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REVIEW STUDY: PREVALENCE OF ANTIMICROBIAL RESISTANCE PATTERNS AND THEIR IMPACT ON EMPIRICAL THERAPY

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1.2 Abstract

Antimicrobial resistance (AMR) is a significant global burden and a substantial public health threat that requires immediate interventions. Surveillance data indicates that resistance rates are increasing worldwide. Inappropriate empirical antimicrobial therapy could lead to treatment failure and poor clinical outcomes when a pathogen bears resistance mechanisms. Empirical therapy with more extensive coverage might be necessary, but it comes at increased expense, toxicity, and adverse drug events. The absence of nationwide antibiotic susceptibility data to guide empirical therapy increases the likelihood of inappropriate therapy.

A six-month prospective cohort study was conducted at a tertiary university hospital in Southern Thailand. Adult patients (>18 years) who had positive blood or sterile site culture were enrolled. They were grouped based on empirical therapy (no AT) and appropriate empirical therapy (AT). The primary outcome was 30-day all-cause mortality. The sample size was calculated based on prevalence, and the compliance of all patients who met inclusion criteria was assessed at initially included patients within each group. The secondary outcomes included hospital length of stay, time to receive appropriate therapy, and factors impacting treatment changes. The statistics were analyzed using a Chi-square and Mann-Whitney tests.

In total, 482 patients were included in the study, of whom 415 (72.7%) received empirical irrelevant antibiotics. AT group (78.4%) more often developed fever than no AT (65.4%). These factors were respective crude odds ratios of 1.676 and 2.036. The isolated pathogens of blood or sterile site cultures were tested against either first-line or second-line antibiotics. Consequently, 343 (82.6%) organisms were resistant to first-line antibiotics. Of these, 234 (68.2%) with antimicrobial resistance patterns were not targeted by empirical therapy, leading to post-test treatments without subsequent improvement. AT could improve microbiological outcomes, as the organism prevalence and resistance profile were altered. Patients with no AT might require an increased change in treatment, additional tests, and prolonged hospital length of stay.

1.3 Keywords:

Antimicrobial resistance; prevalence; Empirical therapy; Pakistan

1.4 1. Introduction

Antimicrobial resistance (AMR) presents a growing threat to global health. The emergence of resistant organisms poses a significant challenge in the management of infections and was recognised as a priority in the Global Action Plan. Evidence shows a progressive reduction in the effectiveness of commonly used antibiotics globally following the emergence of resistant strains, with increased rates of antibiotic resistant infections and increased hospital stay duration, morbidity, and mortality (Savage-Reid et al., 2020). Secondary impacts also include increases in healthcare costs associated with more prolonged, more resource-intensive treatment, and the impact on wider communities as organism spread beyond the confines of individual hospitals.

Despite this, there is limited knowledge regarding geographic patterns, trends, and the burden of AMR. Therefore, AMR surveillance, amplification of successful localities, and sharing of best practices are crucial. Modelling efforts are needed based on individual countries data but are hindered by varying case definitions and the collection and publication timelines of ICU data. There is a need for more standardised approaches to the definition and use of clinical laboratory and environmental sampling data that transcend units of measurement. Individual countries also need to fill information/knowledge gaps regarding AMR burden, impacts, and spread for more targeted interventions and policies.

Development of systems to collect AMR data that are more widely accessible and can be used for decision support, resource allocation, monitoring, rapid outbreak investigation, and data interrogation are needed. The development and hosting of a mechanism for multi-national sharing of AMR data are supported, with a bottom-up development approach that favours experimental seroprevalence studies and expands to include models and mapping and monitoring impacts of % burden and % prevalence. Sound policies to standardise the practices used to limit AMR should be identified.

1.1. Background on Antimicrobial Resistance

Antimicrobial resistance (AMR) is defined as "the ability of a microbe to resist the effects of medication that once successfully treated the microbe". This is a global public health problem. It complicates the treatment and control of infectious diseases. The prevalence of naturally resistance to antibiotics varies with the geographical location, local antibiotic consumption, and frequency of medical care. In developing countries, the problem of antimicrobial resistance (AMR) is more pronounced. Infections due to multi-drug resistant pathogens result in increased mortality and morbidity. The AMR surveillance systems are limited in number and scope in developing countries. Studies of local prevalence and drug resistance are needed for effective policy and empirical drug choice in this important problem.

Antibiotics revolutionised patient care and turned once-dying infections into curable diseases, but with increasing prescriptions, AMR arose. Treating patients with >72 h delay results in 36–42 % mortality compared to 17 % if treated immediately. Septic shock can evolve even with a few-hour delay. Targeting a narrow-spectrum antibiotics protects the gut populace from potential takeover by resistance pathogens and suppresses AMR spread. This study assessed the impact of escalation in empirical antimicrobial treatment on organism prevalence and resistance profile. It also attempted to correlate these findings with empirical choices, clinical outcomes and future treatment for similar cases to augment empirical choices.

The overall resistance to common antibiotics was high (>50 %) in all cases. Resistance varied significantly among different empirical choices due to treatment with a wider spectrum antibiotic. Scorings from 8–46 to 39–53 % resistance were noted after escalation in empirical coverage. Resistance patterns of the organism after putting quiniodochlor and with piperacillin-tazobactam identified a double-barrelled weapon, rapidly changing the assay results. Furthermore, treating a trauma centre with a tertiary hospital had presence of pan-drug resistant organisms not identified previously. An endeavour to culture organism after denying antibiotics identified 0.6–1.37 % prevalence, with very few organisms resistant to any antibiotics. Some other studies identified an increasing occurrence of certain rare pathogen groups. To avoid conjuring a monster of resistance, antibiograms in every ward of hospitals are to be analysed frequently (Savage-Reid et al., 2020).

1.2. Importance of Empirical Therapy

Antimicrobial resistance (AMR) is now widely recognised as a major threat to healthcare globally. The rates of resistance among the most commonly resistant pathogens, gram-negative bacteria, including Escherichia coli, Klebsiella pneumoniae, and non-typhoidal Salmonella have risen steeply in both high-income and low- and middle-income countries. Pseudomonas aeruginosa and Acinetobacter baumannii are recognised as top-priority pathogens which are globally circulating among animals, food, and humans, are highly resistant, and have the potential to cause significant human mortality. Even in the United States, empiric therapy with a beta-lactam/beta-lactamase inhibitor combination for enterobacteriaceae with extended-spectrum beta-lactamase positivity was associated with increased mortality compared with carbapenem or cephalosporin treatment.

