Antibiotic resistance- A review

Author details:

1. Dr.Riddhi Tandon,

Junior Resident,

Mahabir Institute of Medical Sciences, Bhopal

2. Dr. Suresh Bhambhani

Associate Professor,

Department of Medicine,

Chirayu Medical College and Hospital,

Bhopal

Corresponding author:

1. Dr.Riddhi Tandon,

Junior Resident,

Mahabir Institute of Medical Sciences, Bhopal

ABSTRACT

Background: Through the selection of resistant mutants, activation of latent resistance mechanisms, or acquisition of resistance determinants genes, bacteria may become more resistant after exposure. All of these processes may be sped up by antibiotic pressure.**Objectives:** To evaluate appropriate investigations and ascertain the condition of antibiotic resistance. **Methods:** After a thorough search of the online journals, 103 documents were found in total, and 54 of the papers were initially chosen. Then, 22 similar/duplicate articles were removed, leaving 41 investigations that were initially available. After reviewing the submissions' abstracts and titles, 17 more articles were disqualified. Finally, 21 papers that satisfied the inclusion and exclusion requirements were selected, including study articles and control trials.**Results:** All the 21 articles reported extensive antibiotic resistance to antimicrobial therapies, especially in cases of gram-negative bacterium. **Conclusion:** Finding strategies that can effectively lessen the burden of bacterial resistance towards antibiotics is the primary concern, whether they are applied in a variety of settings or are precisely tailored to the resources available and the most effective pathogen-drug combinations in a given environment.

Keywords: Antibiotic resistance, Antimicrobial therapy, E.coli, Gram negative bacteria, Multi-drug resistance

INTRODUCTION

Antibiotic resistance, or ABR, in human bacterial pathogens as a result of its use is widely acknowledged to be a severe threat to global public health. Recent studies suggest that more than 1 million deaths occur each year as a result of resistant bacterial infections [1]. In low- and middle-income countries, where resistance surveillance is typically weak, the majority of disease burden is concentrated. For instance, according to a 2016 estimate, sepsis caused by resistant bacteria is considered to be the cause of more than 200 000 neonatal deaths annually, most of which occur in the aforementioned countries; many of these cases were not included in the aforementioned global total.

Since acquired ABR infections frequently have serious consequences for human health (and, conversely, effective antibiotics have enormous benefits), the harms of resistant infections are

frequently unequally distributed, and human actions are significant contributors to the issue, acquired ABR is an important subject for ethical analysis. Making and executing legislation to address drug resistance necessitates striking a balance between numerous ethical principles and various types of advantages and drawbacks[2].

Bacteria that can harm humans are present everywhere, including the external environment, other humans' microbiomes with whom each person comes into touch, and the human microbiome, which contains more bacterial species than the cells of the host organism[3]. The majority of the global burden of bacterial disease in humans is associated with organisms that healthy people carry for extended periods of time, frequently asymptomatically, either as temporary colonisers or as components of the typical human microbiome.

Antibiotic use inevitably exposes this microbiome to varying concentrations of substances that are differently deadly to various bacterial species (or subpopulations within a species)[4]. Pathogens may develop more resistance after exposure through the selection of resistant mutants, activation of latent resistance mechanisms, or acquisition of mobile resistance determinants from other species, all of which may be accelerated by antibiotic pressure. Antibiotic pressure also contributes to the widespread spread of resistance to any specific antibiotic by enabling the clearing of niches for more resistant bacteria. Antibiotics can also expose bacteria in the natural environment, such as in human waste, medical waste, and veterinary or agricultural settings. Furthermore, individuals who are not receiving antibiotic medication might directly contract resistant microorganisms by contact with diseased or colonised individuals, animals, or other environmental reservoirs[5].

Using antibiotics can result in, or at least hasten, the development of acquired ABR in bacteria that can subsequently go on to cause disease, even while the enormity of the advantage of living in the antibiotic era is difficult to overstate. The major issue that clinicians, among others, have sought to address is the contradiction between the advantages of having efficient antibiotics available to cure infectious infections and the development of resistance through their usage.

Modern medicine was completely transformed by the discovery, widespread use, and commercialization of antimicrobial drugs to treat infections. Antibiotics are now one of the most crucial medical treatments required for the advancement of sophisticated medical techniques, including cutting-edge surgical methods, organ transplantation, and the management of cancer patients, among others. Unfortunately, this therapeutic success is now under jeopardy due to the dramatic rise in antibiotic resistance among common bacterial

infections, endangering the recovery of critically ill patients. In fact, one of the top three risks to public health in the twenty-first century, according to the World Health Organization, is antibiotic resistance[6].

Multidrug-resistant (MDR) infections have been linked to higher fatality rates than infections brought on by susceptible bacteria, and they are also thought to be a significant economic burden, costing over $20 billion annually in the US alone. According to a conservative estimate from the Centres for Disease Control and Prevention, an infection with an antibiotic-resistant bacteria causes at least 23,000 deaths every year in the USA [7]. Additionally, a recent study estimates that antibiotic resistance would result in 300 million premature deaths by 2050, costing the global economy up to $100 trillion (£64 trillion) [8]. The lack of a strong pipeline of antibiotics makes the issue worse by encouraging the establishment of illnesses that are nearly incurable and depriving clinicians of trustworthy alternatives to treat infected patients.

Hence, through the means of this systematic review, we aim to assess selected studies and determine the status of antibiotic resistance and observe if the levels of this phenomenon have witnessed any change due to recent major events such as the COVID-19 pandemic.

MATERIALS AND METHODS

Protocol employed

This systematic review was performed as per the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) strategy and rules from the Cochrane group and the book Orderly reviews in Health care: Meta examination.

