found that FDA approval of new antibacterial agents decreased by 56% over the past 20 years (1998-2002 vs. 1983-1987). Projecting future development, new antibacterial agents constitute 6 of 506 drugs disclosed in the developmental programs of the largest pharmaceutical and biotechnology companies. Despite the critical need for new antimicrobial agents, the development of these agents is declining. Solutions encouraging and facilitating the development of new antimicrobial agents are needed.
20)	Livermore, D. M.	Minimizing antibiotic resistance	*The Lancet infectious diseases*	The author of this study focused on the fact that even though problems associated with antibiotic resistance has led to	the author found that rather than being overly optimistic about the benefits of reducing antimicrobial

				numerous agencies and governmental reports since 1998, these documents have failed to stress the desirability of reducing antimicrobial prescribing, which has subsequently fallen in many countries. Thus, the author points out various methods which will help combat this resistance.	prescriptions, we must also emphasize the use of those antibiotics that prove less prone to select resistance. Furthermore, we must be careful that guidelines are not so narrow as to rail-road prescribing and its contingent selection pressure in single directions--as happened with gonorrhea--and to consider the likelihood that limited diverse prescribing may have the least detrimental effect upon the resistance ecology. Last, there is a need to re-invigorate antimicrobial development, which has been downgraded by many major pharmaceutical houses.
21)	Shah, P., Shrestha, R., Mao, Z., Chen, Y., Chen, Y., Koju, P., ... & Li, H.	The challenge of Knowledge, Attitude, and Practice Associated with Antibiotic Use among University Students: A Survey in Nepal. resistance	*International journal of environmental research and public health*	The purpose of this study was to conduct a preliminary study to assess knowledge, attitude, and practice (KAP) associated with antibiotic use among medical students (MS) and non-medical students (NMS) at Kathmandu University, Nepal	A *t*-test and Chi-square test were applied to analyze the data. A total of 25 out of 39 questions in the KAP survey were found to have statistical significance. The MS showed higher levels of knowledge/attitude/practice associated with antibiotic use than the NMS. Significant gaps were found in and between the MS and NMS in the first and final years of study. Interventions, such as lectures, courses, workshops, and seminars on antibiotic use, along with internet and media campaigns, etc., are needed to improve the awareness and change the behavior of both the MS and the NMS of universities with regards to the rational use of antibiotics.
22)	Nicasio, A. M., Eagye, K. J., Kuti, E. L., Nicolau, D. P., & Kuti, J. L.	Length of stay and hospital costs associated with a pharmacodynamic-based clinical pathway for empiric	*Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*	To determine hospital costs associated with the use of a clinical pathway implemented in our intensive care units (ICUs) to optimize antibiotic regimen selection for patients with ventilator-	The study found that although aggressive dosing of more costly antibiotics was empirically prescribed using the clinical pathway, patients in this group exhibited a shorter duration of

		antibiotic choice for ventilator-associated pneumonia		associated pneumonia (VAP) compared with costs in a historical control group treated according to prescriber preference.	treatment, reduced hospital length of stay after VAP, and lower hospital costs without any significant increase in antibiotic expenditures.
23)	Owens Jr, R. C.	Antimicrobial stewardship: concepts and strategies in the 21st century	*Diagnostic microbiology and infectious disease*	The author aims to study the emergence of what has been termed as pan-drug-resistant and extremely-drug-resistant pathogens.	This article outlines the development of an effective ASP and the key components and operating principles and provides insight into the production of materials that will facilitate the execution of these programs at healthcare facilities. In this discussion, education of healthcare providers is emphasized, and a rationale is provided about the health, safety, and financial benefits that can be obtained from an ASP. A brief history of antimicrobial stewardship is included, providing the context for several studies of antimicrobial stewardship practice, which are also reviewed. Programs for optimal use are illustrated, including a prospective audit and feedback strategy and preauthorization procedure.
24)	Drew, R. H.	Antimicrobial stewardship programs: how to start and steer a successful program	*Journal of Managed Care Pharmacy*	To summarize ASP tactics that can improve the appropriate use of antimicrobials in the hospital setting. Several measures can be used to implement such programs and gain multidisciplinary support while addressing common barriers.	ASPs have the potential to reduce antimicrobial resistance, health care costs, and drug-related adverse events while improving clinical outcomes. The efforts and expense required to implement and maintain ASPs are more than justified given their potential benefits to both the hospital and the patient.
25)	Moehring, R. W., & Anderson, D. J.	Antimicrobial stewardship as part of the infection prevention effort	*Current infectious disease reports*	This study aims to outline the benefits of effectively conducting an Antimicrobial Stewardship Program (ASP) in combat against multi-drug resistant organisms (MDRO).	The study found that ASPs achieve these goals through several types of interventions that can occur before or after the antimicrobial has been prescribed; interventions can also be "active" or "passive." It believes that

