International Journal of Humanities Social Science and Management (IJHSSM)
Volume 3, Issue 6, Nov.-Dec., 2023, pp: 123-133 www.ijhssm.org

A Review on Antibiotics Resistance and Evaluation of Antibiotics

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Date of Submission: 10-11-2023 Date of Acceptance: 26-11-2023

Abstract:
Antibiotics either are cytotoxic or cytostatic to the micro-organisms, allowing the body's natural defences, such as the immune system, to eliminate them. They often act by inhibiting the synthesis of a bacterial cell, synthesis of proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), by a membrane disorganizing agent, or other specific actions. After mutation occurs, the binding site is altered, and the antibiotic is unable to bind to the mutant bacteria and is unable to kill it. These bacteria will proliferate creating new resistant colony. Campylobacter, especially C. Jejune, is recognized as one of the most common causes of Food-borne gastroenteritis in humans. The frequency of mutations of the genes responsible for macrolide resistance in Campylobacter is much less common than in the case of fluoroquinolone resistance. Moreover, Emergence of high-level resistance may require multiple mutation steps; thus, macrolide resistant Campylobacter mutants usually develop more slowly under selective antibiotic Pressure than under the influence of fluoroquinolones, so they need prolonged exposure to Macrolide antimicrobial agents. To the drug and the region of the connection 'Connection Of the antibiotics' target areas are different. They Can be various enzymes and ribosomes. Resistance Associated with alterations in the ribosomal target are the most frequently observed in macrolide antibiotics.

Keywords: Antibiotics, drug resistant, β-Lactamase, hygiene, microbes

I. Introduction:

Antibiotics either are cytotoxic or cytostatic to the micro-organisms, allowing the body's natural defences, such as the immune system, to eliminate them. They often act by inhibiting the synthesis of a bacterial cell, synthesis of proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), by a membrane disorganizing agent, or other specific actions .Antibiotics may also enter the cell wall of the bacteria by binding to them, using the energy-dependent transport mechanisms in ribosomal sites, which subsequently leads to the inhibition of the protein synthesis. Millions of metric tons of newer classes of antibiotics have been produced in last 60 years since its inception. Increased demand for antibiotics across many sectors has allowed for less expensive and off-label uses of drugs. Conversely, due to the enormous and irresponsible use of the antibiotics, has contributed significantly to the advent of the resistant strains .**1** In the previous days, the production of new antibiotics was directly proportional to the development of resistant strains. However, the mainstream approach in fighting against the diseases is now focused on the modification of existing antibiotics to combat emerging and re-emerging resistance of pathogens. The present review is one such way to educate the public by showing the development and plausible future of antibiotic resistance and existing regulation to reduce the antibiotic resistance crisis. Antibiotics are usually effective against them, but when the microbes become less sensitive or resistant, it requires a higher than the normal concentration of the same drug to have an effect. The emergence of antimicrobial resistance was observed shortly after the introduction of new antimicrobial compounds [10]. Antibiotic resistance can occur as a natural selection process where nature empowers all bacteria with some degree of low-level resistance .**2**

There are many mechanisms That bacteria exhibit to protect themselves from antibiotics and Understanding the mechanisms by which bacteria resist antibiotics Will become critical to solving the crisis. Misuse of antibiotics may Contribute to the development of resistant bacteria; an incomplete Course of antibiotics risks not entirely eradicating the colony thus Allowing the development of resistant bacteria. Mechanisms of Drug resistance fall into several broad categories, including active Efflux pumps, drug inactivation/alteration, modification of drug Binding sites/targets, changes in cell permeability resulting in Reduced intracellular drug accumulation, biofilm formation and Others, Efflux Pumps inactive such as the enzymatic hydrolysis of

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antibiotics, group Transfer and redox process. The production of β- lactamases that Hydrolyse the β-lactam ring of penicillin's is the classical example Of antibiotic inactivation. A critical issue at the regional level is the need for and difficulty in taking effective measures as the responsibility for health remains essentially a national problem. In the present context, national commitment to understand and address the problem and the designation of authority and responsibility are the major prerequisites. Effective action requires the introduction and enforcement of appropriate regulations and allocation of appropriate resources for education and surveillance.**3**

The economic cost of drug-resistant infections For doctors and for those who have experienced first-hand the anxiety of an Infection that is drug-resistant, as a patient or when caring for a loved one, There is little need to prove the importance of tackling AMR. However for the majority of people, including in leading policy and business circles Around the globe, the threat of drug resistance might seem a distant and abstract Risk, if it is known at all.. First, the studies looked only at a subset of drug-resistant bacteria and public Health issues, because of the lack of readily available data for this initial research. Bacteria that already shows Concerning resistance levels Broader public health.