Review hypotheses

Through the selection of studies, this systematic review sought to examine the current state of antibiotic resistance and determine whether its levels have changed over the years.

Study selection

There were a total of 103 documents discovered after extensive search on the online journals and 54 of the papers were selected initially. Following that, 22 similar/duplicate articles were

eliminated, which resultantly made 41 separate papers available at first. The abstracts and titles of submissions were then reviewed, and a further 17 papers were eliminated. Finally, 21 documents that met the inclusion and exclusion criteria were chosen, which included study articles and randomised/non-randomised control trials.

Inclusion criteria

Articles that contained relevant data for the review objectives, which included all age populations, were selected for full-text screening. Studies that reported randomised/non-randomised studies, systematic reviews containing substantial sample volume, detailed case reports and validated questionnaire-based were considered for inclusion in our review.

Exclusion criteria

The following were excluded from the scope of our systematic review: incomplete data, seminar presentations, scholarly articles and opinion articles.

Since the literature available on this topic is quite scant in volume with respect to our study objective, we did not limit our search in terms of the time period when the studies were published i.e. we took into account all the papers that were published with context to our topic (where the number of papers itself was found to be quite sparse in number).

Placebo-controlled studies were not included in the analysis. Also excluded were literature reviews and cases published in languages other than English.

Search strategy

Using relevant keywords, reference searches, and citation searches, the databases PubMed-MEDLINE, Web of Science, Cochrane, and Scopus were all searched. "Antibiotic resistance," "E.coli," "Multi-drug resistance" and“Gram negative bacteria" were the search terms used to search the database.

Data selection and coding

Two independent reviewers searched relevant articles by using the appropriate keywords in various databases and online search tools. The chosen articles were compared, and a third reviewer was brought in if there was a dispute.

After choosing the articles, the same two reviewers independently extracted the following data: author, year of publication, country, kind of publication, study topic, population demographics (n, age), outcome measure(s), relevant result(s), and conclusion (s). The data was compared and any differences were discussed with a third reviewer.

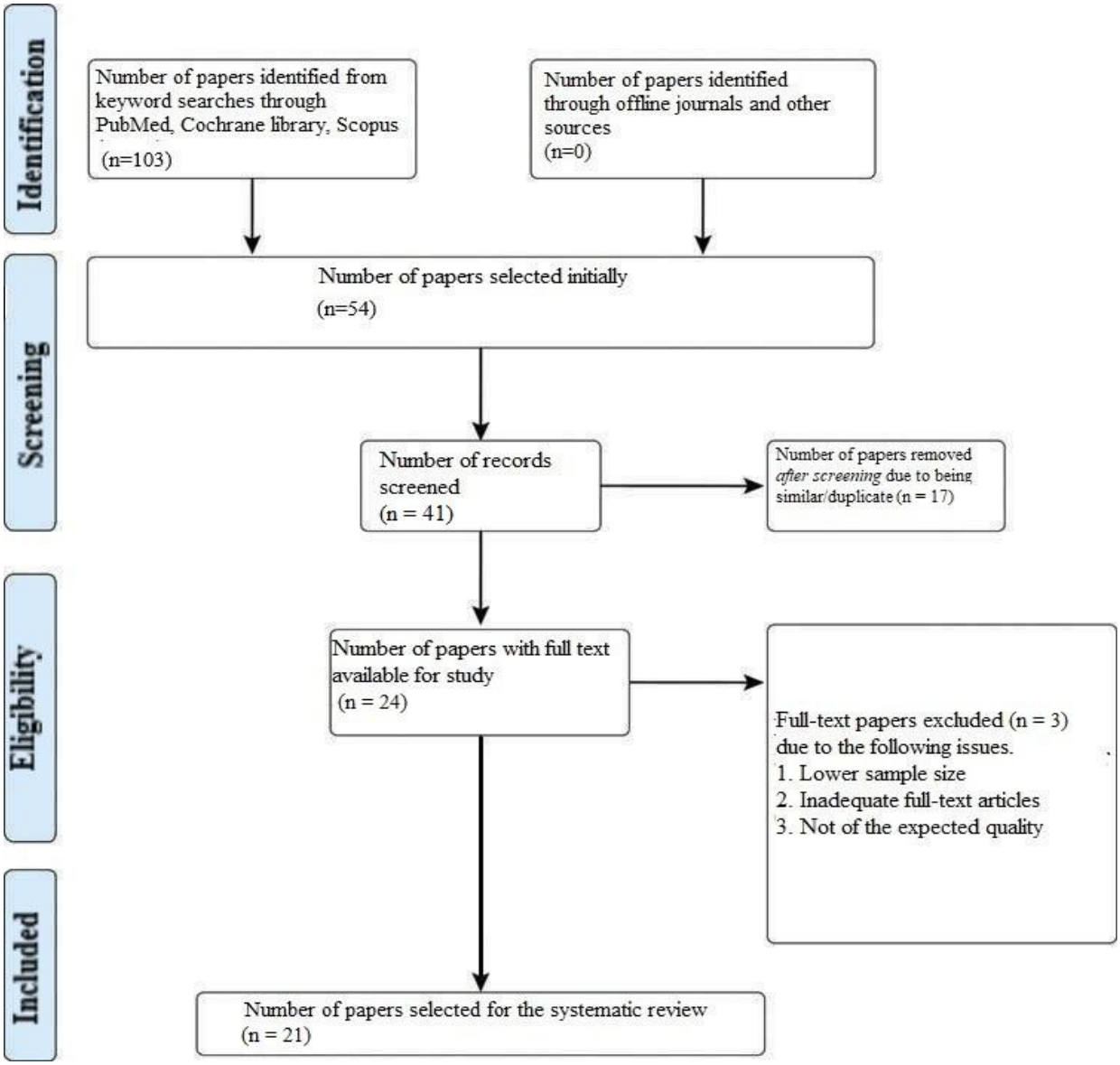

Figure 1: Representation of selection of articles through PRISMA framework

RESULTS

Given below in table 1 are the demographic characteristics of the studies that were selected after applying the relevant inclusion/exclusion criterion. The table also presents information about the type of studies, their sample sizes, age groups of selected participants and the study's outcomes.