					active post-prescription interventions such as post-prescription audit and feedback have the most supportive evidence and most promise. Stewardship activities must be integrated into already established efforts for infection prevention. It believes that it is critical that the antimicrobial stewardship, infection control, pharmacy, information technology, and clinical microbiology work collaboratively to decrease the incidence of infection due to MDRO.
26)	Standiford, H. C., Chan, S., Tripoli, M., Weekes, E., & Forrest, G. N.	Antimicrobial stewardship at a large tertiary care academic medical center: cost analysis before, during, and after a 7-year program	*Infection Control & Hospital Epidemiology* ,	A descriptive cost analysis was done before, during and after the conduction of an Antimicrobial Stewardship Program. This study aims to show the cost effectiveness of conducting an effective ASP.	The utilization costs decreased from $44,181 per 1,000 patient-days at baseline prior to the full implementation of the program (FY 2001) to $23,933 (a 45.8% decrease) by the end of the program (FY 2008). There was a reduction of approximately $3 million within the first 3 years, much of which was the result of a decrease in the use of antifungal agents in the cancer center. After the program was discontinued at the end of FY 2008, antimicrobial costs increased from $23,933 to $31,653 per 1,000 patient-days, a 32.3% increase within 2 years that is equivalent to a $2 million increase for the medical center, mostly in the antibacterial category.
27)	Caron, W. P., & Mousa, S. A.	Prevention strategies for antimicrobial resistance: a systematic review of the literature	*Infection and drug resistance*	The study aims to engage into the workings of different prevention strategies for antimicrobial resistance and thus narrow down the most effective methods for the same.	The emergence of drug-resistant bacteria is to some extent an inevitable consequence of the patterns of use of antibiotics in society today. Given the time and cost required to bring new, more effective antimicrobial therapeutics to market, drug discovery may not be the most effective approach to

					limiting antimicrobial resistance. Rather, there is substantial evidence to support that more appropriate and careful use of antibiotics, with particular attention to the variable PK and PD properties of different formulations, and even avoiding antibiotic treatment altogether in some cases, can significantly decrease or limit drug-resistant bacteria.
28)	Cantón, R., & Morosini, M. I.	Emergence and spread of antibiotic resistance following exposure to antibiotics.	*FEMS microbiology reviews*	The study focuses on the growth and spread of antibiotic resistance within a susceptible wild-type population.	The study found that this subpopulation has mutations that impede antimicrobial action, allowing their selection during clinical treatment. Emergence of resistance occurs in the frame of a selective compartment termed a mutant selection window (MSW). Early treatment avoiding an increase of the inoculum size as well as a regimen restricting the time within the MSW can reduce the probability of emergence of the resistant mutants. It also found that emergence of a resistant bacterial subpopulation within a susceptible wild-type population can be restricted with a regimen using an antibiotic dose that is sufficiently high to inhibit both susceptible and resistant bacteria.
29)	Goff, D. A., Jankowski, C., & Tenover, F. C.	Using rapid diagnostic tests to optimize antimicrobial selection in antimicrobial stewardship programs	*Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*	This study focuses on the new advances in rapid diagnostic tests which provide several collaborative opportunities for stewardship teams.	This review focuses on the use of molecular diagnostic methods to rapidly identify Staphylococcus species, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Clostridium difficile, and Candida species from clinical samples and summarizes studies that describe the application of rapid