Antimicrobial resistance will have a different Impact in different parts of the world Our results suggest that countries that already have high malaria, HIV or TB rates are likely to particularly suffer as resistance to current treatments Increases. This is exacerbated by the fact that the regional variation is much Greater for these three public health issues than for the three named bacteria Studied. Particular countries at risk include India, Nigeria and Indonesia (malaria), And Russia (TB). In addition, if malaria and HIV drug resistance is not tackled, Africa as a continent will suffer greatly, and the debilitating impacts of HIV and TB co- morbidity already seen in many of the poorest parts of the world will likely Get worse. Furthermore, drug-resistant malaria could constrain the economic Progress achieved by some countries in Asia. It is also possible that the hard Work China and Brazil have undertaken to almost eradicate malaria in the second Half of the 20th century could be undermined if resistance is unchecked, and this =Could have a negative impact on their large export sectors. For countries in the OECD, the cumulative loss of economic output by 2050 will amount to between USD 20 and 35 trillion. **4**. Mechanisms of Transfer of Resistance Based on Examples of Various Species Of Bacteria

3.1. Campylobacter spp.- Campylobacter, especially C. Jejune, is recognized as one of the most common causes of Food-borne gastroenteritis in humans .

Resistance to Macrolides

The frequency of mutations of the genes responsible for macrolide resistance in Campylobacter is much less common than in the case of fluoroquinolone resistance. Moreover, Emergence of high-level resistance may require multiple mutation steps; thus, macrolide resistant Campylobacter mutants usually develop more slowly under selective antibiotic Pressure than under the influence of fluoroquinolones, so they need prolonged exposure to Macrolide antimicrobial agents [37]. Resistance of Campylobacter to this class of antibiotics Is usually the result of modification of the ribosome target binding site by mutation of 23SrRNA at positions 2074 (A2074C, A2074G, or A2074T), 2075 (A2075G or A2075C), or both of the adenine residues in all three copies of this gene (rrnB operon) [37]. However, high-level macrolide resistance is mainly associated with a modification at A2075G in domain V of23S rRNA. Such resistance mechanisms to erythromycin have also been shown to correspond With cross-resistance to other macrolides and related drugs of the lincosamide and Streptogramin classes .

Resistance to β-Lactams

The above-mentioned multidrug efflux pumps, such as Comeback, also play a role in The prevalence of resistance of Campylobacter to β-lactam antibiotics, e.g., ampicillin [35].A significant increase in susceptibility to ampicillin has been demonstrated in CmeABC inactivated. jejune mutants, and a decrease in susceptibility in CmeABC-overexpressing Mutants [45]. Another mechanism of β-lactam resistance in Campylobacter is the production Of chromosomally encoded β-lactamase OXA-61 [28]. The expression level of this Gene modulates the susceptibility of the bacteria to this class of antimicrobials, e.g., a Single nucleotide mutation (G–T transversion) in the promoter region of blaOXA-61 led to Overexpression of the gene and consequently to a high increase in β-lactam resistance inC. jejune [46]. Campylobacter bacteria are capable of intrinsic production of β-lactamases In the absence of selective (antibiotic) pressure. The blaOXA-61 gene has been shown to be Widely distributed among Campylobacter isolated from poultry but has also been identified In isolates from non-food producing animals and environments [47,48]. On the other hand-lactam antibiotics are known to have limited efficacy against Campylobacter, and resistance To this class of antimicrobials appears to be mediated by

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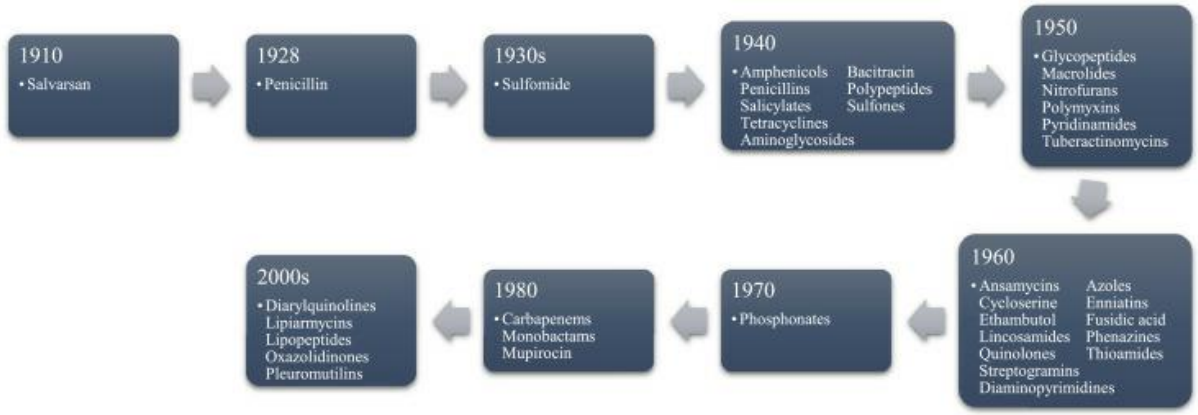
both intrinsic resistance andB-lactamase production [26] **5**

