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NARRATIVE REVIEW

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The impact of antibiotic resistance on the rampant spread of infectious diseases in Pakistan: Insights from a narrative review

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Abstract

Background and Aims: Antibiotic resistance (ABR) is a global public health emergency which has seen an uptick in low- to middle-income countries in recent times due to a plethora of aggravating factors and has led to a whole host of setting-specific pathogens registering high rates of resistance, causing outbreaks with graver mortality and morbidity. This review analyzes available literature to determine the causes and effects of ABR and recommend solutions to the problem in a Pakistani setting.

Methods: Sources for this narrative review were identified via electronic databases using keyword search methods. The information was retrieved using databases such as PubMed and Science Direct. Additionally, websites such as CDC and World Health Organization were used to attain pertinent information. All the sources were selected as per their relevance and appropriateness toward the purpose of this review.

Results: This review details the causes by dividing them into three primary strata, namely (1) under-regulation, (2) over-prescription and self-medication, and (3) lack of medical stewardship. This is made much graver when the COVID-19 pandemic and the subsequent erratic treatment response is considered, with the pandemic augmenting already high levels of consumption. These factors have led a cascade of effects including, but not limited to, a considerable increase in ABR in pathogens to first-line drugs

Conclusion: ABR is a serious and growing issue which will result in undesirable personal, local, and national consequences if unchecked. Mitigation and reversal of this trend is necessary by developing existing programs and investing in novel therapies and pharmaceutical research and strengthening regulatory policies and mechanisms.

KEYWORDS

antibiotic resistance, Drug Regulatory Authority of Pakistan, Pakistan, phage therapy

1 | INTRODUCTION

According to the World Health Organization (WHO), antibiotic resistance (ABR) is one of the major global health challenges faced today.[1] ABR occurs when bacteria adapt the ability to resist medications that are designed to eradicate them.[2] A combination of microorganisms when exposed to antimicrobials, as well as the proliferation of those microorganisms and their resistance mechanisms leads to the existence of ABR.[3] In the past 3 years, more than 1.2 million people have died as an outcome of ABR infections. These effects are more prevalent in lower-middle-income countries (LMICs) such as Pakistan and India, however higher-income countries (HICs) such as the United States and France are also reporting alarmingly high levels of ABR,[4] leading to a rise in mortality rates of common and recently preventable infections that have now developed drug-resistant to the standard treatment.[5]

Pakistan is the 3rd greatest consumer of antibiotics among the LMICs after India and China. Between 2000 and 2015, antibiotic consumption boosted from 3.2 billion to 6.5 billion defined daily doses (DDD) with a 103% growth rate in India, from 2.3 billion to 4.2 billion DDD in China with a 79% growth rate, and in Pakistan surged by 65% growth rate, from 800 million to 1.3 billion DDD,[6] leading to the exponential rise of ABR. The study reported that the lowest drug resistance index (DRI) scores were seen in HICs, the researchers explain this by highlighting that these countries used a lot of narrow-spectrum penicillin and had access to more effective and expensive antibiotics while access to newer, more potent antibiotics is limited in LMICs, where broad-spectrum penicillin consumption is widespread.[7] The lack of data related to mortality and morbidity from ABR indicates the lack of a strong surveillance network in the country. The study strives to establish awareness of ABR in Pakistan by approaching it from root to stem and proposing attainable solutions to combat it.

To reiterate, Pakistan does not stand as an isolated case in the region when it comes to high ABR. Fair points of comparison may be drawn when one looks at the immediate neighborhood of South Asia, to nations like China. China registered a 10-fold increase in carbapenem-resistant *Klebsiella pneumoniae* in one decade, ticking up from 2.4% to 24%, and an uptick in carbapenem-resistant acinetobacter from 31% to 71.4%.[8] However, we believe that what sets Pakistan apart in the data set is a "perfect storm": a subpar national health infrastructure, medical malpractice in various forms, and patient unawareness to name just a few elements. Thus, this review is especially warranted to closely examine the drivers, effects, and remedies to countrywide ABR.