					diagnostic tests in antimicrobial stewardship programs.
30)	Cosgrove, S. E.	The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stays, and health care costs	*Clinical Infectious Diseases*	This study aims to focus on the association between the development of AMR in different microbes.	It found that for many patients, inadequate or delayed therapy and severe underlying disease are primarily responsible for the adverse outcomes of infections caused by antimicrobial-resistant organisms. Patients with infections due to antimicrobial-resistant organisms have higher costs (approximately 6,000-30,000 dollars) than do patients with infections due to antimicrobial-susceptible organisms; the difference in cost is even greater when patients infected with antimicrobial-resistant organisms are compared with patients without infection. Strategies to prevent nosocomial emergence and spread of antimicrobial-resistant organisms are essential
31)	Roe, M. T., & Pillai, S. D.	Monitoring and identifying antibiotic resistance mechanisms in bacteria.	*Poultry Science*	This study focuses on the identification of AMR mechanisms and their effects on animals because animals contribute into the food chain.	Studies suggest that there is a link between the agricultural use of antibiotics and antibiotic-resistant human infections. Antibiotic-resistant organisms from animal and human wastes reenter the human and animal populations through several pathways including natural waters, irrigation water, drinking water, and vegetables and foods. Antibiotic usage in the United States for animal production (disease prevention and growth promotion) is estimated to be 18 million pounds annually. As much as 25 to 75% of the antibiotics administered to feedlot animals are excreted unaltered in feces. Once the mechanisms and magnitude of resistance gene transfer

					are clearly understood and quantified, strategies can be instituted to reduce the potential for dissemination of these genes.
32)	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	*Journal of antimicrobial chemotherapy*	This study focuses on the European Ban and disseminates its consequences in both the humans and the animals.	The efforts and expenditure involved in the imposition of the ban would have been better spent on achieving rational antibiotic use in humans and animals, and on much greater efforts to understand the complex epidemiology of resistant pathogens and resistance genes, as well as adequate risk assessments of both the ban, the 'precaution', in parallel with that of the 'threat', i.e. the continued use of growth promoters. The evidence suggests that the remaining growth promoting antibiotics still in use in Europe should not be banned until the relationship between growth promotion and prophylaxis is clarified, and the adverse consequences of the current ban can be remedied in Europe as a whole.
33)	De Souza Mendes, C. D. U., & de Souza Antunes, A. M.	Pipeline of known chemical classes of antibiotics	*Antibiotics*	This study focuses on the different approaches that are used to discover antibiotic compounds.	It found that the new antibiotics in the pipeline belong to the following chemical classes: quinolones, aminoglycosides, macrolides, oxazolidinones, tetracyclines, pleuromutilins, beta-lactams, lipoglycopeptides, polymyxins and cyclic lipopeptides.
34)	Lloyd, D. H.	Alternatives to conventional antimicrobial drugs: a review of prospects	*Veterinary Dermatology*	As more antibiotics are rendered ineffective by drug-resistant bacteria, focus must be shifted towards alternative therapies for treating infections. This study focuses on the advancements within biotechnology, genetic	This review introduces the various promising approaches that have been adopted in this regard. Whilst the use of bacteriophages and antibodies has been partly implemented, other promising strategies, such as probiotics, lysins, and

				engineering and synthetic chemistry that have opened new avenues.	antimicrobial peptides, are in various stages of development. Propitious concepts such as genetically modified phages, antibacterial oligonucleotides, and CRISPR-Cas9 are also discussed.
35)	Joseph, J., & Rodvold, K. A.	The role of carbapenems in the treatment of severe nosocomial respiratory tract infections	*Expert opinion on pharmacotherapy*	This study focuses on the prevalence of MAR bacteria particularly in patients with Nosocomial pneumonia.	The intention of this review is to provide an overview of severe nosocomial pneumonia, carbapenems and the problem of bacterial resistance to antimicrobial agents. Attention was focused on the efficacy, safety, and pharmacodynamics of imipenem, meropenem, ertapenem and doripenem. Issues on the impact of appropriate empiric antibiotic therapy for nosocomial pneumonia patients considered at risk for resistant pathogens are discussed. Critical decision making regarding the use of carbapenems for treating severe nosocomial pneumonia requires careful consideration of the four Ds of optimal antimicrobial therapy: right Drug, right Dose, De-escalated to pathogen-directed therapy and right Duration of therapy.
36)	Bansal, D., Malla, N., & Mahajan, R. C.	Drug resistance in amoebiasis	*Indian Journal of Medical Research*,	This study focuses on the AMR in Amoebiasis.	It found that Amoebiasis caused by Entamoeba histolytica, is a major public health problem in developing countries the cost of treating asymptomatic individuals is highly exorbitant and not justifiable. The indiscriminate use of ant amoebic drugs can result in increased minimum inhibitory concentration (MIC) values against Entamoeba species, and treatment failure may emerge as an important public health problem. This review discusses the factors involved in drug