Five mechanisms to resistance have been identified so far, and each of them involves the alteration of a different microbial structure. Resistance to antibiotics can be caused by five general mechanisms: 1) alteration of targets (antibiotics can no longer bind to the target); 2) alternation of membrane permeability; 3) development of enzymes (□-lactamases exist in various bacteria and they are capable of breaking □-lactam ring in penicillin's); 4) alteration of enzymes; and 5) alteration of metabolic pathways (MC MANUS, 1997; SCHMIEDER and EDWARDS, 2012). Mechanisms of antibiotic resistance in bacteria are shown in Table 1. Table 1. Mechanisms of antibiotic resistance in bacteria (SCHMIEDER and EDWARDS, 2012) Antibiotic Aminoglycosides Amphenicols Ant folates β-lactams Glycopeptides Rapamycin's Aminoglycosides β-lactams Aminoglycosides β-lactams Macrolides Quinolones Tetracycline's Sulphonamides Trimethoprim Aminoglycosides β-lactams Fluoroquinolones Glycopeptides Macrolides Rifampicin's Tetracycline's Mode(s) resistance Antibiotic inactivation Decreased influx Increased efflux Target amplification Target site alteration Bacteria can develop resistance to antibiotics.. **6**

Development of antimicrobial industry

The use of antimicrobial agents dates back to the dawn of antimicrobial agents' discovery. Since 2500 BC, the Chinese have employed a variety of traditional herbs to cure injuries and infections . Modern antibiotic research in the 17th to 20th centuries led to a better knowledge of the presence of antimicrobial agents. In 1877, Louis Pester first discovered the properties of antibacterial compounds with the inhibition of anthrax by saprophytic bacteria. Later, Alexander Fleming discussed antibiotic responses in detail in 1928. Alexander Fleming observed that the growth of S. Aureus in Petri dishes was inhibited by substances produced by the fungus Penicillium chrysogenum, which led to the discovery of the first antibiotic, penicillin (Aminov, 2017). In the following centuries, the discovery of various antimicrobial compounds such as sulphonamides, aminoglycosides, tetracycline's, lip peptides, oxazolidinones, glycopeptides, streptogramins, and quinolones ushered in the golden era of antibiotics.



Technologies in antibiotic production

Active compounds with positive effects (antimicrobial, antioxidant, or antineoplastic) could be used in novel disease treatments encouraging scientists to invent new antimicrobial medications (FDA, 2018). Antimicrobial screening is necessary for antibiotic discovery, in which molecules from plants, animals, or microbes are isolated and identified for their antimicrobial characteristics. Antimicrobial screening begins with extracting active compounds from raw materials (plants, animals, or microbes), followed by detecting and identifying the antimicrobial activity of the derived active compounds. Table 1 summarizes the methods commonly used in antimicrobial screening. More than a thousand active compounds are selected early in the discovery process, with each one potentially turning into a medication. However, only a few compounds are deemed worthy of further study following a series of experiments. **7**

Materials and methods

A bibliometric analysis of publications in the field of ARB published between 2010 and 2020 is presented in this paper. Data were obtained from the Science Citation Index Expanded database (SCI-E) and Social Sciences Citation Index database (SSCI). Scopus, PubMed and Google Academic

indeed cover more publications than Web of Science. At almost all of the top 10 countries in publications have ever cooperated with each other. The line between the USA and China is the thickest, which indicates that the number of cooperative publications between the USA and China is the largest in this field, followed by the number of cooperative publications between the USA and Canada.**8**

Overview

We developed an approach for estimating the burden of AMR that makes use of all available data and builds on death and incidence estimates for different underlying conditions from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019, which provides age-specific and sex-specific estimates of disease burden for 369 diseases and injuries in 204 countries and territories in 1990–2019.14 Our approach can be divided into ten estimation steps that occur within five broad modelling components (a flowchart of the estimation steps is given in the appendix p 123). First, we obtained data from multiple data sources, including from published studies (eg, microbiology data, inpatient data, data on multiple causes of death, and pharmaceutical sales data) and directly from collaborators on the Global Research on Antimicrobial Resistance project,15 members of the GBD Collaborator Network, and other data providers.**9** Indeed, the most striking feature of The environmental microbiome is its immense diversity, Providing numerous genes that potentially could Be acquired and used by pathogens to counteract the Effect of antibiotics26–30. All approved antibiotic classes So far, whether they be natural, semi-synthetic or synthetic Compounds, have been met by resistance in at Least some of the pathogens they target. This suggests That external environments already harbour resistance Factors for all antibiotics that will ever be developed, Unless we start thinking radically differently about how Antibiotics are designed.**10**