2 | FACTORS CONTRIBUTING TO ABR AND DRUG-RESISTANT INFECTIONS

In Pakistan, drug-resistant superbugs have been identified to be both extensively drug-resistant (XDR) and multidrug-resistant (MDR). In 2016, 100% resistance to fluoroquinolones was developed during the epidemic of XDR Salmonella,[9] and in the past 10 years, Enterobacteriaceae have acquired greater quinolone resistance.[10] Research on bloodstream infections (BSI) also found that 93.7% of the isolates were resistant to a 3rd-generation cephalosporin.[11] Human isolates have been reported to have a high incidence of Metallo—lactamase (MBL) up to 71% and Extended Spectrum β-Lactamase (ESBL) up to 40%, as well as carbapenem-resistant bacteria possessing the blaNDM, blaKPC, and mcr-1 genes that exhibit resistance to colistin, the last antibiotic of choice.[12]

The primary causes of ABR and drug-resistant infections are misuse, overuse, and often unneeded and nonprescribed use of antibiotics in humans. Moreover, overcrowding, failures in sanitation, and poor infection control methods are all contributing factors to the emergence of resistant infection in hospitals and the community.[13] When compared to the pre-pandemic period, antibiotic use increased amid the COVID-19 pandemic. For example, azithromycin use increased from 11.5 DDDs per 100 occupied bed-days (OBDs) in 2019 to 17.0 DDDs per 100 OBDs in 2020, while ceftriaxone use increased from 20.2 DDDs per 100 OBDs in 2019 to 25.1 DDDs per 100 OBDs in 2020.[14]

3 | ABR IN A HISTORICAL CONTEXT

Before the 19th century, the Indian subcontinent largely relied on the Unani and Ayurvedic systems of herbal medicine for both prophylactic, and therapeutic purposes. Herbs like *Caralluma tuberculata* and *Thymus serphyllum* were used to treat a broad range of diseases, ranging from the common cold to diarrhea.[15] However, with western colonization allopathic antibiotic treatments were marketed as being faster, more reliable and were endorsed by a new system of western medical education. Their impact can be seen best by the fact that while in the 19th century, nearly a third of all mortalities were due to infectious diseases, that number had dropped to around 4% in the 20th century.[16] However, repeated and often needless exposure to antibiotics has given rise to newer strains of several bacteria showing ABR, which mutate in the face of selective pressure applied with the abuse of antibiotics.[17] Nowhere is this more of a dilemma than Pakistan where several factors elaborated upon below have led to a much higher rate of drug resistance than is expected.

4 | THE CURRENT LANDSCAPE OF ABR IN PAKISTAN

According to a 2018 study by Klein et al., antibiotic consumption increased by 65% between 2000 and 2015, with the uptick contributed mostly by LMICs.[18] Pakistan is classified as an LMIC where both antibiotic abuse and subsequent resistance is rampant. It has five main drivers: (1) under-regulation, (2) over-prescription, (3) self-medication, (4) noncompliance, and (5) a complicit callous attitude toward ABR by licensed doctors and pharmacists. One factor which merits further study is the role of antibiotic-treated

cattle and poultry consumption in developing ABR in humans. National research on this aspect is lacking, and it has thus been only briefly mentioned.