					resistance mechanisms developed by the parasite.
37)	Li, X. Z., & Nikaido, H.	Efflux-mediated drug resistance in bacteria	*Drugs*	Efflux-mediated drug resistance in bacteria as they play a key role in drug resistance and serve other functions in bacteria. There has been a growing list of multidrug and drug-specific efflux pumps characterized from bacteria of human, animal, plant, and environmental origins	The study researched for new technologies with show significant progress in this field. This has been demonstrated in multiple aspects that include but are not limited to: further molecular and biochemical characterization of the known drug efflux pumps and identification of novel drug efflux pumps; structural elucidation of the transport mechanisms of drug transporters; regulatory mechanisms of drug efflux pumps; determining the role of the drug efflux pumps in other functions such as stress responses, virulence and cell communication; and development of efflux pump inhibitors. Overall, the multifaceted implications of drug efflux transporters warrant novel strategies to combat multidrug resistance in bacteria.
38)	Tenover, F. C.	Mechanisms of antimicrobial resistance in bacteria	*The American journal of medicine*	This study focuses on the main mechanisms that aid in increasing the resistance to antimicrobials in bacteria.	It found that the main mechanisms of resistance are limiting uptake of a drug, modification of a drug target, inactivation of a drug, and active efflux of a drug. These mechanisms may be native to the microorganisms or acquired from other microorganisms. Understanding more about these mechanisms should hopefully lead to better treatment options for infective diseases, and development of antimicrobial drugs that can withstand the microorganisms attempts to become resistant.
39)	Hamilton, K. W., & Fishman, N. O.	Antimicrobial stewardship interventions: thinking inside and outside the	*Infectious Disease Clinics*	The study aims to describe the effective methods of successfully conducting an Antimicrobial Stewardship Program.	This Study found that by targeting areas that are vulnerable to inappropriate antimicrobial use and by

		box			using novel strategies to increase the reach of stewardship interventions, providers can make antimicrobial stewardship a universal practice in all health care settings. This review discusses how stewardship can make large impacts in areas where it has traditionally been absent in facilities both with and without formal antimicrobial stewardship programs.

Discussion and Conclusion

- Recent estimates for the AMR burden strongly suggest that it is a growing level of global public health threat. It is also becoming a drain on the economy and the GDP of many nations as strategically and effectively combating it requires funds which not many have.
- In 1956, several publications believed that the mortality and morbidity from bacterial diseases had fallen so much that they were supposedly no longer among the important unsolved problems of medicine. They were unaware of the evolutionary ability of the bacteria to adapt easily to new environments, such as over-exposure to antibiotics. Moreover, these beliefs are even kept by several people of the public such as politicians and country leaders in today's day and age.
- Even though the treatments of many of the diseases have improved over time, the environment for bacterial infections have gradually worsened in nature due to the lack of new drugs causing the bacteria to adapt and gain increased level of antibiotic resistance.
- Antimicrobial resistance (AMR) has seen a gradual increase over the past two decades and now can be observed all over the world. This AMR although would be very difficult to eliminate, can be managed through judicious use of different resources and methods.
- To manage AMR, continuous efforts to educate the public is important. Most of the recent education efforts was towards medical professionals and to the adult public. However, as they have already established their knowledge, attitudes, and behaviours about antibiotic use, it will be difficult to change their deeply established views. It would have to be an initiative taken by the governing bodies to now educate children also.

- Many studies have shown that the educational efforts towards children, non-medical undergraduate students have helped in minimizing the incidences of AMR-Bacteria in those regions.

Limitations

- *Limited access to data* –No local library could be accessed due to the COVID-19 situation which had caused a long-term lockdown on the country.
- *Lack of available and/or reliable* data - Much of the material easily found was on unverified articles. For the verified research papers, special access was needed as many online libraries had a pay-to-read policy.
- *Presence of self-reported data* – Many pieces of literature had self-reported data and conclusions based on biased values assumed by their authors.
- *Cultural Bias* – Presence of cultural bias is admitted as the author is based mainly in city, and as much of the data and studies collects information from sub-urban and rural backgrounds the views and behaviours of the people (presiding in those areas) regarding this research topic may be different.