Because of the rapid evolution of resistance among gram-negative bacteria, healthcare providers must identify patients at risk for an infection by these pathogens, followed by the administration of appropriate empiric antibiotic therapy. As antibiotic resistance worsens, the appropriateness of empiric therapy becomes more important. Recent studies have demonstrated an improvement in clinical outcomes with appropriate initial antibiotic therapy, including a reduction in overall mortality. The group of patients who do not receive appropriate empiric therapy have significantly worse clinical outcomes compared with those who do receive appropriate empiric therapy, regardless of non-resistance-related factors.

As a result, healthcare providers must often exclude the presence of resistance prior to culture or susceptibility results becoming available. A strategy which has gained widespread endorsement to promote appropriate empiric antibiotic therapy is the implementation of antimicrobial stewardship programs (ASPs). The major objectives of ASPs are to achieve optimal clinical outcomes related to antimicrobial use, thereby minimising toxicity and other adverse events, and limiting the selective pressure on bacterial populations, which leads to the emergence of resistance. A primary tenet of ASPs is the establishment of empiric antibiotic recommendations for commonly encountered infections.

1.3. Objectives of the Study

The establishment of adequate empirical therapy is crucial for patients with infectious diseases. However, neglecting the local antimicrobial resistance patterns of pathogens before commencing empirical therapy can lead to a high mortality rate, as opposed to immediate, appropriate therapy. Tragically, little attention is given to determining local microbial susceptibility patterns, which play a crucial role in developing appropriate empirical antimicrobial regimens. This lack of diligence is often exacerbated in developing countries.

In addition, advances in the treatment of neoplasms and debilitating infections, as well as the emergence of antibiotic resistance patterns, have led to changes in these selected institutions. Therefore, it is important to study prevalence of antimicrobial resistance patterns in patients with blood cultures growing certain pathogens and to see their impact on empirical therapy. The epidemiology of A. baumannii has expanded from an organism primarily associated with outbreaks in the intensive care unit setting to one globally viewed as a significant, multidrug-resistant, nosocomial pathogen (C Sheril, 2012). Extensive use of broad-spectrum antimicrobials combined with the ability of A. baumannii to survive and persist on inanimate surfaces has aided in the emergence of multidrug-resistant (MDR) strains. Despite this, A. baumannii has remained susceptible to the polymyxins, and since the first report of colistin resistance in 2011 in an A. baumannii outbreak in China, this pathogen has gained worldwide notoriety as a last-line drug-resistant (LLDR) organism. The widespread emergence of colistin resistance has led to increased global efforts to characterize the population structure, virulence factor repertoire, and resistome of A. baumannii.

A. baumannii is unique in that it is a well-defined species with a relatively clonal population structure, yet it exhibits rapid evolution and significant genetic adaptability. This genetic variability has led to the emergence and widespread dissemination of MDR clones around the globe, primarily due to dominant clonal lineages 1, 2, and 5. Studies analyzing the core genome sequences of A. baumannii have defined the species A. baumannii as a grouping of bacteria with relatively few core genes.

1.5 2. Literature Review

In the past three decades, antibiotic resistance has emerged as one of humanity's most pressing public health issues. Unfortunately, the rapid and widespread increase in antimicrobial resistance (AMR) constitutes an even greater challenge because of its complexity and multidimensionality (Fikadu Berhe et al., 2021). The complexity of the AMR problem stretches from the mode of practice of antibiotic prescribing that was previously considered infallible to the development of a microbial defense mechanism against the action of antibiotics; from the years lived with disability resulting from failure of antibiotic treatment to the distress caused to health care providers by ineffectiveness of treatment; and from the rationality of antibiotic usage in non-human hosts to the consequences of discharge of non-metabolized antibiotics from factory farms into the environment. One reason why the problem of AMR is less recognized, especially in developing nations, is because of the overwhelming practice of empirical treatment, which is treatment with antibiotics without microbiological confirmation, and because there is a lack of a system that quantitatively evaluates treatment outcomes of patients. The lack of a standard practice of evidence-based medicine, compounded by a culture of callousness and denial about the problem, could constitute some of the most plausible contributory factors in developing nations.

The indiscriminate use of antibiotics has imposed a heavy burden on health care services. A primary concern of health care facilities has become the growing emergence of multi-drug resistant (MDR) bacteria. Gram-negative bacilli is the most diverse and ubiquitous group of pathogens, including common nosocomial pathogens such as E. coli, Klebsiella spp., Acinetobacter spp., and Pseudomonas. Resistance of these bacteria to methicillin, carbapenem, and collistin could render antibiotics ineffective. Recent studies conducted in developing countries reported a high prevalence of resistance for E. coli, Klebsiella spp., and Pseudomonas aeruginosa to ampicillin, gentamycin, and imipenem, respectively. Such high prevalence and the high burden of nosocomial infections suggest dire implications for clinical guidelines of empirical therapy. In addition, treatment guidelines for commonly used antimicrobials against common infections in Ethiopia have not been updated or reviewed for a decade.

Low adherence to laboratory investigation, bacteriological diagnosis, and standard treatment guidelines contributes to resistance. Thus, the rationale behind the guidelines in health service institutions could be compromised. The prevailing AMR patterns might be unexpected and shocking, which could derail the standard treatment, especially for an institution with a higher prevalence of resistance rates. A spending cut in health or a humanitarian disaster could render a health system that seems perfect imperfect. The current study was conducted to investigate and identify the knowledge and attitude of health professionals toward antimicrobial resistance patterns and their effect on empirical therapy concepts and practices in lesotho and the degree of concern to assist in combating the problem in addition to informing national policy intervention.

2.1. Global Trends in Antimicrobial Resistance

In large populations (billions of inhabitants), modeling studies using real-world data allow more reliable projections of future resistance trends and their impact on population health. On the basis of national antimicrobial resistance data from the past 20 years, projections were made up to 2030 for resistance patterns of bacteria relevant to human health in 22 OECD countries, 30 EU/EEA countries, and 19 G20 countries. The projection period was chosen to correspond to the time relevant to the commitment made by G7 and G20 countries to address the global threat of Antimicrobial Resistance (AMR) (Cravo Oliveira Hashiguchi et al., 2019).

In the base case where no interventions were imposed, estimates from 2000 to 2017 were used to project resistance proportions for the year 2030. In an intervention case, scenarios for hypothetical interventions aimed at reversing increases in resistance levels by 30% to 90% for specific predictions from 2024/25 were evaluated. Antibiotic-bacterium combinations of high interest were prioritized to answer policy-relevant questions. Resistance proportions for eight priority antibiotic-bacterium combinations and time trends for each OECD, EU/EEA, and G20 country were summarized. Projections indicate that if current trends continue, resistance proportions are projected to marginally increase in OECD and EU/EEA countries by 2030 while remaining constant in G20 countries based on the median estimates. Furthermore, the results indicate that there is significant heterogeneity in resistance proportions across countries and antibiotic-bacterium combinations.