MECHANISMS OF RESISTANCE TO ANTIBIOTICS

To the drug and the region of the connection 'Connection Of the antibiotics' target areas are different. They Can be various enzymes and ribosomes. Resistance Associated with alterations in the ribosomal target are the Most frequently observed in macrolide antibiotics. Mutations In penicillin-binding proteins (beta-lactamase Enzymes) and Staphylococcus aureus, Streptococcus Pneumoniae, Neisseria meningitides and Enterococcus Francium strains can develop resistance to penicillin . Such resistance is in control of the plasmid and chromosomal. Active pumping systems are effective in resisting Quinolones, 14-membered macrolides, streptogramins ,Chloramphenicol and beta-lactams .Using an alternative metabolic pathway: Unlike Some of the changes in the target in bacteria, a new pathway For drug-susceptible eliminate the need to develop Objective. In this way resistance seen among the sulphonamide And trimethoprim. Bacteria's can gain property of Getting ready folate from the environment instead of synthesizing Folate .**11**

How does AMR develop, transmit and spread in the environment?

Microbes, in particular bacteria in water, soil and Air can develop resistance following contact with other resistant microbes. Horizontal and Vertical AMR transmission can happen in the Absence of any antimicrobial compound being Present.. Water, soil and air then serve as vehicles For spreading antimicrobial resistant microbes Between and among people, animals and other Environmental reservoirs (e.g. food production Environments, including aquaculture) (EFSA Panel On Biological Hazards 2021).**12** There is much more work to be done in generating Data on antibiotic use and resistance in agriculture in LMICs. There is also much to be done on Surveillance and understanding of the spread of AMR in the wider environment. Promote new rapid diagnostics to cut unnecessary use The Review recommended that high-income countries support point-of-care rapid diagnostics, Including measures to make their use mandatory, where they are available, by 2020. For LMICs It advocated a subsidy to manufacturers to promote development and use. In spite of a number of initiatives to stimulate the development of diagnostics, such as prizes offered In Europe,35 the UK36 and the US,37 a multitude of barriers limit the use of diagnostics in clinical Practice and hinder the development of new ones. This applies in countries at all income levels but Is particularly acute in LMICs. Even existing rapid diagnostic tests, such as that for detecting levels **13**

Policy review process

To respond effectively to AMR and associated AMU controls, a review of national policies Should accompany national actions and responses within a country. This Framework offers Insights into how policies interact and affect AMR-related outcomes. This section presents The policy domain areas and questions to guide a review of national policies that directly or Indirectly address AMR. The process allows the user to identify gaps in existing policies that Need to be addressed and is only

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one part of the process for improving policy response .**14**

Stimulating antibiotic development – 'push' Improved global innovation funding to provide new Public funding opportunities for researchers:

• Proposed that we need an extra $2bn over five Years

• Governments are already acting on this – more Than £600m in new government funding globally Announced in past two year Stimulating antibiotic development – 'pull 'Also need new funding to ensure a proper market 'pull' for New products – via new market models that 'de-link' the Profitability of an antibiotic from the volume sold.

• Globally-administered market entry rewards of $1-1.3bn for antibiotics meeting most urgent unmet needs, Pegged to objective criteria of 'value'

• Conditions attached for global access and stewardship

• Supporting 15 new drugs over a decade would cost Approx. $16bn.**15**

Why does antibiotic resistance happen?
Why is it important?

Although antibiotic resistance can be considered To be an inevitable consequence of antibiotic use, injudicious Use of antibiotics is a major factor facilitating The emergence of resistance worldwide. In many Areas, the availability of antibiotics 'over the counter 'Or via the internet allows the non-prescriber to have Free and unrestricted access to these agents. Once Resistance has emerged, subsequent dissemination of Resistant strains is facilitated by the selection pressure Exerted by further antibiotic use, failure to adhere to Infection control measures and by poor hygiene(notably in terms of hand hygiene, sanitary conditions And food preparation), which can occur both within And outside healthcare settings. Antibiotic resistance has significant costs to society In terms of increased mortality, morbidity, use of Healthcare resources and time off work. In Addition, because of concern about resistance, new Agents are typically used sparingly and as a last resort. Worldwide, the availability of cheaper generic products Potentiates this issue. As a result, developing New antibiotics is unattractive as a business model forThe pharmaceutical industry, and many of the larger Companies have withdrawn from this market. **16**

Causes of antibiotic resistance

Bacteria with resistance to antibiotics predate Medical use of antibiotics by humans. However, Widespread antibiotic use has made more bacteria Resistant through the process of evolutionary Pressure. For example, 70 to 80 percent of diarrhoea is Caused by viral pathogens, for which antibiotics are not Helpful. But nevertheless, approximately 40 percent of These cases are attempted to be treated with Antibiotics.[28] In some areas even over 80 percent of Such cases are attempted to be treated with Antibiotics.