Recommendations

- It is observed that the public is largely ignorant of such rising cases and is firmly entrenched in the historic methods of just living-by. This can be seen by the fact that the simple case of effective and regular hand hygiene dramatically decreases the number of new incidences in hospital-acquired infections.
- Another fact is that simply educating the public about the associated complications and risks of excessive consumption of antimicrobial agents can show a significant decrease in newly found disease-causing microbes being largely non-antimicrobial resistant in nature. This education of the public can be conducted in programs known as Antimicrobial Stewardship (AMS). There are enough studies which prove and describe the steps to be followed and the goals to aim for when conducting such programs.
- Among other steps to be followed is that of the enforcement of Governmental Laws prohibiting the over-the-counter sale of antibiotics. This will help in greatly curbing the excessive consumption of antimicrobial agents by the public.

- General Practitioners could be advised to limit overprescribing certain antimicrobials as it is very much associated with an increased risk of adverse effects and complications of various natures.
- Several Studies strongly recommend that valid rapid point-of-care tests should be utilized instead of bulk prescribing antimicrobials. This would enable doctors to complete their diagnosis accurately and thus prescribe the correct dose, dosage for the correct time.
- Communication with patients should be enhanced with the aid of information brochures and the performance of more pragmatic studies in primary care with outcomes that will be specific the clinician's interest, such as potential complications and outcomes.

References

1) Lee, C. R., Cho, I. H., Jeong, B. C., & Lee, S. H. (2013). Strategies to minimize antibiotic resistance. *International journal of environmental research and public health*, *10*(9), 4274-4305.

2) Ancillotti, M., Eriksson, S., Veldwijk, J., Fahlquist, J. N., Andersson, D. I., & Godskesen, T. (2018). Public awareness and individual responsibility needed for judicious use of antibiotics: a qualitative study of public beliefs and perceptions. *BMC Public Health*, *18*(1), 1153.

3) Lowy, F. D. (2003). Antimicrobial resistance: the example of Staphylococcus aureus. *The Journal of clinical investigation*, *111*(9), 1265-1273.

4) Tanwar, J., Das, S., Fatima, Z., & Hameed, S. (2014). Multidrug resistance: an emerging crisis. *Interdisciplinary perspectives on infectious diseases*, *2014*.

5) Nikaido, H. (2009). Multidrug resistance in bacteria. *Annual review of biochemistry*, *78*, 119-146.

6) Cortez, K. J., & Maldarelli, F. (2011). Clinical management of HIV drug resistance. *Viruses*, *3*(4), 347-378.

7) Hurt, A. C. (2014). The epidemiology and spread of drug resistant human influenza viruses. *Current opinion in virology*, *8*, 22-29.

8) Llor, C., & Bjerrum, L. (2014). Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Therapeutic advances in drug safety*, *5*(6), 229-241.

9) Akram, M., Shahid, M., & Khan, A. U. (2007). Etiology and antibiotic resistance patterns of community-acquired urinary tract infections in JNMC Hospital Aligarh, India. *Annals of clinical microbiology and antimicrobials*, *6*(1), 4.

10) Biswas, D., Gupta, P., Prasad, R., Singh, V., Arya, M., & Kumar, A. (2006). Choice of antibiotic for empirical therapy of acute cystitis in a setting of high antimicrobial resistance.

11) Vromen, M., Van der Ven, A. J. A. M., Knols, A., & Stobberingh, M. E. E. (1999). Antimicrobial resistance patterns in urinary isolates from nursing home residents.

Fifteen years of data reviewed. *Journal of Antimicrobial Chemotherapy*, *44*(1), 113-116.

12) Hillier, S. L., Magee, J. T., Howard, A. J., & Palmer, S. R. (2002). How strong is the evidence that antibiotic use is a risk factor for antibiotic-resistant, community-acquired urinary tract infection? *Journal of antimicrobial chemotherapy*, *50*(2), 241-247.

13) Mathai, D., Rhomberg, P. R., Biedenbach, D. J., Jones, R. N., & India Antimicrobial Resistance Study Group. (2002). Evaluation of the in vitro activity of six broad-spectrum β-lactam antimicrobial agents tested against recent clinical isolates from India: a survey of ten medical center laboratories. *Diagnostic microbiology and infectious disease*, *44*(4), 367-377.