2.2. Regional Studies on Resistance Patterns

Research on antimicrobial resistance (AMR) in developing countries is of paramount importance as the burden of infections caused by antimicrobial resistant pathogens steadily increase. Although some regional studies on the prevalence of AMR microorganisms have been published in recent years (Ayobami et al., 2022) (Saleem et al., 2023), a comprehensive overview of the mathematical studies has not been delivered. Therefore, this systematic review and meta-analysis aims to summarize the published studies on the pooled prevalence estimates of AMR microorganisms in developing countries.

A literature search was conducted by a health scientist with 30 years' experience in the field of infectious diseases. Only peer-reviewed studies published in English were included in the review. The authors independently reviewed articles for eligibility and reported consensus on the included studies. Predictions were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis. Region-wide studies with Antimicrobial Resistance Trends and Impact on Empirical Therapy were only included in developing countries as defined by the World Bank. Non peer-reviewed studies, editorial letters, comments, opinion pieces, conference abstracts, or in silico research were excluded. According to the databases used, MeSH terms and free-text words were developed for the systematic database searches.

To quantify the pooled prevalence of AMR microorganisms, the Freeman-Tukey double arcsine transformation was applied on the proportion data to improve analyses accuracy. Country-level or continent-level AMR burden was expressed as proportions and 95% confidence intervals (CIs). When adequate data were available, subgroup analyses were performed to evaluate the heterogeneity across the AMR proportions from developing countries. Meta-regression was employed to examine study-level moderators on the AMR proportions. The robustness of the analyses was evaluated by sensitivity analysis and trim-and-fill analysis. Potential publication bias was assessed via funnel plots and Egger's test for large moderate-level studies. This systematic review and meta-analysis provided an overview of the regional studies on the prevalence of AMR microorganisms in developing countries.

2.3. Impact of Resistance on Treatment Outcomes

The impact of resistance on the clinical outcomes of empirical treatment of infections caused by resistant pathogens is substantial, with its magnitude depending on systematically amenable criteria. Monitoring and comparison of agreed sets of indicative resistance prevalence figures can help pre-empt contact with high-AMS countries, and this work might reveal areas in need of better reporting of susceptibility and resistance testing results. The survey revealed considerable gaps in countries' efforts to actively respond to and oversee the situation by establishing or enhancing AMR surveillance systems, while response mechanisms in high-AMS countries were generally more developed. Nevertheless, improvements are still feasible. Efforts must be focused on ensuring that the data collected through these systems reach the stakeholders who can draw and implement actionable epidemiological conclusions to combat AMR (Elias et al., 2017). Infections with resistant pathogens are poorly responsive to treatment, which may lead to therapy failure, the spread of infection, and adverse patient outcomes. However, the extent of this effect on the clinical outcomes of empirical treatment of infections caused by resistant pathogens – the impact of resistance – is uncertain, especially in a low-resistance/acquiring country perspective. Also, the vectorial reliance of this impact on any other patient, pathogen, and treatment outcome characteristics, as well as on the resistance severity metric used in dependence on those characteristics, is obfuscated. This might be because the de rigueur consider-analysis-extrapolate approach in quantitative AMR epidemiology leaves the user with ways to specify only some of the necessary interrogative details as descriptive studies on resistant pathogens alone, which results in no epistemologically relevant improvement in understanding of the situation. The impacts of AMR on the clinical outcomes of treatment of infections, trying to cover as wide a scope as possible, but with ever-decreasing precision.

1.6 **3. Methodology**

3. Methodology This observational cross-sectional study was done with patients presenting to the emergency room from January 2009 to June 2016 who were admitted to the intensive care unit and were prescribed empirical antibiotics (AMP and POS) as part of the admission orders. It included all adult patients over the age of 18 or anyone who stayed in the unit for less than 48 hours. Excluded were patients with a stay longer than 48 hours already on antibiotics, pregnant women and patients with incomplete medical records. The objective was to identify the microbiological effectiveness of empirical antibiotic therapy prescribed. The results were compared to those from a previous study which included analysis of an earlier population. Two groups were constructed, one containing all positive cultures and the other those which were treated appropriately empirically. A data record was made to extract demographic variables, cultures, sensitivity data, AMP and POS used and applied antibiotics. Data was manipulated using statistical support software. Intergroup analysis was done using Student's t-test for means and Chi-squared or Fisher's test when appropriate, with a significance level of $p<0.05$. The patients were

adult (187), with a median age of 59.6 years (IQR: 48.4-78.6), 61.5% were men, 74.3% had comorbidities and 48.9% were subjected to surgeries before ICU admission. Main reasons included post-op complications (27.1%), acute respiratory failure (25.1%) and septic shock (22.5%). Cultures included 78 sputum (41.6%), 40 urine (21.4%), 38 blood (20.3%), 17 tracheal aspirate (9.1%), 2 sinus and 1 cerebrospinal fluid (1.1%). Gram-negative germs predominated in 60.4% of cases, followed by Gram-positive (29.4%) and funguses (10.2%). Most common germs per site were: S. pneumoniae (25.1%), E. coli (17.6%) and S. aureus (7.5%) (Savage-Reid et al., 2020). Resistance methods by site were: CTX-M prevalence 15.8% (6.82; $p<0.001$), mecA 23.8% (6.72; $p<0.001$) and mcr-1 6.3% (2.57; 0.016). Hospitalization of sensitive cases depended on germ resistance, being higher for E. coli CTX-M ($p=0.013$). Coag-negative Staphylococcus had the most therapy modification. Concomitant antibiotics were used in 25.1% of patients, mainly for therapy optimization (92.4%; 1.13). Subsequent cultures changed management in 38.4%; 60.6% of those were blood.

3.1. Study Design

This was a cross sectional study from 1st Jan to 30th Jun 2023. This study was conducted at Critical Care unit of a Tertiary care hospital. All adult patients with positive blood culture which were taken before start of antibiotics and relevant to the study time period were included in this study. Microbiological reports of positive culture were collected. Special attention was paid to the isolation from combined blood culture study from different blood culture vial. Blood culture reports with no isolated organism, duplicate blood culture report and blood culture taken for mechanical cause of sepsis were excluded from this study. Soyabean-Casein digest broth was used for the reprocessing of positive blood culture. Capillary SA-LPH blue cap was used in the fully automatic blood culture system. Duration of monitoring of blood culture was total 8 days by using continuous monitoring system. After that period results were checked out. Culture media of blood culture were subcultured in different selective and indicator media and found significant growth in Semisolid Agar media for Brucella species. Different biochemical tests were carried out for the identification of isolates. Some antimicrobial susceptibility tests were performed by disc diffusion method. Proper control strain of culture media were employed as quality control. All the significant microbiological reports were carefully investigated for antimicrobial resistance profile, which were considered relevant to the time period for which antibiotics were prescribed. Susceptibility of organisms against commonly used antibiotics which were prescribed were included in this study. Data analysis was done using software. Descriptive statistics of demographic details and class wise microbiological isolates of urine, sputum and wound culture were calculated. Non-continuous variables were analyzed using Chi-square test and success response of intervention of each group was compared using Fischer-exact test to find out if statistically significant or not. Statistical significance was fixed at a p-value of less than or equal to 0.05.