Author and year of study	*Sample size and mean age*	*Study design*	*Study description*	*Study inference*
Amanati et al 2021 [9]	414 patients; >18 years	Retrospective study	This study looked into the risk factors, microbiology, and epidemiology of multi-drug resistant bacterial bloodstream infections (BSIs) and mortality in adult cancer patients in Shiraz, Iran. Also presented were BSI antimicrobial resistance patterns over a four-year period.	While the prevalence of multi-drug resistant gram-negative BSI grew annually between 2015 and 2018, the mortality rate of gram-negative BSI remained constant at around 20%.
Becerra et al 2019 [10]	10160 household contacts of 3339 index patients	Prospective cohort study	In this study, the risk of tuberculosis infection and sickness among household contacts of patients with pulmonary tuberculosis was compared to the phenotypic drug resistance.	Household connections of multi-drug resistant tuberculosis patients were more likely to contract the disease than contacts exposed to drug-sensitive tuberculosis. Contacts in both groups were equally at risk of contracting tuberculosis.
Burr et al 2022 [11]	40 adults	Randomised control trial	In a randomised, single-blinded, parallel-group trial of 4 weeks of twice-daily oral 400 mg erythromycin ethylsuccinate or twice-daily oral 125 mg azithromycin, the authors examined the effects of prolonged exposure to azithromycin or	Both erythromycin and azithromycin caused a proportional increase in the oropharyngeal streptococci's macrolide resistance, which persisted above baseline levels for the azithromycin group after washout. With azithromycin and erythromycin, resistance gene levels dramatically rose; only the erythromycin group's levels returned to baseline after washout. The lack of concurrent

			erythromycin on phenotypic and genotypic macrolide resistance within the oropharyngeal microbiome of 20 healthy adults and their 20 close contacts.	changes in resistance gene levels reported in close contacts indicated that they did not discover any proof of forward transfer of resistance to close contacts.
Doan et al 2020 [12]	3232 samples; age range: 1-59 months	Randomised control trial	Children who received azithromycin twice a year for four years had their gut resistomes examined by the investigators. They enrolled 30 communities in a parallel study where they were randomised to receive either azithromycin or a placebo, which was given to all infants and toddlers between the ages of 1 and 59 months, every six months for four years. Rectal swabs from the individuals were taken at baseline, 36 months, and 48 months to analyse their gut resistome. The ratio of macrolide-resistance markers in the azithromycin group to those in the placebo group at 48 months served as the primary outcome.	Antibiotic resistance was more prevalent in the villages that received azithromycin than in the villages that received placebo among the villages that were randomly assigned to receive large distributions of either medication twice a year for four years.
Harris et al 2018 [13]	391 individuals; ≥18 years	Randomised control trial	For a minimum of 4 days and a maximum of 14 days, with the total duration being decided by the treating physician, patients were randomly assigned 1:1 to intravenous piperacillin-tazobactam, 4.5 g, every 6 hours (n = 188 participants), or meropenem, 1 g, every 8 hours (n = 191).	In patients with bloodstream infections caused by E. coli or K.sulphonam and ceftriaxone resistance, definitive treatment with piperacillin-tazobactam did not result in a noninferior 30-day mortality when compared to meropenem.
Hulten et	345 patients;	Randomi	A fixed-dose triple-therapy	In comparison to earlier publications, it was

al 2021 [14]	46.4 years	sed control trial	regimen of amoxicillin, rifabutin, and omeprazole was compared to a fixed-dose dual-therapy comparator in a double-blinded phase III clinical research that included 455 patients (amoxicillin–omeprazole). At 51 facilities in 20 states, minimum inhibitory concentrations (MICs) were discovered for 345 clinical isolates acquired from patients who had never received treatment.	discovered that a higher percentage of US isolates had metronidazole (43.6%), levofloxacin (57.8%), and clarithromycin (17.6%) resistance. This study demonstrated substantial rates of metronidazole resistance in every region, as was already mentioned. Rifabutin was not resistant to any isolate. Although at low rates (amoxicillin resistance, 6.4%; tetracycline resistance, 2.8%), amoxicillin and tetracycline resistance were both found.
Jo et al 2021 [15]	14 adults	Prospecti ve randomis ed study	The authors examined microbial changes on skin following treatment using systemic antibiotics in healthy human volunteers in a prospective, randomised study of four therapeutically relevant antibiotic regimens (doxycycline (20mg or 100mg), cephalexin, or trimethoprim/sulfamethoxaz ole). Shotgun metagenomic sequencing was done on samples from various skin and oral locations, stool, and before, throughout, and up to a year after antibiotic use.	Bacterial culture along with whole-genome sequencing identified distinct emergence, growth, and persistence of antibiotic-resistant staphylococci carrying genes in each individual who had received 100mg of doxycycline, respectively.
Kayigire et al 2017 [16]	14 adults	Prospecti ve cohort study	The longest period of time deemed safe for monotherapy was 14 days, during which time the authors treated 14 newly diagnosed, rifampicin (RIF)-susceptible TB patients with RIF at the standard dose of 10 mg/kg of body	After 30 days of monotherapy, a statistical model predicted that 1% of the live mycobacteria might be RIF resistant. This suggested that RIF monotherapy time and space windows due to unequal medication distribution within lung lesions might have aided in the development of RIF resistance.