PREVENTION OF ANTIBIOTIC RESISTANT

Defensive measures include only using antibiotics When needed, thereby stopping misuse of antibiotics. Narrow-spectrum antibiotics are preferred over broad spectrum Antibiotics when possible, as effectively and Accurately targeting specific organisms is less likely to Cause resistance, as well as side effects. There have been Increasing public calls for global collective action to Address the threat, including a proposal for international Treaty on antimicrobial resistance.. **17** Activation of efflux mechanism: Bacteria use efflux pumps To get rid of antibiotics that enter the cell. Eg: Pseudomonas aeruginosa use efflux pumps to prevent Several antibiotics such as fluoroquinolones, beta-lactams, Chloramphenicol, and trimethoprim from entering the cell. Global cell adaptation: By evolution, bacteria have Developed intricate mechanisms to survive hostile Environments including the human body. Resistance to Distamycin and vancomycin is an illustration of global cell Adaptive response. Mechanism of antibiotic resistance by gene Mutation Horizontal Gene Transfer (HGT): It is the process by which Foreign DNA material is obtained either by transformation (incorporation of naked DNA), transduction (phage Mediated), or conjugation (cell-to-cell contact). Mobile Genetic elements (MGEs) such as plasmids and Transposons act as vehicles to share valuable genetic Information **18**

VIRULENCE FACTORS OF ESWCHERICHIA COIL

Escherichia coli is a normal opportunistic flora in the Digestive tract, that is, if the number is within normal Limits, the bacteria can be beneficial, but if there is an Increase in the number from normal, the bacteria will Become pathogenic (28). Pathogenic Escherichia coli can Cause disease in the intestinal tract as well as outside the Intestine (29). There are six intestinal path types of Escherichia coli including Shiga toxin-producing Escherichia coli (STEC), enter-toxigenic Escherichia coli (ETEC), enter pathogenic Escherichia coli (EPEC), Diffusely adherent Escherichia coli, and enter invasive Escherichia coli.**19**

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MECHANISM OF RESISTANCE ON ESWCHERICHIA COIL

Escherichia coli belongs to the Gram-negative bacteria Group. Gram negative bacteria are more easily resistant Because they have an outer membrane that is not owned By the Gram-positive bacteria group. The outer membrane Of Gram negative is an essential structure in protection Against antibiotics (81). The inner structure of this outer Membrane is composed of phospholipids (PLs) and Lipopolysaccharides (LPs) in the outer structure (82). PLs And LPs act as bacterial membrane defences because they Are composed of saturated chains so that they are Hydrophobic (83). The molecules making up PLs and LPs Each carry a negative charge which allows for Intermolecular linking interactions through the binding of Divalent cations (84) and the presence of poring as ion Selective channels so as to limit the absorption of Antibiotics.**19**

RECOMMENDAIONS FOR FUTURE STUDIES

This mapping exercise indicates that AMR research studies in India were Of limited scope in all areas, including Humans, animals, environment, And others. In humans, the majority Were retrospective single-centre Surveillance-based studies examining The prevalence of phenotypic resistance And molecular characterization of Resistance for various pathogens. Animal studies were confined to Examining resistance profiles of Bacteria isolated from food animals; Studies examining the frequency of Antibiotic use and reasons for use during animal rearing were absent. **20** Mechanistic Basis of Antimicrobial Resistance in Bacteria Resistance According to the biochemical route Involved, resistance to antibiotics is due to the Following mechanisms: Bacteria have become resistant to antimicrobials Through a Number of Here are the mechanisms Used by the bacteria to create resistance.

Antibiotic Degradation

The main mechanism of β-lactam resistance is destructing the related molecule by β-lactamases. These enzymes break the amide bond of the β-lactam Ring, rendering the antimicrobial agent ineffective. The first β-lactamase was described in 1940, one Year before the introduction of penicillin into Clinical practice. There is always population of resistant bacterial cells that multiply at higher concentrations in insufficient Antibiotic concentration which kill the subpopulation so that micro-organisms survives in the environment Resistance to an antibiotic may be an inherent property of the microorganism or acquired resistance result from mutation or from Transfer of an extra chromosomal genetic material followed by selection of resistant organisms during therapy.