A concise and powerful measure of the effects of antibiotic resistance can be found in a 2021 systematic review, which analyzed 93 original articles and reported on the overall resistance of 13 types of bacteria in an exclusively Pakistani setting.[19] The review used median resistance (MR) as a metric to judge resistance to several antibiotics. *Escherichia coli* was shown to be resistant to levofloxacin and tetracyclines. Salmonella spp. to fluoroquinolones (MR: 90.5%), Shigella to co-trimoxazole (MR: 80%), *Heliobacter pylori* to metronidazole (MR: 89.95%), *Acinetobacter* spp. to meropenem, and *Pseudomonas* spp. to colistin (MR: 20%). In short, this piece shows that whole classes of bacteria are now resistant. This is mostly due to selective pressure applied to strains of these bacteria which have developed resistant genes (ARGs) like ESBL and carbapenem-resistant blaNDM-1 and blaKPC-2 genes, as well as the mcr-1 gene.[20]

Pakistan-specific research has repeatedly shown the presence of MDR and XDR samples of bacteria in patient populations. A multicenter matched case-control study which attempted to investigate the biggest outbreak of ceftriaxone-resistant salmonella Enterica Serotype typhi in Hyderabad showed that a history of antibiotic use had a significant direct correlation with ceftriaxone-resistant salmonella Enterica Serotype typhi acquisition.[9]

Extensive administration of antibiotics has even resulted in neonatal resistance acquisition. According to the novel BARNARDS trial, which aimed to investigate the effects of ABR on neonatal mortality and morbidity rates in several LMICs including Pakistan, neonates have ARGs in their gut flora. The trial specifically screened for blaCTX-M-15, blaNDM, blaKPC, and blaOXA-48-like genes and found positive matches in most of the 36,285 neonates enrolled. Significant associations were found between presence of ARGs in neonates, substandard hand hygiene, and an intake of antibiotics 3 months predelivery.[21]

These findings are in no way constrained to humans. Rather, in the process of reviewing literature, a report in the Pakistan Veterinary Journal stated that around 90% of retail meat supplies were host to MDR *Campylobacter* spp., which was resistant to colistin, gentamicin, neomycin, ciprofloxacin, and amoxicillin.[22] This is proof positive of a vicious cycle between FPAs and human consumers, which lends credence to the hypothesis that ABR has infiltrated every route of transmission.

The latest studies conducted in tertiary hospitals show that MDR and XDR-TB comprises anywhere from 24% to 69% of all TB cases.[23,24] This is a huge increase from just a decade ago when a study measured the resistance rate to be 4.5% in 2009.[25]

Outside of a laboratory setting, these lab findings have very real impacts. According to Maha Talat, the WHO EMRO regional coordinator for infection control, MDR and XDR bacteria cause 700,000 deaths globally per annum.[26] Although empirical data regarding mortality due to XDR-bacteria in a Pakistani setting is hard to come by, we can safely assume that many deaths occurring due to infection can be attributed to drug-resistant bacteria.

5 | THE CAUSES OF ABR IN PAKISTAN

5.1 | Regulatory laxity and its sequelae

The responsibility of regulating drug inflow into the market falls on the Drug Regulatory Authority of Pakistan (DRAP). Interestingly, the Governing Body of DRAP has representatives from private pharmaceutical companies, bureaucrats, and politicians, with a scant two seats being reserved for public health specialists. DRAP is unaccountable to any federal oversight when it comes to budget allocation, which is decided by the aforementioned Governing Body.[27] This clear conflict of interest has allowed for increased laxity in regulation, resulting in 3295 drugs and 29 drug manufacturers being registered with DRAP from 2012 to 2014.[28] The drugs produced are dispensed from 80,000+ dispensaries, which are policed by only 225 DRAP drug inspectors.[29] This has induced lucrative conditions wherein local and poorly overseen antibiotic manufacturers push their drugs to market aggressively and often without adequate quality control.