			weight/day. This was followed by the full course of standard combination therapy to guarantee cure for those subjects.	
Korkmaz et al 2022 [17]	210 individuals; ≥ 18 years	Prospecti ve study	In this study, the nasal and nasopharyngeal surfaces were subjected to aerobic microbiological examination. The social insurance database was used to retrieve the past six months' worth of antibiotic administration data. By using Pearson's chi-square test or Fisher's exact test, the culture outcomes of participants who had received antibiotic treatment and those who had not were compared.	Although the incidence of methicillin resistance in coagulase-positive and –negative Staphylococci had demonstrated significant increase when patients received antibiotic during the previous month, antibiotic exposure did not cause perturbations in the overall composition of upper airway flora within 6 months. That was supposed to be taken into account while using a broad-spectrum antibiotic, as nosocomial Staphylococcus infections had a higher morbidity and mortality rate due to methicillin resistance.
Leo et al 2021 [18]	56 individuals; ≥ 18 years	Nested prospecti ve cohort study	In this nested prospective cohort study, adult patients hospitalised at Geneva University Hospitals (Switzerland) who were enrolled in the PIRATE randomised trial comparing shorter (7 days vs. 14 days) antibiotic courses for gram-negative bacteraemia were referred to as "cases" while hospitalised patients with a similar demography and comorbidity who were not receiving antibiotic therapy were referred to as "controls." In both the case and control groups, stool samples were taken on days 7, 14, 30 and 90 following	In patients being treated for gram-negative bacteraemia, cutting the length of antibiotics in half had no impact on the variety of the microbiota or the abundance of antibiotic resistance genes.

			the start of the antibiotics (day 1) and on days 7 and 14 following admission, respectively.	
Pilmis et al 2021 [19]	55 individuals	Prospective clinical trial	55 individuals who received intravenous ceftriaxone (1 g/24 h) or cefotaxime (1 g/8 h) for at least three days participated in a prospective clinical trial. To evaluate the emergence of third-generation cephalosporin (3GC)-resistant Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, Pseudomonas aeruginosa, toxigenic Clostridioides difficile, and vancomycin-resistant enterococci, three fresh stool samples were taken from each patient on days 0, 3, and 7 or at the conclusion of intravenous treatment.	There were no appreciable differences in the appearance of gram-negative enteric bacilli that are 3GC-resistant (Enterobacteriaceae), Enterococcus spp., and non-commensal microorganisms across the groups. Both drugs decreased the overall gram-negative enteric bacilli counts and the cultivable diversity of the microbiota, although there was no statistically significant difference between the groups, which meant there was no discernible difference in the establishment of resistance between ceftriaxone and cefotaxime.
Reyman et al 2022 [20]	147 infants	Randomised control trial	Three commonly prescribed intravenous antibiotic combinations, namely penicillin + gentamicin, co-amoxiclav + gentamicin, or amoxicillin + cefotaxime, were administered to 147 infants who required broad-spectrum antibiotics for the treatment of early-onset neonatal sepsis in their first week of life.	In comparison to penicillin + gentamicin, amoxicillin + cefotaxime had the greatest effects on the antimicrobial resistance gene profile as well as the composition of the microbial community.
Rueda et al 2019 [21]	4088 infants	Prospective study	In three Neonatal Care Units in Peru, a prospective study was conducted as a secondary analysis of a	Antibiotic resistance was more likely to develop when premature new-borns were given antibiotics for longer than what was recommended. Neonates with lower BW

			clinical trial. The clinicians included new-borns with a birth weight (BW) of less than 2000g in the first 72 hours of life and defined the usage of antibiotics in terms of antibiotic courses and length of therapy (LOT) per 1000 patient days (PD).	exhibit increased antibiotic usage. The most often used antibiotic was vancomycin.
Shaikh et al 2016 [22]	769 children; 2-71 months old	Randomised control trial	In order to identify the risk factors for bacteria that were resistant to narrow spectrum antibiotics in urinary tract infections, 769 children were included in this study.	The researchers came to the conclusion that uncircumcised males, Hispanic children, children with bladder bowel dysfunction, and kids who had recently finished an antibiotic course had a higher risk of developing a urinary tract infection brought on by pathogens that were resistant to one or more narrow-spectrum antibiotics.
Singh et al 2019 [23]	120 children; ≤ 5 years	Randomised clinical trial	120 E. coli isolates (both diarrheagenic and non-pathogenic), recovered from fresh stool samples taken from children under the age of five in Delhi, India, were examined for antibiotic resistance genes and single nucleotide polymorphisms (SNP) in the gyrA and parC genes in the quinolone resistance-determining region (QRDR). Testing for antibiotic susceptibility was done in accordance with the norms set by the Clinical and Laboratory Standards Institute (CLSI).	The development, spread, and transport of antibiotic resistance in the gut of healthy children was indicated by the presence of antibiotic resistance genes in E. coli isolates from those children.
Skalet et al 2010 [24]	Age range 1-10 years	Cluster randomised trial	In this study in Ethiopia to manage trachoma, children aged 1 to 10 years were randomly assigned to receive mass azithromycin treatments at months 0, 3,	This cluster-randomized clinical research showed that nasopharyngeal pneumococcal resistance to macrolides was considerably higher in communities randomised to extensive azithromycin therapy compared to untreated control areas.