Mechanism of antibiotic resistance:

There are various ways in which antibiotic acts by destroy or inning the growth of microorganisms and there are also various Mechanism by which the resistance occurs which includes time of exposure to the antibiotics. Resistance genes transferred between Organisms via mobile genetic elements (MGEs) is common and clinically more important in multi-drug resistance to the Gram negative Bacteria .**22**

RISK FACTORS FOR ANTIMICROBIAL-RESISTANT INFECTIONS:

The use of antimicrobial agents has been identified As an important factor in the emergence of antibiotic resistance Bacterial infections in the ICU. Several investigator Have demonstrated a close association between Previous use of antibiotics and the emergence of subsequent Antibiotic resistance in both gram-negative and Gram-positive bacteria (15–22). The recent experience With scheduled antibiotic class changes also demonstrates How rapidly antibiotic-resistant bacteria can Emerge in the ICU and in hospitals as patterns of antibiotic Use change (23–25). Trouville and co-workers (26)Examined 135 consecutive episodes of ventilator-associated Pneumonia, of which 77 (57%) were caused by Potentially antibiotic-resistant bacteria (methicillin-resistant Staphylococcus aureus, Pseudomonas aeruginosa, AcinetobacterBaumannii, and Stenotrophomonas malt philia).At least 7 days of mechanical ventilation, previous antibiotic Use, and previous use of broad-spectrum antibiotics(third-generation cephalosporin, fluoroquinolone, Carbapenem, or a combination) were the most important Risk factors associated with the development of Ventilator-associated pneumonia caused by antibioticresistantPathogens.**23**

International plans and efforts to tackle antimicrobial resistance.

International efforts to tackle AMR have existed for a number of years (figure 9). Early WHO efforts include the 1998 World Health Assembly Resolution, urging Member States to develop Measures for containing antimicrobial use and strengthening legislation surrounding their use. Subsequent activities in human health highlighted in the 2015 Road Map (EC, 2015) and 2015 Progress Report (EC, 2015) include a wide-ranging set of

actions to Promote surveillance systems, to foster research and to develop recommendations and guidelines. Particular attention is devoted to collaboration both across different agencies within the EU (i.e. the European Centre for Disease Prevention and Control, the European Surveillance system of Antimicrobial consumption, the European Antimicrobial Resistance Surveillance Network) and with Other countries (e.g. China and Russia). **24**

Appropriate use of antibiotics

The antibiotic resistance cycle starts with increased antibiotic use, Which leads to an increase in resistant strains. Increased hospitalization, Death, and healthcare use follow with even more antibiotics. Then there Are limited treatment alternatives resulting in increased mortality and Even more antibiotic use. Therefore, the life of existing antibiotics can be continued only If educational awareness on proper use of antibiotics is received by Healthcare providers as well as health care consumers. Antimicrobial Stewards programs, for example, instruct physicians, residents, and Medical students on the appropriate use of antibiotics. **25** Data synthesis and meta-analysis The extracted data were imported from a Microsoft Excel spreadsheet into STATA MP 16 statistical Software (StataCorp LP, 4905 Lakeway Drive, College Station, TX 7845, USA) for analysis. Subgroup meta-analysis Based on the participants as covariates, meta-regression, and sensitivity analyses were Also performed to investigate the source of statistical heterogeneity. Publication or dissemination Bias was examined subjectively using funnel plots and objectively using the nonparametric Rank correlation test of Begg [42] with $P < 0.05$ being taken into consideration to declare Potential publication bias.**26**

Methodology Search strategy

Two investigators initially reviewed the listed databases and then additional two investigators did a follow-up search to identify new antibiotics in development by searching the FDA, WHO, European medicine agency, and Central Drugs Standard Control Organization (India) platforms. Using the 25 new antibiotics identified between January 1st, 2017 and January 31, 2021, we formulated keywords and a search strategy for further databases. Two investigators independently searched electronic databases MEDLINE, NIH U. S. National Library of Medicine (clinicaltrial.gov), and Science Direct for articles as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for the period January 2017 to November 30th, 2020. When necessary, websites of pharmaceutical companies responsible for the development of the drug were accessed for further relevant information. Only English language articles were selected.**27**Thus, the emergence of antibiotic-resistance among the most important bacterial pathogens causing more harm. In this context, the classification of antibiotics, mode of action of antibiotics, and mechanism of resistance and the process of overcoming antibiotic resistance are discussed broadly.**28**