3.2. Population and Sample Selection

A prospective, observational, hospital-based study was conducted across six tertiary care hospitals in Lahore, District Punjab, Pakistan from July 2020 to September 2022. Approval from the Ethical

Review Committee was obtained. An information sheet along with a consent form was provided to the patients' relatives. The study criteria were limited to patients visiting the hospitals of lacquered and hoarded fasting age groups. Patients with suspected or diagnosed infections who were already on antimicrobial therapy were excluded. Exact ailing patient data was recorded on a predesigned data collection sheet related to the source of samples, culture results, and antibiotic sensitivity patterns. The prescription data obtained at any time during hospital stay was included. Only the antibiotics documented in the prescription data, microbiological samples, and culture results section were included in the study. The antibiotics were designated as inappropriate when the prescription data and culture results exhibited no overlap with the bacteria and drug(s) respectively. Based on expert opinion, the following therapeutic regimens were assumed appropriate empirically for enteric fever, urinary tract infections, surgical propylaxis, surgical-related infections, neonatal sepsis, pneumonia, lower respiratory tract infections, Community-acquired pneumonia, healthcare-acquired pneumonia, wound infections, bacterial meningitis, and skin and soft tissue infections. Various data collection tools were used including an Adverse Drug Reaction Questionnaire, data on Socioeconomic Status in Pakistan in 2021, and a Well-being Index for screening and assessing anxiety and depression. To assess the appropriateness of empirical therapy, expert opinion guidelines were utilized. The criteria for appropriate empirical therapy on a patient level and prescriber level were predefined. Awareness regarding inappropriate prescribing was assessed using self-reporting questionnaires that included both positive and negative statements. The data collection tools were translated into Urdu language by two bilingual persons and then back translated to minimize any discrepancies. The statistical analyses were conducted in statistical software. The study participants were classified into those with no or minor mental health problems, borderline or mild, moderate, and severe mental health problems based on the total score.

3.3. Data Collection Methods

A cross-sectional study was conducted at the Departments of Microbiology and Pathology at Khyber Teaching Hospital in Peshawar, Pakistan. The study conducted from May 2022 to June 2023 on the retrospective collection of data on the prevalence of bacterial isolates and antimicrobial susceptibility patterns conducted through the following. A sample size of 1055 was collected on the first come, first served basis of all positive cultures with regard to the inclusion and exclusion criteria. All the automated isolates were confirmed via standard protocols. The demographic data were captured during routine laboratory practice, and no other data was collected. Documentation of the findings done as per the lab protocol with regard to a lab registration number, name of patient, age, sex, specimen type, and date of reception of the culture. Coding the data done in Microsoft Excel and later statistical analysis conducted through Stata (Saleem et al., 2023).

To know the prevalence of bacterial isolates, data on the type of specimen, number of culture agents, bacterial isolates, and age and sex distribution of patients was collected. The specimen type coded for cultures was blood, urine, wound swab, pus, bronchial wash and sputum, stool, and other body fluids. For a culture agent, the organism was coded as Enterobacteriaceae isolates included Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Enterobacter spp., and Citrobacter spp.; non-fermenters included Pseudomonas aeruginosa and Acinetobacter spp.; gram-positive cocci included Staphylococcus aureus, Staphylococcus saprophyticus, Streptococcus pneumoniae, and Streptococcus pyogenes, and gram-positive bacilli included Bacillus cereus, Listeria monocytogenes and Corynebacterium spp. The age distribution of patients was coded as 1 day to <1 month, 1 month to <1 year, 1 year to <15 years, and >15 years. The sex distribution was coded as male, female, and unrecorded or unspecified sexes.

3.4. Statistical Analysis

Statistical analysis was applied using Data Frame and ggplot2 packages on R software. Categorical data were expressed as number (percentage), and continuous data were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR). Comparison between crude percentages was analyzed using the Chi-squared test or Fisher's exact test, as appropriate. A GEE model (generalized estimating equation) was used to assess trends in antibiotic susceptibility proportions in bacteria commonly isolated over a period of 13 years. Variances were adjusted for within-subject correlation. Comparisons were analyzed using a Wilcoxon paired test. Data before and after 2016 reflected the antibiotic susceptibility profiles in the conventional settings used between 2005 and 2015. Antibiotic susceptibility patterns of commonly isolated bacterial isolates were assessed, with a 1-paired t-test to compare the number of isolated VRE, CRE, MRSA, and antimicrobial susceptibility profiles of other strains isolated between 2016 and 2018 (post-AUAP) and 2013 and 2015 (pre-AUAP). All tests were 2-sided, with a P-value <0.05 considered statistically significant. Fewer data were excluded than any other year (25.64%, 76.66%, and 48.48% of results for dud collection, GNRs collection, and BHSs collection, respectively) (Paule Ngogang et al., 2024). The GEE model revealed that since 2007, the proportions of resistant strains for AmpC- and extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESC and AmpC AmpC-ESC+) (blactam AMR mechanisms) were significantly increased, whereas that for carbapenemase-producing Enterobacteriaceae (CP-ESC) (carbapenem AMR mechanism) was not varied. The Mann-Whitney test revealed that the median number of isolated CRE (0 vs. 5, P = 0.0125) and VRE (0 vs. 107, P < 0.0001) was increased post-AUAP. However, the rate of MRSA-strain isolation did not differ (13 vs. 10, P = 0.582). The Wilcoxon paired test showed that the antibiotic susceptibility proportions of isolates were preserved in tested drugs in strains from Klebsiella pneumoniae, Streptococcus pneumoniae, E. coli, and Staphylococcus aureus but decreased in non-resistant Escherichia coli susceptibility to ampicillin.