			and 6 and 9. Randomly assigned to receive no antibiotic treatments whatsoever until the study's conclusion were twelve control villages. Nasopharyngeal swabs were taken from children in the treatment group at baseline, month 12, and in the control group at month 12 who were chosen at random. Using Etest strips, Streptococcus isolated from the swabs were tested for antibiotic susceptibility.	
Street et al 2001 [25]	150 individuals; 2-18 years	Randomised control trial	Each of Groups 1 and 2 contained 75 consecutive patients. Patients in group 2 received amoxicillin and clarithromycin for eight days along with either ranitidine or omeprazole, whereas those in group 1 received two antibiotics based on antibiotic susceptibility tests. Six months following therapy, the eradication rate in both groups was evaluated.	As a very high percentage of test subjects recovered from their illnesses, antibiotic susceptibility testing was helpful in children. Although expensive, the strategy limited the spread of antibiotic resistance by using just certain antibiotics.
Van Duijn et al 2022 [26]	1613 individuals; 61.2 years	Prospective cluster-randomised control study	Patients who had at least one complete culture taken and a first negative culture were included. Community acquisitions (admitted within two days or less) were not included. Acinetobacter species and Pseudomonas aeruginosa species with reduced susceptibility to piperacillin-tazobactam or	The probability of developing resistance to Gram-negative ARB during cycling and mixing did not differ between individuals.

			carbapenems, as well as Enterobacterales species with reduced susceptibility to third- or fourth-generation cephalosporins or piperacillin-tazobactam, were the primary outcomes.	
Willmann et al 2019 [27]	41 individuals; 55.75 years	Longitudinal multicentre cohort study	The authors measured changes in the gut microbiome in two cohorts of haematological patients who were taking prophylactic antibiotics using shotgun metagenomics; one cohort received ciprofloxacin treatment in a hospital in Tübingen and the other received cotrimoxazole treatment in a hospital in Cologne.	By analysing the extensive longitudinal data, it was discovered that, while impacts on the gut resistome varied, reductions in gut microbial diversity were similar in both treatment cohorts. The Cologne cohort, but not the Tübingen cohort treated with ciprofloxacin, showed a substantial increase in the relative abundance of 96ulphonamide antibiotic resistance genes (ARGs) by 148.1% per cumulative specified daily dose of cotrimoxazole.
Wittekamp et al 2018 [28]	8665 individuals; 64.1 years	Randomised control trial	This randomised experiment was carried out from December 1, 2013, to May 31, 2017, in 13 European ICUs where extended spectrum –lactamase-producing Enterobacteriaceae are responsible for at least 5% of bloodstream infections.	Chlorhexidine (CHX) mouthwash, selective oropharyngeal decontamination (SOD), and selective digestive tract decontamination (SDD) use among patients receiving mechanical ventilation in ICUs with moderate to high antibiotic resistance prevalence was not linked to decreases in ICU-acquired bloodstream infections brought on by multi-drug resistant gramme negative bacteria when compared to standard care.
Zegers et al 2017 [29]	176 children	Randomised control trial	In a cohort of 176 patients with spina bifida, 88 were maintained on antibiotic prophylaxis (AP) and 88 stopped. A catheterized urine sample collected every two weeks for 18 months was cultured for bacterial infections. The investigators contrasted the proportion of	Reduced bacterial resistance to antibiotics in kids with spina bifida was related to stopping antibiotic prophylaxis for urinary tract infections.

			isolated bacteria in the two groups that were resistant to widely prescribed antibiotics.	

Table 1: Characteristics of selected articles for the review

DISCUSSION

Antimicrobial resistance is a long-standing phenomenon that is an expected outcome of the interactions between numerous species and their surroundings[30]. Since the majority of antimicrobial substances are naturally occurring chemicals, bacteria have developed strategies to thwart their effects in order to survive. As a result, these organisms are frequently thought of as having "intrinsic" resistance to one or more antibiotics. Bacteria carrying inherent resistance determinants are not the main concern when talking about the antimicrobial resistance conundrum, though. The expression of "acquired resistance" in a bacterial population that was initially susceptible to the antimicrobial drug is what is commonly meant in clinical situations[31]. The emergence of acquired resistance can be caused by changes in chromosomal genes or by the acquisition of external genetic determinants of resistance, probably acquired from naturally occurring, inherently resistant animals. It's also critical to understand that in clinical practise, the idea of antibiotic resistance/susceptibility is a relative phenomenon with multiple levels of complexity.

In the study by Doan et al [12], it was found that villages receiving azithromycin had higher rates of antibiotic resistance than villages receiving a placebo. This result concurs with the review conducted by Zhou et al [32], which found moderate levels of azithromycin resistance in individuals infected with N. gonorrhoeae. Amanati et al 2021 [9]investigated the correlation between bloodstream infections and gram-negative bacterium induced resistance, something which was also investigated by Wirtschafter et al [33], where antibiotic-use measures were about 10-fold higher which was an upper limit of neonatal intensive care unit infection burden. Children under the age of 18 years were reported in 8 studies selected for our review [12, 20-25, 29], with 5 of these investigations involving infants [12, 20-23]. Zegers et al [29] investigated the incidence of antibiotic resistance in children afflicted with spina bifida, which was a pioneering study in this regard. Bell et al [34] investigated the relationship between antibiotic consumption and antibiotic resistance, and the outcome of the study is similar to the articles by Leo et al and Pilmis et al [18-19]. Fixed dose combinations of

antibiotics were investigated in 3 of our studies [13, 14, 20] depicting antibiotic resistance against the newer antibiotics, with available literature [35-37] reporting similar instances of resistance development against newer antibiotics and the need for further advancements in this field.