Tripartite Joint Secretariat on Antimicrobial Resistance

The political declaration at the UN High Level Meeting on AMR, committed to by Heads of State at The United Nations General Assembly in New York in September 2016, confirmed a strong focus on a broad, Coordinated approach that engages all including The human, animal, plant and environmental health Sectors. WHO is working closely with FAO and OIE in A 'One Health' approach to promote best practices to Reduce the levels of AMR and slow its development. The Interagency Coordination Group (IACG) on AMR was convened by the Secretary-General of the United Nations after the UN High-Level Meeting on Antimicrobial Resistance in 2016. The IACG brought Together partners across the UN, international Organizations and individuals with expertise Across human, animal and plant health, as well as The food, animal feed, trade, development and Environment sectors, to formulate a plan for the fight Against antimicrobial resistance. The Interagency Coordination Group on AMR submitted its report "No Time to wait: Securing the future from drug-resistant Infections" to the UN Secretary-General in April 2019. Its recommendations are now being implemented. **29**

Facilitate cooperation and synergy across the antibiotic market

Success in antibiotic development largely aligns with public health goals, as discussed further below. Despite the financial risks involved, great potential exists for synergistic cooperation in development, regulation, distribution and monitoring. An ideal incentive mechanism would encourage cooperation among the various stakeholders, including local and national governments, international health organizations, industry leaders, as well as regulatory and medical personnel. Public health objectives (access and stewardship)The optimal incentive will not only encourage participation and development of compounds via the four domains listed above, it will

also seek to influence distribution and utilization of this unique resource. The efficacy of antibiotics is directly related to their utilization, so profligate prescribing may render them relatively impotent due to the emergence of resistant bacteria. High prices can restrict use, but also hinder appropriate access by those with less means. A delicate balance must be struck between judicious prescribing and ease of access regardless of income **30**

WHO Global action plans

The World Health Organisation, working with the World Organisation For Animal Health (OIE), and the Food and Agriculture Organisation (FAO) has led the work to acknowledge, monitor and address the Progress of AMR. Detailed information on this activity is provide on the WHO website. In 2014, the WHO published the first global surveillance report on AMR. The WHO express concern about the results of the report- noting that Resistance to even to 'last resort' antibiotics was present globally. The World Health Assembly endorsed a Global Action Plan on AMR in May 2015. This plan was developed in co-ordination with the FAO and OIE. The goal of the plan is to keep effective prevention and treatment Of infectious diseases available to all for as long as possible. There are Five strategic aims within the plan: To improve awareness and understanding of antimicrobial Resistance; To strengthen knowledge through surveillance and Research; to reduce the incidence of infection; to optimize the use of antimicrobial agents;**31**

Evaluations of antibiotics:

Antimicrobials are medications used to treat diseases caused by microbes (bacteria, viruses, fungi, and parasites).[1] Antimicrobial resistance (AMR) occurs when microbes change gradually and become unresponsive to the drugs designed to kill them.**32** This study was carried out in three healthcare facilities in Ibadan Metropolis namely Adeoyo Maternity Teaching Hospital, Yemetu; Oni and Son Children Hospital, Ring Road; and the University Health Service (UHS), Jaja, University of Ibadan, Ibadan, all in Oyo state, SouthWestern Nigeria. Adeoyo Maternity Teaching Hospital is a tertiary facility that caters for the healthcare needs of several categories of ambulatory and institutionalised patients, and it is a well-known hospital for maternity services and children care **33** The models used were described according to the WHO 2019 AWaRe classification of antibiotics, in which antibiotics were classified into four groups: access, watch, reserve and not-recommended combinations [26]. For medical prescriptions containing more than one antibiotic, their classification would be made by giving priority to the highly restricted antibiotic. For example, if the medical prescription contained both access group and watch group antibiotics, the prescription will be classified as containing the watch group antibiotics. We also used the anatomical, therapeutic and chemical classification, developed by the WHO to prioritize the consumption of pharmacological classes of antibiotics.**34**

II. Methods

2.1. Study Design and Setting

A retrospective cross-sectional study was conducted at the pediatric wards of a teaching referring hospital in the state of Pahang, Malaysia.

2.2. Study Population and Data Collection

Data collection and analysis were conducted in early 2020. Electronic database of pediatric patients (≤12 years old) who were admitted to the pediatric wards during the previous year (January to December 2019) was reviewed. Patients who were prescribed at least one systemic antibiotic and hospitalized for at least 24 h were considered eligible for inclusion in the study. As the study focused on the general pediatric wards, patients who were admitted to the intensive care unit (ICU) were excluded. In addition, because the dosing regimen for patients above 12 years old is usually similar to that used in adults, pediatric patients aged 13–18 years old were also excluded. Patients' demographic information, medications, past medical history and length of hospitalization were collected .**35**

2.3. Antibiotic utilization

Defined daily dose (DDD) and drug utilization index (DU90%) were the metrics used for quantifying antibiotic use. The dose and duration of prescribed antibiotics were collected from patients' case files. Consumption was calculated as DDD normalized for 100 bed-days.[9] DDD per 100 bed-days is an important indicator of inpatient antibiotic use .DDD/100 bed-days = (consumption of antibiotics during study period [g] × 100)/ (DDD coefficient [g] × total bed-days)