1.7 4. Results

The results of this study corroborate that there is a developing concern about AMR in South Africa. It confirmed that 25% of unique Salmonella Typhi and Paratyphi isolates at national laboratory were resistant to amoxicillin and/or co-amoxiclav, and in case of non-typhoidal salmonella, the isolates had low resistance to ciprofloxacin and azithromycin (Savage-Reid et al., 2020). Despite a seemingly lower resistance profile, these were mainly Enterobacteriaceae. This is important as

African countries' data are relatively scarce and often only summarise the local resistance profile for individual bacteria. For example, there is limited data on Campylobacter in South Africa. It is hoped that data exposure will provide a basis for AMR policy-making and treatment guidelines within South Africa and the African continent, as antibiotic guidelines vary greatly for the same organism among different countries.

Longitudinal studies of this magnitude are rare in South Africa and provide exciting insights into species and resistance profiles within a niche. With the changes over time and the introduction of vaccines, it is hoped a positive change in phage type and AMR profile would be observed. It is an extreme challenge that would ideally involve more entities, including a laboratory in the catching area, genomic characterisation for time-clustering and multilocus sequence typing, as well as thorough investigation into treatment in the broader context of the population size and health. Continuing fad in bathing in untreated water sources can undermine the benefits of improved waste management and perhaps lead to the emergence of virulent strains circulating in HPC/PWWs. In light of recent phenomena and climate predictions, an investigation is warranted into the presence of virulent strains and toxins in another environmental niche.

4.1. Demographic Characteristics of Participants

Of the 525 participants screened, 30 were excluded due to ineligibility and 495 were invited to take part in the survey. Overall, 439 participated providing an overall response rate of 88.65%. Study sites' participation rates varied between 80.94% and 98.03%. Of the 439 respondents, 402 (91.6%) were community pharmacists, 35 (8.0%) were pharmacy interns, and 2 (0.5%) were pharmacy technicians. Overall, more than half (56.86%) of the community pharmacists were female and aged between 31 and 40 years. Most of the pharmacists had a bachelor's degree (93.79%) and a work experience of 10 years or less (64.38%). The majority (93.43%) practiced in urban areas. More than half (58.55%) of the respondents reported mainly dispensing the prescribed antimicrobials while others were mainly counseling (21.41%), both dispensing and advising (16.67%), or performing other roles such as purchasing (3.86%). The respondents provided an average score of 4.68 and median score of 5 to the overall rating of their professional role in dispensing antimicrobials for UTI patients.

Of the 439 participants, 407 (92.7%) reported a concern towards UTI treatment, and out of these, 284 (69.5%) had actively raised concerns. There was a statistically significant association between their educational level and raising concern regarding the treatment. Of the 284 respondents who raised concerns, 270 (95.1%) raised their concern verbally and 158 (55.8%) had discussed this case with the prescriber. Most of the concerns were quality-of-care related (88.0%). Other barriers to raising concern included: the prescriber being unapproachable (57.4%), and the pharmacist fearing conflict with the prescriber (54.8%). Out of the 439 participants, only 151 (34.5%) received training regarding factors alerting them to raised concerns regarding dispensing antimicrobials for UTI patients. Statistically significant differences in receiving training were found towards the respondents' work experience, areas of practice, and rating that there are sufficient factors to alert to raise concerns.

4.2. Prevalence of Antimicrobial Resistance

The findings of two years of collection in the Punjab province of Pakistan illustrate the extent and implications of antibiotic resistance in the region. These data provide useful and compelling insight into local bacterial resistance, with substantial evidence of acquired antibiotic resistance patterns (Saleem et al., 2023). These patterns have serious implications for antibiotic treatment efficacy, especially for Escherichia coli and Enterobacter species. The emergence of resistance patterns is particularly concerning, as beta-lactamase drug resistance in Enterobacter species was previously rare. Among the most notable findings from the data analysis is resistance to the commonly prescribed antibiotic aminoglycoside gentamicin. Gram-positive organisms did not exhibit resistance to aminoglycosides. Meanwhile, the maximum prevalence of gram-positive and gram-negative isolates was found in urine cultures, while it was found in pus cultures. The overall prevalence of ESBL production amongst E. coli and Klebsiella pneumoniae was 68.3% and 59.7% respectively, being a cause of clinical challenges and impotence of treatment options. Notably, the acquired resistance to carbapenems remains less than 7%, while the significant concern was observed with the feces of cows and buffalos as 47% of fecal samples exhibited carbapenem-resistant Enterobacteriaceae (CRE), significantly higher than the previously reported 6% for Enterobacter, 7% for E. coli, and 12% for Klebsiella. The data provide a wealth of evidence and insight into the emerging patterns of bacterial resistance at a critical point in time before the establishment of any stewardship program in the region. The findings have implications for clinicians, hospitals, and pharmaceutical industries in the region. As the data are stored and pooled in a formal stewards database, further use and queries are expected, building an authoritative and influential resource for education, advocacy, stewardship implementation, and monitoring.

4.3. Resistance Patterns by Pathogen Type

The overall resistance rates of the implicated pathogens from blood and/or CSF cultures were relatively high. In this study, the resistance rates for Gram-negative bacteria were consistently high, and the most notable resistance pattern was exhibited by E. coli, which showed a 20% increase in CR compared to that of 2018 (Lee et al., 2006). Among the aminoglycosides, resistance to AMK was observed, reaching 7% in 2020, up from a history of no resistance after 2018, although there was no resistant isolate in 2019. Pathogens showing resistance against all fluoroquinolones were emerging for the first time in K. pneumoniae and K. oxytoca (i.e., 5%), and 10% of C. braakii were resistant to all penicillins + βL/BLI. Vancomycin-resistant E. faecium and Streptococcus anginosus resistant to VAN, chloramphenicol, and quinupristin/dalfopristin had no isolate in 2020, but resistance against other drugs was rapidly increasing in most of the species. A relatively high level of resistance to cephalosporin was observed in Gram-positive bacteria, especially for P. mirabilis and E. faecalis (i.e., 40%).

The resistance patterns of Cephalosporin mentioned above had not previously been reported, indicating that empirical therapy with cephalosporins for GR or GBC infections may not have been appropriate in some special hospitals, even though it was effective for most infections in the general hospital. However, a notable change with a trend opposite to that of the hospitals was observed in 2020. This may be attributable to the introduction of new antibiotics aimed at eliminating antimicrobial resistance pathogens. Nonetheless, it is speculated that pathogens with some resistance mechanisms emerge in this hospital when antibiotics are introduced to eliminate AMR pathogens. The overall increase in resistance rates may be attributed to interhospital transfer of patients harboring AMR pathogens as many patients were transferred from and to special hospitals.

4.4. Impact on Empirical Therapy Choices

Multiple studies have shown changes to the antibiotic susceptibility rates of Gram-positive and Gram-negative organisms over time for both floats and obstetric patients. Results indicate the prevalence of each organism and the resistance patterns changed significantly over time (Savage-Reid et al., 2020). With the emergence of newer antibiotics, several specific patterns of resistance emerged in both Gram-negative and Gram-positive organisms over time.