This under regulation serves as a lead-in to over-prescription and self-medication. Many doctors prescribe antibiotics as prophylactics. One multicenter study conducted in Punjab showed that of 1516 patients prescribed antibiotics, a staggering 57.4% were broad-spectrum prophylactics for obstetric, gastrointestinal, or respiratory infection indications.[30] Of more concern is the fact that another multicenter study found that 97% of neonates across 16 health facilities in Punjab were being administered antibiotics, with an average of 2.6 antibiotics per patient. Almost 25% of the patient population was prescribed ceftriaxone.[31] Ceftriaxone is classified under the Watch category of the WHOs AWaRe classification of antibiotics, which means that it is at relatively high risk of selection of bacterial resistance.[32] In fact, data as of March 2019 pertaining to antimicrobial-containing registered brands showed that 8 out of 10 antimicrobials in the Pakistani pharma market were of the Watch category.[33] In amalgamation, due to such irresponsible prescriptive practices, studies like Zaidi et al. find that the average number of drugs prescribed per patient in Pakistan is 4.55, higher than the LMIC average of 2–3.[29]

5.2 | Poor prescribing practices

Challenges posed to countering ABR are largely the same as the causes discussed above. Namely a significant lack of awareness regarding the societal implications of ABR, treatment interruption, a lack of stewardship and poor regulatory policies by DRAP. However, there are two aspects which prove a menace from a public health perspective. First, the absence of vibrant prescription monitoring. Many pharmacies dispense antibiotics without an official prescription. According to a report from the Health Services Academy (HSA) assessing prescription practice around Islamabad, 136 out of 386 respondents regularly received antibiotics without a medical prescription. Almost 77% of the respondents received their medication from technicians, without due consultation with a doctor or pharmacist. Most of those indulging in this practice cited cost as a deciding factor, where unofficial drug purchase is cheaper, with

medicines dispensed unofficially costing around PKR 12,733. The same type of medicines on an official prescription cost around 31,401 PKR.[34] Over-consumption to this degree accelerates mutations in bacteria, causing faster emergence of an ever more resistant generation of microbes. Second, the novel threat of COVID-19 significantly increased the risk of ABR growth. A retrospective observational study from Pakistan assessing treatment options for COVID-19 in four tertiary care hospitals came up with alarming results. Antibiotics, primarily azithromycin, were used as the first-line treatment for the virus. Even antibiotics for MDR infections were prescribed without due regard to severity or progression of infection.[35,36]

5.3 | Treatment interruption and a lack of stewardship

The issue of treatment interruption is a major one in Pakistan. It has been shown to increase ABR significantly.[37,38] The most apt disease to analyze such phenomena is pulmonary tuberculosis (TB). Local studies have been conducted to assess the magnitude and determinants of noncompliance. One such study showed that 7.4% of 421 TB patients were noncompliant, with predictors of increased risk being travel and cost.[39]

Both official and unofficial over-prescription can be largely mitigated if a patient's physician duly counsels them on the implications of antibiotic overuse. This concern for the patients' well-being and subsequent appropriate counsel is described by the WHO as 'stewardship'. However, a study assessing the status of antibiotic stewardship in three major tertiary care hospitals in Pakistan found that whereas all 17 doctors surveyed agreed that ABR was a major problem, only those who had practiced in large private hospitals were familiar with the concept of stewardship. Furthermore, 12 out of the 17 respondents considered the use of broad-spectrum antibiotics justified, rational, and a cornerstone of 'empirical therapy'.[40] A survey in a tertiary hospital in Karachi further reinforces the lack of stewardship, with 47% of the 200 medical doctors surveyed admitting they overprescribed antibiotics, either due to a lack of confidence in their diagnostic ability or as an acquiescence to patient demand.[41] The biggest blow to the principle of stewardship comes from the pharma-physician nexus that has been reported in Pakistan. According to Dr Muhammad Aslam, the former CEO of DRAP, pharmaceutical companies offer foreign trips, payments, and other benefits provided a physician over-prescribe their drug.[42] This actively undermines the Hippocratic axiom of "do no harm" and fuels ABR.