14) Palmer, A. C., & Kishony, R. (2013). Understanding, predicting, and manipulating the genotypic evolution of antibiotic resistance. *Nature Reviews Genetics*, *14*(4), 243-248.

15) Rossolini, G. M., Mantengoli, E., Docquier, J., Musmanno, R. A., & Coratza, G. (2007). Epidemiology of infections caused by multiresistant gram-negatives: ESBLs, MBLs, pan resistant strains. *MICROBIOLOGICA-BOLOGNA-*, *30*(3), 332.

16) Spellberg, B., Guidos, R., Gilbert, D., Bradley, J., Boucher, H. W., Scheld, W. M., ... & Infectious Diseases Society of America. (2008). The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. *Clinical infectious diseases*, *46*(2), 155-164.

17) Lee, J. H., Jeong, S. H., Cha, S. S., & Lee, S. H. (2009). New disturbing trend in antimicrobial resistance of gram-negative pathogens. *PLoS Pathog*, *5*(3), e1000221.

18) Lee, J. H., Jeong, S. H., Cha, S. S., & Lee, S. H. (2007). A lack of drugs for antibiotic-resistant Gram-negative bacteria. *Nature Reviews Drug Discovery*, *6*(11), 938-938.

19) Spellberg, B., Powers, J. H., Brass, E. P., Miller, L. G., & Edwards Jr, J. E. (2004). Trends in antimicrobial drug development: implications for the future. *Clinical infectious diseases*, *38*(9), 1279-1286.

20) Livermore, D. M. (2005). Minimizing antibiotic resistance. *The Lancet infectious diseases*, *5*(7), 450-459.

21) Levy, S. B. (1998). The challenge of antibiotic resistance. *Scientific American*, *278*(3), 46-53.

22) Nicasio, A. M., Eagye, K. J., Kuti, E. L., Nicolau, D. P., & Kuti, J. L. (2010). Length of stay and hospital costs associated with a pharmacodynamic-based clinical pathway for empiric antibiotic choice for ventilator-associated pneumonia. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *30*(5), 453-462.

23) Owens Jr, R. C. (2008). Antimicrobial stewardship: concepts and strategies in the 21st century. *Diagnostic microbiology and infectious disease*, *61*(1), 110-128.

24) Drew, R. H. (2009). Antimicrobial stewardship programs: how to start and steer a successful program. *Journal of Managed Care Pharmacy*, *15*(2 Supp A), 18-23.

25) Moehring, R. W., & Anderson, D. J. (2012). Antimicrobial stewardship as part of the infection prevention effort. *Current infectious disease reports*, *14*(6), 592-600.

26) Standiford, H. C., Chan, S., Tripoli, M., Weekes, E., & Forrest, G. N. (2012). Antimicrobial stewardship at a large tertiary care academic medical center: cost analysis before, during, and after a 7-year program. *Infection Control & Hospital Epidemiology*, *33*(4), 338-345.

27) Caron, W. P., & Mousa, S. A. (2010). Prevention strategies for antimicrobial resistance: a systematic review of the literature. *Infection and drug resistance*, *3*, 25.

28) Cantón, R., & Morosini, M. I. (2011). Emergence and spread of antibiotic resistance following exposure to antibiotics. *FEMS microbiology reviews*, *35*(5), 977-991.

29) Goff, D. A., Jankowski, C., & Tenover, F. C. (2012). Using rapid diagnostic tests to optimize antimicrobial selection in antimicrobial stewardship programs. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *32*(8), 677-687.

30) Siegel, J. D., Rhinehart, E., Jackson, M., & Chiarello, L. (2007). Management of multidrug-resistant organisms in health care settings, 2006. *American journal of infection control*, *35*(10), S165-S193.

31) Cosgrove, S. E. (2006). The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stays, and health care costs. *Clinical Infectious Diseases*, *42*(Supplement_2), S82-S89.

32) Roe, M. T., & Pillai, S. D. (2003). Monitoring and identifying antibiotic resistance mechanisms in bacteria. *Poultry Science*, *82*(4), 622-626.