Clinical susceptibility breakpoints (susceptible, intermediate, and resistant) are established mostly based on an antibiotic's in vitro effectiveness against a sizable bacterial sample in conjunction with specific pharmacological factors (e.g., blood and infection site concentrations of the antimicrobial, among others)[38]. As a result, depending on the clinical situation and the available options for therapy, the interpretation of susceptibility patterns may change when treating bacteria that are resistant to antibiotics. For instance, the level of gentamicin found in the urine may be high enough to treat a lower urinary tract infection brought on by a gentamicin-resistant bacteria. For Streptococcus pneumoniae, various penicillin breakpoints have been defined based on whether the isolate is causing meningitis vs. other types of infections, taking into account the amounts of medication that actually reaches the cerebral fluid [39-40]. Additionally, the size of the bacterial inoculum may affect an organism's in vivo susceptibility to a certain antibiotic; this phenomenon has been extensively studied in Staphylococcus aureus infections with various cephalosporins. In fact, there is data that suggests some cephalosporins (such as cefazolin) may not work in the case of deep-seated infections brought on by S. aureus that is susceptible to cephalosporins[41].

Speaking about the limitations of the study, we tried to keep them to a minimum by selecting studies that had a very large initial sample size as well as follow-up sample strength. However, the representation of gram positive bacterium in our study was slightly less than what is expected from an investigation on antibiotic resistance. Moreover, the bacterial spectrum observed in our selected studies was somewhat narrow, but the available literature in online databases was itself lacking in studies depicting antibiotic resistance against gram-positive bacterium which we believe offsets this limitation to a certain extent.

CONCLUSION

According to the studies we reviewed, antibiotic resistance has been increasing over the past ten years, particularly in the wake of the epidemic that ravaged the medical community. The main goal is to identify strategies that can successfully lessen the burden of bacterial resistance to antibiotics, regardless of the context in which they are used or how precisely

they are adapted to the resources at hand and the most efficient pathogen-drug combinations in a particular setting.

REFERENCES

1. The Review on Antimicrobial Resistance. Tackling a crisis for the health and wealth of nations. In: Chaired by. In: O'Neill J (ed.). The Review on Antimicrobial Resistance. December, 2014.
2. Jamrozik E, Selgelid MJ. Drug-resistant infection: causes, consequences, and responses. In: Jamrozik E, Selgelid MJ (eds.). Ethics and Drug Resistance: Collective Responsibility for Global Public Health. Public Health Ethics Analysis. Cham, Switzerland: Springer, 2020
3. Littmann J, Viens AM. The ethical significance of antimicrobial resistance. Public Health Ethics 2015; 8:209–24.
4. Boden L, Mellor D. Epidemiology and ethics of antimicrobial resistance in animals. In: Jamrozik E, Selgelid M (Eds.). Ethics and Drug Resistance: Collective Responsibility for Global Public Health. Cham: Springer International Publishing, 2020,109–21
5. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoSBiol 2016; 14:e1002533.
6. Jamrozik E, Selgelid MJ. Surveillance and control of asymptomatic carriers of drug-resistant bacteria. Bioethics 2019; 33:766–75.
7. Blanquart F. Evolutionary epidemiology models to predict the dynamics of antibiotic resistance. EvolAppl 2019; 12:365–83.
8. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. Clin Infect Dis. 2006 Jan 15; 42(Suppl 2):S82–9.
9. Amanati A, Sajedianfard S, Khajeh S, Ghasempour S, Mehrangiz S, Nematolahi S, Shahhosein Z. Bloodstream infections in adult patients with malignancy, epidemiology, microbiology, and risk factors associated with mortality and multi-drug resistance. BMC Infect Dis. 2021 Jul 2; 21(1):636. doi: 10.1186/s12879-021-06243-z. PMID: 34215207; PMCID: PMC8254331.

10. Becerra, Mercedes & Huang, Chuan-Chin &Lecca, Leonid &Bayona, Jaime & Contreras, Carmen &calderón, Roger &Yataco, Rosa & Galea, Jerome & Zhang, Zibiao& Atwood, Sidney & Cohen, Ted & Mitnick, Carole & Farmer, Paul & Murray, Megan. (2019). Transmissibility and potential for disease progression of drug resistant Mycobacterium tuberculosis: Prospective cohort study. BMJ. 367. L5894. 10.1136/bmj.l5894.
11. Burr LD, Taylor SL, Richard A, Schreiber V, Lingman S, Martin M, Papanicolas LE, Choo JM, Rogers GB. Assessment of Long-Term Macrolide Exposure on the Oropharyngeal Microbiome and Macrolide Resistance in Healthy Adults and Consequences for Onward Transmission of Resistance. Antimicrob Agents Chemother. 2022 Apr 19; 66(4):e0224621. doi: 10.1128/aac.02246-21. Epub 2022 Mar 16. PMID: 35293783; PMCID: PMC9017296.
12. Doan T, Worden L, Hinterwirth A, Arzika AM, Maliki R, Abdou A, Zhong L, Chen C, Cook C, Lebas E, O'Brien KS, Oldenburg CE, Chow ED, Porco TC, Lipsitch M, Keenan JD, Lietman TM. Macrolide and Nonmacrolide Resistance with Mass Azithromycin Distribution. N Engl J Med. 2020 Nov 12; 383(20):1941-1950. doi: 10.1056/NEJMoa2002606. PMID: 33176084; PMCID: PMC7492079.
13. Harris PNA, Tambyah PA, Lye DC, Mo Y, Lee TH, Yilmaz M, Alenazi TH, Arabi Y, Falcone M, Bassetti M, Righi E, Rogers BA, Kanj S, Bhally H, Iredell J, Mendelson M, Boyles TH, Looke D, Miyakis S, Walls G, Al Khamis M, Zikri A, Crowe A, Ingram P, Daneman N, Griffin P, Athan E, Lorenc P, Baker P, Roberts L, Beatson SA, Peleg AY, Harris-Brown T, Paterson DL; MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN). Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients with E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftriaxone Resistance: A Randomized Clinical Trial. JAMA. 2018 Sep 11; 320(10):984-994. doi: 10.1001/jama.2018.12163. Erratum in: JAMA. 2019 Jun 18; 321(23):2370. PMID: 30208454; PMCID: PMC6143100.
14. Hulten KG, Lamberth LB, Kalfus IN, Graham DY. National and Regional US Antibiotic Resistance to Helicobacter pylori: Lessons From a Clinical Trial. Gastroenterology. 2021 Jul; 161(1):342-344.e1. doi: 10.1053/j.gastro.2021.03.045. Epub 2021 Mar 31. PMID: 33798524; PMCID: PMC8267964.
15. Jo JH, Harkins CP, Schwardt NH, Portillo JA; NISC Comparative Sequencing Program, Zimmerman MD, Carter CL, Hossen MA, Peer CJ, Polley EC, Dartois V,