To assess the quality of drug utilization, antibiotics were ranked according to the volume of DDDs prescribed. Those antibiotics that accounted for 90% of the total volume, i.e. the DU90%, were identified and compared within the wards. **36**

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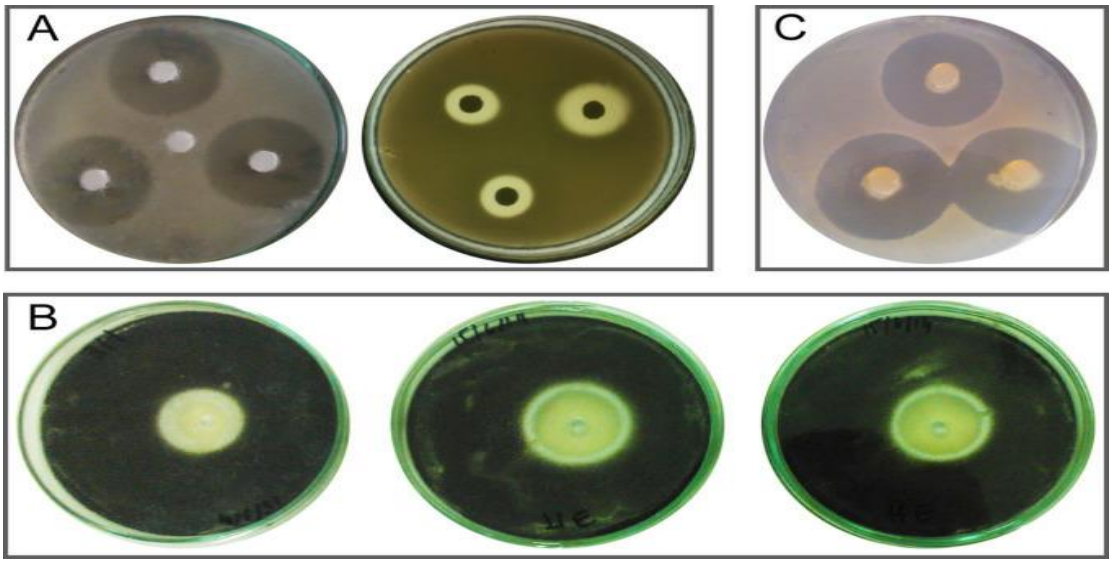
Statistical analysis

Statistical parameters (such as mean, standard deviation, and variances) were calculated using the Microsoft® Excel® program for Microsoft 365 MSO version 2204. We used the Fisher-Snedecor test (*F*-test) to analyze the equality of variances and the Student's *t*-test to determine statistical significance, both tests were performed at the 95% confidence interval (CI) **37**

Diffusion methods

2.1. Agar disk-diffusion method

Agar disk-diffusion testing developed in 1940 , is the official method used in many clinical microbiology laboratories for routine antimicrobial susceptibility testing. Nowadays, many accepted and approved standards are published by the Clinical and Laboratory Standards Institute (CLSI) for bacteria and yeasts testing.**38**



The Selection Conditions of Patients Studied

Consolidation criteria for this consideration were based on an overview that each suspected COVID-19 patient completed treatment after additional testing for lactate dehydrogenase (LDH), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) at the Ayatollah Alimoradian Hospital Medical Center in Namaland, Hamadan All information was recorded by the Laboratory Information System (LIS). Patients with suspected COVID-19 illness had a real-time PCR test negative. Sampling was carried out utilizing the persistent purposive testing methodology, in which all COVID-19 patients who came and met examination criteria concurring with the goals were included until the required number of subjects was selected for data examination. **39** Pediatric population is prone to suffer from recurrent infections of the respiratory tract and gastrointestinal system. Although most of the common childhood infections such as diarrhea and upper respiratory tract infections are caused by viruses, and large volumes of antibiotics are prescribed for these infections in children in the primary care settings. It is estimated that 90% of upper respiratory tract infections are self-limiting viral illnesses and even bacterial infections like acute otitis media often run a self-limiting course. Clinical trials have shown that antibiotic use to treat common upper respiratory tract infections like sore throat, nasopharyngitis and otitis media has no or minimal benefit on the clinical outcome. Lower respiratory tract infections are one of the leading cause of death in children below 5 five years of age.**40**

III. Conclusion:

Clinical guidelines, direct education, and regular reports on antibiograms may contribute to more prudent use of antibiotics. Overall, the problem of antibiotic resistance is global. However, measures need to be taken at an individual, institutional, and ultimately at national healthcare level.

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