33) Casewell, M., Friis, C., Marco, E., McMullin, P., & Phillips, I. (2003). The European ban on growth-promoting antibiotics and emerging consequences for human and animal health. *Journal of antimicrobial chemotherapy*, *52*(2), 159-161.

34) De Souza Mendes, C. D. U., & de Souza Antunes, A. M. (2013). Pipeline of known chemical classes of antibiotics. *Antibiotics*, *2*(4), 500-534.

35) Lloyd, D. H. (2012). Alternatives to conventional antimicrobial drugs: a review of prospects. *Veterinary Dermatology*, *23*(4), 299-e60.

36) World Health Organization. (2019). Antimicrobial stewardship programmes in health-care facilities in low-and middle-income countries: a WHO practical toolkit.

37) Doron, S., & Davidson, L. E. (2011, November). Antimicrobial stewardship. In *Mayo Clinic Proceedings* (Vol. 86, No. 11, pp. 1113-1123). Elsevier.

38) Joseph, J., & Rodvold, K. A. (2008). The role of carbapenems in the treatment of severe nosocomial respiratory tract infections. *Expert opinion on pharmacotherapy*, *9*(4), 561-575.

39) Bansal, D., Malla, N., & Mahajan, R. C. (2006). Drug resistance in amoebiasis. *Indian Journal of Medical Research*, *123*(2), 115.

40) Li, X. Z., & Nikaido, H. (2004). Efflux-mediated drug resistance in bacteria. *Drugs*, *64*(2), 159-204.

41) Tenover, F. C. (2006). Mechanisms of antimicrobial resistance in bacteria. *The American journal of medicine*, *119*(6), S3-S10.

42) Alekshun, M. N., & Levy, S. B. (2007). Molecular mechanisms of antibacterial multidrug resistance. *Cell*, *128*(6), 1037-1050.

43) Moehring, R. W., & Anderson, D. J. (2012). Antimicrobial stewardship as part of the infection prevention effort. *Current infectious disease reports*, *14*(6), 592-600.

44) Owens Jr, R. C. (2008). Antimicrobial stewardship: concepts and strategies in the 21st century. *Diagnostic microbiology and infectious disease*, *61*(1), 110-128.

45) Hamilton, K. W., & Fishman, N. O. (2014). Antimicrobial stewardship interventions: thinking inside and outside the box. *Infectious Disease Clinics*, *28*(2), 301-313.

46) Shah, P., Shrestha, R., Mao, Z., Chen, Y., Chen, Y., Koju, P., ... & Li, H. (2019). Knowledge, Attitude, and Practice Associated with Antibiotic Use among University Students: A Survey in Nepal. *International journal of environmental research and public health*, *16*(20), 3996.

47) Jawetz, E. (1956). Antimicrobial chemotherapy. *Annual review of microbiology*, *10*(1), 85-114

Part 2: Report on Online Course

1. **Name of the Course –** The Fundamentals of Digital Marketing
2. **Course Description –** This course is part of the "Google Digital Unlocked" platform. It is designed to help students master the basics of digital marketing with their free interactive Advertising Bureau-accredited course. There are 26 modules to explore, all created by Google trainers. It filled with practical exercises and real-world examples to help students turn knowledge into action.
3. **Objectives of the Course –**
    - Teach students the key-insights gained from analyzing data.
    - Engage the customers online in a way that markets one's presence**.**
    - Create a detailed business strategy that will help in gaining more customers.
    - Introduce students to different types of search ads
    - How to optimize the Web so that more visibility can be attained
    - Optimize content for the Mobile Web
    - Marketing via E-Mail and on other websites
    - Deep understanding of Display Advertising
    - Introduction to video content for advertising and marketing
    - Introduction to E-Commerce
    - Optimizing content for the international audience.
4. **Course Contents –**
    - *The Online Opportunity*
        - Introduction to Digital Unlocked
        - The Digital Opportunity
    - *First Steps Online*
        - Online Goals
        - Building online presence
        - Marketing online presence
        - Analyze and Adapt
    - *Build web presence*
        - Choosing online presence
        - How websites work
        - Website key points
        - Websites and student's business goals
        - Making one's website easy to use
        - Website design do's and don'ts
    - *Planning online business strategy*
        - The benefits of an online strategy
        - Taking a business online
        - Understanding customer behavior
        - How to stand out from the competition