Figg WD, Moutsopoulos NM, Segre JA, Kong HH. Alterations of human skin microbiome and expansion of antimicrobial resistance after systemic antibiotics. Sci Transl Med. 2021 Dec 22; 13(625):eabd8077. doi: 10.1126/scitranslmed.abd8077. Epub 2021 Dec 22. PMID: 34936382; PMCID: PMC8878148.

16. Kayigire XA, Friedrich SO, van der Merwe L, Diacon AH. Acquisition of Rifampin Resistance in Pulmonary Tuberculosis. Antimicrob Agents Chemother. 2017 Mar 24; 61(4):e02220-16. doi: 10.1128/AAC.02220-16. PMID: 28167550; PMCID: PMC5365665.
17. Korkmaz H, Çetinkol Y, Korkmaz M, Çalgın MK, KaşkoArıcı Y. Effect of Antibiotic Exposure on Upper Respiratory Tract Bacterial Flora. Med Sci Monit. 2022 Jan 6; 28:e934931. doi: 10.12659/MSM.934931. PMID: 34987147; PMCID: PMC8750656.
18. Leo S, Lazarevic V, von Dach E, Kaiser L, Prendki V, Schrenzel J, Huttner BD, Huttner A. Effects of antibiotic duration on the intestinal microbiota and resistome: The PIRATE RESISTANCE project, a cohort study nested within a randomized trial. EBioMedicine. 2021 Sep; 71:103566. doi: 10.1016/j.ebiom.2021.103566. Epub 2021 Sep 4. PMID: 34492446; PMCID: PMC8426194.
19. Pilmis B, Jiang O, Mizrahi A, Nguyen Van JC, Lourtet-Hascoët J, Voisin O, Le Lorc'h E, Hubert S, Ménage E, Azria P, Borie MF, Mahé A, Mourad JJ, Trabattoni E, Ganansia O, Zahar JR, Le Monnier A. No significant difference between ceftriaxone and cefotaxime in the emergence of antibiotic resistance in the gut microbiota of hospitalized patients: A pilot study. Int J Infect Dis. 2021 Mar; 104:617-623. doi: 10.1016/j.ijid.2021.01.025. Epub 2021 Jan 13. PMID: 33453395.
20. Reyman, M., van Houten, M.A., Watson, R.L. et al. Effects of early-life antibiotics on the developing infant gut microbiome and resistome: a randomized trial. Nat Commun 13, 893 (2022). https://doi.org/10.1038/s41467-022-28525-z
21. Rueda MS, Calderon-Anyosa R, Gonzales J, Turin CG, Zea-Vera A, Zegarra J, Bellomo S, Cam L, Castaneda A, Ochoa TJ; NEOLACTO Research Group. Antibiotic Overuse in Premature Low Birth Weight Infants in a Developing Country. PediatrInfect Dis J. 2019 Mar; 38(3):302-307. doi: 10.1097/INF.0000000000002055. PMID: 29613975; PMCID: PMC6168436.
22. Shaikh N, Hoberman A, Keren R, Ivanova A, Gotman N, Chesney RW, et al. Predictors of antimicrobial resistance among pathogens causing urinary tract infection in children. J Pediatr. 2016; 171:116-21.