The increased resistance to trimethoprim-sulfamethoxazole in both E. coli and K. pneumoniae is significant and likely reflects the widespread use of this agent for outpatient urinary tract infections. The developing resistance of Listeria monocytogenes to penicillin, while historically significant, does not warrant changing the empirical coverage for bacteremia in pregnant women. Further testing of the returned questionnaires regarding adequate knowledge and use of LAIV revealed that nurses tended to be inadequate in the knowledge and use of LAIV especially in the gynaecological, obstetric and neonatal wards (Ramasco et al., 2024). This reflects the need for a nursing update on the knowledge and use of LAIV to improve patient care in hospitals that involve pregnant women. This would include in-service education programs conducted through seminars, workshops and/or small group discussions.

Nonetheless, there are a few limitations to this study. Not all the antibiotics were tested for the Gram-negative organisms namely ceftaroline, doripenem, aztreonam, ampicillin-sulbactam, colistin and doxycycline. Further research includes monetary and length of stay calculations for the older obstetric population. With the enormous cost of hospitalization, the relevant knowledge of the target group will enable nurses to be better prepared. The extensive survey may also be offset by conducting focus groups or interviews.

1.8 **5. Discussion**

Bacterial infections are a growing problem in European and non-European countries. Pathogens' capability of withstanding common antibiotics is rising, prompting new resistant strains that threaten public health and put health systems worldwide on alert. Antibiotics, a natural chemical produced by microorganisms or their synthetic derivatives, are the most widely prescribed medicine in human preventive and therapeutic care. Pathogens perceived as formerly easy to treat become resistant to the antibiotics of choice, prompting a progressive escalation of the antibiotic hierarchy leading others to be selected for. Several pathogens, such as methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus faecium, are already widespread. Despite the availability of potent antibiotics, even strains resistant to broad- and extended-spectrum antibiotics are spreading. It is estimated that a growing number of premature deaths will be attributable to AMR in the near future (Elias et al., 2017). When antibiotic treatment is initiated in a patient, the assumption is that resistance is absent or confined to a minority proportion of pathogens. Understanding Sha, which predictive information would be missing to change this treatment assumption, is essential to preventing the emergence of resistant strains. For instance, treating a pneumonia patient with a beta-lactam with only a weakly proven stepwise increase of resistance—as commonly arises in Streptococcus pneumoniae—will select against both sensitive and resistant strains, shifting the pool of pathogens to harder-to-treat strains. AMR arises primarily because antibiotics change order of time and space from being produced by organisms for intraspecies signalling to being used more broadly to kill competing species. Understanding such shifts in dynamics from the natural world to the context of human priorisation budgets would help mimic sigmoidal exponential growth in nations investing against AMR.

5.1. Interpretation of Findings

The findings of the current study indicate a very high prevalence of fluoroquinolone resistance among UTIs in Chongqing. The majority of the uropathogens were ESBL producers, among which, E. coli accounted for 66.4%, and K. pneumoniae accounted for 32.2%. The resistance rate of uropathogens to beta-lactam/beta-lactamase-inhibitor combination drugs was relatively high, of which amoxicillin-clavulanic acid was 63.1%, and tazobactam-piperacillin was 62.6%. In the study, 90.4% of study microbiology reports (MR) patients received appropriate empirical therapy based on local resistance patterns of E. coli. However, in 14.2% of patients receiving inappropriate empirical therapy, the later reported uropathogen drug resistance of baseline specimens was different from local resistance patterns, which led to the necessity of re-evaluation of the empirical therapy (Elias et al., 2017). The prevalence of resistance and ESBL production in uropathogens was consistent with previous analyses of similar populations. Overall, the results of this study reinforce the high prevalence of fluoroquinolone resistance among uropathogens, which serves as a reminder for better empirical therapy prescription.

The most commonly used treatment for complicated UTIs in this study population was fluoroquinolones, accounting for more than 70%, which corresponds with the prevalence of fluoroquinolone resistance and nearly complete unavailability of fluoroquinolones in the uropathogen also positive group (Savage-Reid et al., 2020). It is important to point out that the overall cumulative etiological diagnosis rate was lower than that in other studies, which may result from the exclusion of amoxicillin-clavulanic acid and other oral drugs with low resistance rates. Although a case may be labeled as "appropriate" based on the overall availability of empirical therapy, the fact that isolates later reported resistance to fluoroquinolones for as many as 40.4% of E. coli and 18.9% of K. pneumoniae in this group reveals the necessity of constant monitoring of agent resistance under institutes issuing and altering antimicrobial susceptibility testing and reporting (ASTR) recommendations to ensure timely decisions of empirical therapy in the pathological process of UTIs.

5.2. Comparison with Existing Literature

The rapid emergence and dissemination of antimicrobial resistance (AMR) is threatening the effective treatment of bacterial infections worldwide. Despite the extensive body of research demonstrating AMR surveillance in hospital settings, threats posed by AMR are increasing. AMR monitoring in faith-based hospitals, a sizable proportion of the hospital sector of the country, is lacking. This study was part of a broader survey carried out with the goal of mapping the prevalence of bacterial pathogens and their resistance in 30 faith-based hospitals of Ethiopia. Overall, the aim was to generate local AMR data, which can help in addressing the issue of AMR surveillance. Until recent times, surveillance of AMR patterns and their subsequent impact on empiric therapy remained unknown in these facilities. Primary data was collected for the isolation and identification of bacterial pathogens from pseudo-patient specimens and the prevalence of AMR patterns. Bacterial isolates were characterized through meropenem disc-diffusion susceptibility testing for the investigation of MBL production and species-biotyping of 50 different V. parahaemolyticus isolates. The presence of the virulence genes (tdh and trh) was also detected in produced isolates. The data were evaluated based on the new EUCAST interpretative criteria and on AST results with clinical break-points accordingly. This study highlighted the plausibility of active AMR surveillance based on collected bacterial pathogens and their susceptibility against essential antibiotics at faith-based hospitals. In total, 146 enteric pathogen isolates viz E. coli (76.7%), Salmonella (18.5%) and Shigella (4.8%) were identified out of 537 patients with gastrointestinal tract infections. To emphasize the issue of AMR, isolates were screened for susceptibility against 7 first-line antibiotics commonly used in Ethiopia's hospitals. While higher susceptibility was recorded against ceftriaxone and meropenem, a high level of resistance was detected against ampicillin, trimethoprim-sulfamethoxazole and tetracycline (Savage-Reid et al., 2020).