    - Using goals to improve business performance
- *Get Started with search*
    - Search engine basics
    - How search engines work
    - How search engines see the web
    - Organic search explained
    - Paid search explained
    - Google Search Console
- *Get Discovered with search*
    - Introduction to Search engine Optimization (SEO)
    - The importance of an SEO plan
    - The SEO process
    - How to choose keywords
    - Setting realistic SEO goals
- *Make Search work for you*
    - Making web pages search friendly
    - How other websites can work for you
    - Cross borders with SEO
- *Be noticed with Search ads*
    - Introduction to search engine marketing (SEM)
    - The SEM auction
    - What makes a good keyword?
    - Make your ads stands out
- *Improve your search campaigns*
    - Achieve relevance with good structure
    - Get the most from your keywords
    - Fine-tune with keywords match types
    - How to know what is working and what is not
- *Get noticed locally*
    - Marketing to the locals
    - The power of local directories
- *Help people nearby find you online*
    - Using digital to advertise locally
    - Reaching locals on their mobiles
    - SEO for local businesses
- *Get noticed with social media*
    - Social media basics
    - The right social media sites for you
    - Setting your goals for social media
    - Getting on social media
- *Deep dive into social media*
    - Your long-term social media plan
    - Advertising on social media
    - Measuring success in social media
    - Avoiding social media pitfalls
- *Discover the possibilities of mobile*
    - The evolution of mobile devices
    - Understanding mobile web and mobile apps
    - Understanding mobile apps

- *Make Mobile work for you*
    - Introduction for advertising on mobile
    - Search campaigns for mobile
    - Display campaigns for mobile
    - Social media campaigns for mobile
    - Video for mobile
- *Get started with content marketing*
    - Introduction to content marketing
    - Get to know your online customers
    - Choosing the right format for your content
    - Writing for online audiences
    - Help your content be seen
    - Measuring your success in content marketing
- *Connect through email*
    - Email marketing basics
    - Your email marketing options
    - Crafting great marketing emails
    - Managing successful email campaigns
    - Measuring success in email marketing
- *Advertise on other websites*
    - What is display advertising?
    - Search advertising vs. Display advertising
    - The ins and outs of display advertising
- *Deep dive into display advertising*
    - Making display ads meet your goals
    - Understanding ad networks
    - How retargeting works
- *Make the most of video*
    - The rise of online video
    - How video fits into your online strategy
    - Creating video content within your budget
    - Sharing and promoting your videos
    - Advertising on video sharing sites
    - Measuring video performance
- *Get started with analytics*
    - What are web analytics?
    - Making web analytics work for you
    - Tracking specific goals with web analytics
- *Find success with analytics*
    - Web analytics and organic search
    - Tools to measure SEM
    - Breaking down your data for insights
- *Turn data into insights*
    - Using data to understand audiences
    - Understanding the Data Cycle
    - Creating actionable insights from your data

    - Managing numbers using spreadsheets
    - Presenting data effectively
- *Build your online shop*
    - Using e-commerce to sell
    - Taking payments and manage orders
- *Sell more online*
    - Creating a smooth e-commerce experience
    - Product promotion and merchandising
    - Retargeting for e-commerce
- *Expand internationally*
    - Introduction to international marketing and export
    - Validating your new market
    - Being understood abroad
    - Advertise across borders
    - The support systems you will need
    - Helping customers abroad buy your products
    - Delivering to customers across the globe.

5. **Learning Methodology used in the course –** There was an abundance of lectures in video format. They also judiciously used case studies when needed as an example for explanation of different parts of theory. Some reading material was available in the form of pdf. It was extra reading material for subjects they had already covered, thus ensuring in providing a deeper understanding of the topic.

6. **Key Learnings from the Course –** This course has some important key learning which are as follows:

- It explains the fundamentals of analytics and data insights
- It explains how to formulate an effective business strategy
- It explains how to create and market content
- It goes into the depths of Display advertising
- It teaches how to appropriately utilize E-Commerce.
- It advises on how to effectively manage email marketing.
- It explains the importance of local marketing
- It explains the Mobile web, that is, utilization of web services specific to mobile users.
- It explains Search Engine Marketing (SEM)
- It explains Search Engine Optimization (SEO)
- It teaches the appropriate usage of Social Media
- It advises on creating quality video content
- It also focuses on Web Optimization.