23. Singh T, Singh PK, Dar SA, Haque S, Akhter N, Das S (2019) Changing paradigm of antibiotic resistance amongst Escherichia coli isolates in Indian pediatric population. PLoS ONE 14(4): e0213850. https://doi.org/10.1371/journal.pone.0213850
24. Skalet AH, Cevallos V, Ayele B, Gebre T, Zhou Z, Jorgensen JH, Zerihun M, Habte D, Assefa Y, Emerson PM, Gaynor BD, Porco TC, Lietman TM, Keenan JD. Antibiotic selection pressure and macrolide resistance in nasopharyngeal Streptococcus pneumoniae: a cluster-randomized clinical trial. PLoS Med. 2010 Dec 14;7(12):e1000377. doi: 10.1371/journal.pmed.1000377. PMID: 21179434; PMCID: PMC3001893
25. Street ME, Caruana P, Caffarelli C, Magliani W, Manfredi M, Fornaroli F, de'Angelis GL. Antibiotic resistance and antibiotic sensitivity based treatment in Helicobacter pylori infection: advantages and outcome. Arch Dis Child. 2001 May; 84(5):419-22. doi: 10.1136/adc.84.5.419. PMID: 11316688; PMCID: PMC1718745.
26. van Duijn PJ, Verbrugghe W, Jorens PG, Spo¨hr F, Schedler D, Deja M, et al. (2022) The effects of antibiotic cycling and mixing on acquisition of antibiotic resistant bacteria in the ICU: A post-hoc individual patient analysis of a prospective cluster-randomized crossover study. PLoS ONE 17(5): e0265720. https://doi.org/10.1371/journal.pone.0265720
27. Willmann M, Vehreschild MJGT, Biehl LM, Vogel W, Dörfel D, Hamprecht A, Seifert H, Autenrieth IB, Peter S. Distinct impact of antibiotics on the gut microbiome and resistome: a longitudinal multicenter cohort study. BMC Biol. 2019 Sep 18;17(1):76. doi: 10.1186/s12915-019-0692-y. PMID: 31533707; PMCID: PMC6749691.
28. Wittekamp BH, Plantinga NL, Cooper BS, Lopez-Contreras J, Coll P, Mancebo J, Wise MP, Morgan MPG, Depuydt P, Boelens J, Dugernier T, Verbelen V, Jorens PG, Verbrugghe W, Malhotra-Kumar S, Damas P, Meex C, Leleu K, van den Abeele AM, Gomes Pimenta de Matos AF, Fernández Méndez S, Vergara Gomez A, Tomic V, Sifrer F, Villarreal Tello E, Ruiz Ramos J, Aragao I, Santos C, Sperning RHM, Coppadoro P, Nardi G, Brun-Buisson C, Bonten MJM. Decontamination Strategies and Bloodstream Infections With Antibiotic-Resistant Microorganisms in Ventilated Patients: A Randomized Clinical Trial. JAMA. 2018 Nov 27; 320(20):2087-2098. doi: 10.1001/jama.2018.13765. PMID: 30347072; PMCID: PMC6583563.
29. Zegers SH, Dieleman J, van der Bruggen T, Kimpen J, de Jong-de Vos van Steenwijk C. The influence of antibiotic prophylaxis on bacterial resistance in urinary tract

infections in children with spina bifida. BMC Infect Dis. 2017 Jan 12; 17(1):63. doi: 10.1186/s12879-016-2166-y. Erratum in: BMC Infect Dis. 2017 Feb 27; 17 (1):175. PMID: 28081719; PMCID: PMC5228098.

30. Diaz Granados CA, Zimmer SM, Klein M, Jernigan JA. Comparison of mortality associated with vancomycin-resistant and vancomycin-susceptible enterococcal bloodstream infections: a meta-analysis. Clin Infect Dis. 2005 Aug 1; 41(3):327–33.
31. Sydnor ER, Perl TM. Hospital epidemiology and infection control in acute-care settings. Clin Microbiol Rev. 2011 Jan; 24(1):141–73.
32. Zhou Q, Liu J, Chen S, Xu W, Han Y, Yin Y. The Accuracy of Molecular Detection Targeting the Mutation C2611T for Detecting Moderate-Level Azithromycin Resistance in Neisseria gonorrhoeae: A Systematic Review and Meta-Analysis. Antibiotics (Basel). 2021 Aug 24; 10(9):1027. doi: 10.3390/antibiotics10091027. PMID: 34572609; PMCID: PMC8471969.
33. Wirtschafter DD, Padilla G, Suh O, Wan K, Trupp D, Fayard EE. Antibiotic use for presumed neonatally acquired infections far exceeds that for central line-associated blood stream infections: an exploratory critique. J Perinatol. 2011 Aug; 31(8):514-8. doi: 10.1038/jp.2011.39. Epub 2011 May 5. PMID: 21546938.
34. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infect Dis. 2014 Jan 9; 14:13. doi: 10.1186/1471-2334-14-13. PMID: 24405683; PMCID: PMC3897982.
35. Terreni, M.; Taccani, M.; Pregnolato, M. New Antibiotics for Multidrug-Resistant Bacterial Strains: Latest Research Developments and Future Perspectives. Molecules 2021, 26, 2671. https://doi.org/10.3390/molecules26092671
36. Lingyan Gao, Haojie Wang, Bo Zheng, Feihe Huang, Combating antibiotic resistance: Current strategies for the discovery of novel antibacterial materials based on macrocycle supramolecular chemistry,
    Giant, Volume 7, 2021, 100066, ISSN 2666-5425, https://doi.org/10.1016/j.giant.2021.100066.
37. Dutescu IA, Hillier SA. Encouraging the Development of New Antibiotics: Are Financial Incentives the Right Way Forward? A Systematic Review and Case Study. Infect Drug Resist. 2021 Feb 5; 14:415-434. doi: 10.2147/IDR.S287792. PMID: 33574682; PMCID: PMC7872909.

38. Antibiotic Resistance Threats in the United States. Centers for Disease Control and Prevention. 2013 Downloaded from http://www.cdc.gov/drugresistance/threat-report-2013/index.html, last accessed on March 9, 2015.
39. Antimicrobial Resistance: Tackling a Crisis for the Future Health and Wealth of Nations. 2014 Downloaded from http://amr-review.org/, last accessed on March 11, 2015.
40. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; 24th informational supplement. Clinical and Laboratory Standards Institute; Wayne, PA: 2014. (CLSI document M100-S24).
41. Nannini EC, Singh KV, Arias CA, Murray BE. In vivo effect of cefazolin, daptomycin, and nafcillin in experimental endocarditis with a methicillin-susceptible Staphylococcus aureus strain showing an inoculum effect against cefazolin. Antimicrob Agents Chemother. 2013; 57(9):4276–81.