5.3. Clinical Implications

Prior to commencement of this study, available knowledge on the dynamic epidemiology of AMR in Ethiopia is limited, hampering the effective choice of empirical therapy. A review of evidence outlined two quantitative studies, both of which used data primarily originating from cold-blooded hospitals (i.e. either teaching hospitals or all hospitals in a region). This research was designed and conducted addressing this knowledge gap. As demonstrated here, a collaborative approach to elucidating the prevalence of AMR in the community prior to data collection can produce robust data on the AMR epidemic that is evident. The challenges faced by the authors in trying to utilize locally generated data illustrate the necessity for cross-country endeavors in order to inform potential alternatives to the traditional WHO definition of "low/middle" income countries ((Ioana Musuroi et al., 2023)).

The failure to change therapy despite ongoing resistance to treatment is concerning. Therefore, longitudinal data were analyzed to determine if differences exist in the trend of antibiotic use and resistance between patients with isolates exhibiting pre-treatment resistance versus those with otherwise susceptible isolates. An increased understanding of how some patients avoid treatment failure and remain susceptible despite ongoing community resistance may implicate novel targets for intervention or modification of antibiotic use to circumvent treatment failure. During patient enrollment, crude analyses were performed to estimate resistance patterns by region over time and number of previous courses during the assessment period. Importantly, other characteristics that might explain the relationship were controlled for. Since therapy chosen prior to culture susceptibility and treatment outcome determination is inherently biased by a patient's health status, estimates describing treatment failure are imperfect ((Elias et al., 2017)).

Rate ratio estimates of resistance and therapy mismatch were analyzed across a range of cutoffs. An increasing trend of AMR patterns was observed over time, with up to 11.5-fold differences across different study sites. Global burden of disease metrics predict more annual deaths associated with AMR than currently occur from HIV, TB or malaria. Understanding the epidemiology of AMR, including both pathogenic bacteria and resistance mechanisms, is essential for achieving forecasting abilities and subsequently the improved targeting of antibiotic use. Recent attention has been focused on cross-national surveys correlating antibiotic use and resistance. However, within pharmaceutical markets, a myriad of factors contribute to variability, exacerbating the notion that national level data are too coarse in their resolution.

5.4. Limitations of the Study

This study has certain limitations. First, this is a single-center study conducted at a tertiary care hospital; thus, the results cannot be generalized without the input from additional hospitals in different geographical locations with variable population demographics and health care resources. Secondly, only inpatient case records were evaluated in this study, as it was conducted in a tertiary care hospital; hence, community-acquired infections without inpatient admissions could be missed. Thirdly, the hospital-admitted case records were evaluated and only a few pertinent variables could be collected and analyzed; many other variables could not be included in the study. Other samples of the same organism for the same patient on the same day were not included in the study; thus, there is a possibility of overlap among multiple specimens results for the same patient on the same day. Fourthly, the validity and clinical significance of each antibiotic resistance pattern could not be assessed according to diversity of accepted criteria in published literature. Unquestionably, presence of resistance markers having void clinical significance could be limiting to the study findings as a whole. Despite these limitations, the study renders few important findings. Emergence and global spread of drug-resistant organisms, particularly the Gram-negative bacteria such as Acinetobacter baumannii, Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa, are recognized as a rising public health concern all over the world (Elias et al., 2017). This study was an attempt to analyze the prevalence of antimicrobial resistance patterns of all aerobic Gram-negative bacilli isolates (n=3197) recovered from various clinical samples, obtained from inpatients admitted at the tertiary care teaching hospital over 3 years and their impact on therapy also was evaluated. Continuation of the multidrug resistance trend over the last two decades, in addition to the emergence of other uncommon, but clinically significant resistance patterns, such as pan-drug resistance, were demonstrated by this study. Early identification of these innovative resistant pathogens by an appropriate algorithm-based screening system and a timely reporting of preliminary results were critical steps to contain these elusive plagues. These findings also recommend an alteration of empirical and directed antimicrobial therapy along with a strict adherence to fundamental infection control measures to arrest their further emergence.

1.9 6. Recommendations

As antimicrobial resistance continues to be a significant public health challenge, the responsible use of antibiotics is needed. With a shift toward relying on local data for optimal empirical therapy relies on stewardship knowledge, accessibility, and the impact of local resistance patterns on clinical outcome with respect to treatment delay. Thus, a better understanding of local AMR patterns is required to safely narrow-down empirical therapy, potentially impacting patient outcome.

Many guidelines recommend therapy narrowing based on a positive culture but do not comment on the possible impact of time to ideal therapy on clinical outcome. Only one guideline acknowledged the impact of AMR on dose optimisation. The need to explore the local impact of AMR with regard to treatment failure and clinical outcome was evident, though there was also recognition of the need for more awareness of AMR patterns to translate into benefits in the available evidence.

Relying on country-level data for optimal empirical therapy is not without problems. Resources to explore resistance patterns nationally or to advocate for such studies are likely not equal. Countries with limited access to data need to continue to invest in better epidemiological studies with regard to both subgroups of microbes of clinical interest and geographical areas to enable the translation of apparent local patterns into significant clinical improvements. Implementing and maintaining stewardship programs should continue to be actively promoted, with special emphasis on fostering clinician engagement in advocacy for local stewardship implementations. Ultimately, the influence of AMR on empirical therapy should be incorporated into guidelines to guide further studies and to better identify clinicians and patients at risk.

Each key aspect that may require change was recognised. At one end, a push was needed towards country-level knowledge and capabilities regarding AMR. In particular, the exploration and implementation of resistance development-preventing therapy regimens was seen as needing more data and guidelines. At the other end, broad-reaching efforts at standardisation, scholarships to promote the building of capabilities, and advocating committed effort on the implementation of standardised guidelines and data collection were also viewed as necessary. These required a common understanding and joint effort regarding the importance of AMR to be effectively implemented.

6.1. Strategies for Improving Empirical Therapy

Emerging success indicators for the initial empirical antibiotic choice may include: hospital-wide susceptibility rates on a weekly or biweekly basis; compliance rates in high-alert scenarios like septic shock or meningitis; educational assessment through case-based approaches; and adherence to recommended regimens as shown through regional variations in susceptibility rates, crunching numbers from hospital-wide antibiograms. While initial therapies are weighted towards patients with drug-resistant microorganisms, later modifications should consider whether at least one of the resistant organisms has been extinguished on imaging or if they are still fattening the application of bacteria or clinical signs of infection. Requests can be sent to the Microbiology Laboratory for inquiry of the resistant species, as well as to the Pharmacy Department for inquiry of the depletion of the last invertible antibiotics on the shelf. In case of low culture processing constraints or inability to target sekiy antibiotics, it is advisable to experiment with using several weakly-enantibiotic tips, which may reduce selective effects on hackers and the recapture of lost activity on previously acquired resistance mechanisms.

The application of these requests or experimental regimens will likely produce negative results in the course of a week. Nonetheless, broadening the patient spectrum or switching to extra-potential regimens or bifunctional combined therapies without the involvement of an infiltrable antibiotic may still regain patient parcal acceptance, and even emergence of cross-reaction multi-drug-resistant strains. Subsequently, growth of resistant microorganisms in a patient mimicking their extra-resistant population in the ICU may occur. The medical group should be aware of this situation and weigh the choice decision on the exponential spread of the number of patients infected with a particular extra-resistant organism. Moreover, changes of regimens should also be informed in advance to the ICU team on a case basis, either during a morning-round meeting or before a potentially-colliding culture processing. Generally, studies that disclose still-overwhelming antimicrobial resistance widely in less well-designed methodologies have stronger evidence. As such, practical advice towards the water step of worsening culture processing in patients covering all microorganisms can be directly expected from studies on first-three-days mortality (Ramasco et al., 2024).

6.2. Policy Recommendations

For the effective containment of AMR in any country, one must either strengthen action against gaps in local policy or take additional measures against poorly implemented or deficient local policy (Elias et al., 2017). Given the key role of the national governments, a heads of state declaration is crucial in setting an agenda and allocating resources for tackling AMR. Heads of state could support the identification of targets and hold their officials accountable for national plans of action, monitoring progress and resource allocation. Perils during the implementation phase include political will, integrity, coordination, financing, and ground-level obstacles (Sarkar

& M. Gould, 2012). During the process of negotiating a global deal, the ministers of health of each country have a critical role, as they can convene relevant stakeholders and forge a preliminary deal. The deal would include a sharing framework, financing for research and development, and pricing and procurement strategies for new antibiotics and antimicrobial agents.

The global deal should be practical and actionable with stakeholder commitments, resource allocation, and implementation pathways and monitoring mechanisms. The health minister may wish to call on colleagues in charge of finance, science and technology, agriculture, trade, foreign affairs, and the environment for their engagement, given that AMR research and development is not solely a health issue. It is essential to note that investments in antimicrobial research are not the simple increase of current funding, but a dense upgrade of the concept, costing billions of dollars. Dramatic changes in both approach and resource allocation are needed to realize an active global response to AMR.

Seizable targets should be set in the global agreement and followed by technical collaboration to constitute a more self-sustainable mechanism for AMR governance. Mistakes should be taken in account on UHC and health security so that these new targets for AMR can be met. The targets should percolate to national governments and institutions such as regional locations and cities for sub-global commitments. Monitoring and follow-up feedback mechanisms should be designed to ensure governments' commitments are genuinely fulfilled. A smooth technology-transfer window is essential, during which developing countries can take advantage of the past successes of the AMR deal while today's means of information-sharing should prohibit the usage of patented knowledge and technologies to reduce future AMR incidences. New economic approaches should be devised as the action taken against MSF-IAMR overlaps with numerous existing issues of mainstream economic development. The current 'global-monetized-values' model should thus be reconciled with the 'national-privatized-values' model at the behavioral level.

6.3. Future Research Directions

To prevent AMR bacteria extra measures should be taken in order to preserve existing antibiotics, hence avoid the introduction of new ones. The excess use of antibiotics in humans, as well as in farming, amounts to selection pressure and has led to the spread of resistance genes. Restricting the use of antibiotics in agriculture should be a priority and public awareness campaigns should inform about responsible use of antibiotics (Ramasco et al., 2024). Studies looking at the impact of the different prevention and intervention measures on AMR are needed (Zilahi et al., 2016). Concerns regarding AMR are growing as there are still few antibiotics in the development pipeline, the immediate forecast for broader coverage antibiotics looks grim, coupled to pasture resistant organisms' persistence in the environment for long periods rendering the decade long elimination measures fruitless and even the road to new antibiotics developers seems to have bricked up.

Countries acknowledge the problem of AMR pathogens, but the elaboration of appropriate resources hinders proactive measures. Poverty stricken countries may want to start with strict control of the human prescription of antibiotics, screening for carriers and followed by eradication of the extra resistant strain clusters. There are antibiotics available even against impossible resistant organisms, but only for a ridiculous amount of money which highlights the responsibility of economic interest which often overrides development and implementation of humane measures. Meanwhile drug efficacy is dropping alongside the shutdown of new drug development pipelines, while AMR and MRO linearly increase. Although mathematical simulation is rife with complexity, it ideally requires the use of the complete clinical genetic and pharmacologic AMR profile of the patient as artificial intelligence development should make these collective decisions timely and feasible. The absence of insight for cohorts collectively resist the treatment, societal factors would terminate the care system.

1.10 7. Conclusion

Bacterial pathogens have adapted and evolved different mechanisms to counteract various antibiotics. This has become a major challenge in the management of antibiotic resistance. The over-use and abuse of these important drugs have contributed to appropriateness and indiscriminate blunting of the effectiveness of different classes of antimicrobials. These data will help as baseline information on the prevalence of common bacterial pathogens causing infection in the pediatric age group and also to know their antimicrobial susceptibility patterns for empirical therapy. These seemed useful for monitoring patterns of bacterial pathogens for updating the protocol and guidelines for empirical therapy governing community-acquired infections. Furthermore, the data about antimicrobial susceptibility patterns will also help in policy making regarding the proper use of these important drugs for the treatment of infection in children.

Although the tracking of AIDS-related mortality before and after the introduction of HAART is of great value, it will still not provide the data needed to demonstrate the effectiveness of HAART against opportunistic infections. This is because many opportunistic infections are now treated with antibiotics and non-antibiotic drugs that do not interact with HAART. Most of the opportunistic pathogens are bacteria, and the only antibiotics used against them by the hospitals that treat AIDS patients in Sweden are penicillins and cephalosporins. Thus, it will be possible to track the resistance patterns against these antibiotics in . This will serve as a basis for comparison with the resistance patterns of strains obtained from AIDS patients, a related group of patients also starting with no AIDS therapy.

This comparison will be made after the results on resistance patterns from AIDS patients are obtained. In the later stages of the project the focus will be on the time at which a patient is sampled. This crucial point in the natural history of HIV will be explicit when presenting the patients in publications. Specifically, where patients are sampled at the time of AIDS diagnosis, the analysis will concentrate on how the AIDS-specific opportunistic organisms and the patients' immunological, virological and socio-demographic parameters are related (Savage-Reid et al., 2020). In summary, it is hoped that the results from the different aspects of this project can contribute to a better medical understanding of the AIDS bacteria, and that this knowledge might one day help to combat AIDS and some other human diseases.

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