An aspect of concern is the inter-specie transfer of antibiotics, mainly through the food-borne route. Existing literature gives us cause to worry, as Khaskheli et al. reports that beta-lactam residues were found beyond the permissible level in 36.5% of milk samples tested.[43] Several antibiotics such as penicillins contain beta-lactam rings. This excessive exposure of food-producing animals (FPAs) to antibiotics provides more selective pressure and causes bacteria to evolve into much stronger strains, and incentivizes them to produce MBLs, enzymes which inactivate the antibiotic by breaking the lactam ring. MBLs have already been detected in a Pakistani healthcare facility, with 39 out of 50 antibiotic-resistant isolates being MBL producers.[44]

6 | IMPLICATIONS

Implications of ABR can be naturally divided into 3 tiers, implications to (1) the individual, (2) the healthcare system, and (3) the nation. It would help to imagine these three categories as steps to a cascade, whereby challenges posed to the individual eventually link to that of the nation. Due to paucity of national data regarding some aspects of this section, parallels have been drawn where deemed necessary with the educated assumption that associations regarding cost, length of stay (LOS), and quality of life (QOL) will hold true regardless of the country studied.

6.1 | QOL and economic hardship

The most obvious difficulty faced on a personal level in the context of increasing ABR is that of a decreasing QOL postinfection. A study conducted on 351 ICU patients showed a significant association between ABR pathogen isolation in subjects and increased post-discharge mortality and morbidity rates.[45] Although the study is conducted in Greece, one can safely extrapolate the markedly adverse results when the same metrics are applied to an objectively poorer country with a subpar healthcare system, such as Pakistan. Similar and more prominent associations are found regarding LOS and hospital costs, as with one study conducted in Ghent, Belgium. Both cost and LOS were higher in groups infected with MDR bacteria.[46]

6.2 | Bystander effect

More alarming is the bystander effect, wherein antibiotics administered to a child in a low-resource setting may develop resistance in pathogens which were not the drug's intended target. Such exposures are termed as "subclinical." It has been shown that Pakistan has one of the highest subclinical exposure incidences (1243.3 exposures per 100 child-years).[47] Should such subclinical exposures continue, resistance across various classes of bacteria may increase manyfold, exacerbating the prevalent ABR problem among children.

6.3 | Overwhelming the healthcare system

The implications if such challenges go unaddressed will transfer onto tier 2: the healthcare system. Should cost of treatments rise, many in Pakistan will seek an alternative in cheaper quack remedies, which are quite prevalent with around 70,000 being found in the 2019 census.[48] Similarly, decreased QOL and increased rates of functional inability will require more frequent hospital visits. The bystander effect might serve as a force-multiplier, where more people may be exposed, through various routes of transmission, to MDR or XDR bacteria, resulting in more patient inflow. This will put more burden on an already overstretched and underfunded public healthcare system.

6.4 | A public relations disaster

Finally, such problems on tier 2 will weigh heavily on tier 3, the nation. Although Pakistan does not have a database for this aspect, our literature search yielded a literature review of 78 studies, which concluded that the increased cost of ABRs, retrofitting hospitals with equipment to deal with such issues, and other associated costs will weigh heavily on the globe ($300 billion to $1 trillion annually). LMICs are expected to fare even worse due to existing poor economic conditions.[49] A ripple effect will also be felt on industries such as tourism. This is evident by the fact that the CDC regularly issues warnings of XDR typhoid outbreaks in Pakistan, cautioning American travelers against going to parts of the country.[50] It should worry relevant authorities as this can lead to less revenue generation and significant bad press for the country.

7 | EFFORTS AND RECOMMENDATIONS

Pakistan is a developing country, with high prevalence of ABR, due to poor hygienic conditions and feeble clinical infrastructure.[19] These conditions allow infectious diseases and consequently, ABR to arise, but there are methods that can be implemented to reduce its incidence, as summarized in Table 1.

The first step toward reducing ABR is prevention of infectious diseases, targeting the upstream etiology of antibiotic use. This can be done by hygiene awareness campaigns like the WASH campaign, which aims to develop hygienic habits, provide clean water, and safe sanitation in Pakistan.[51] Prevention would help decrease the need for antibiotics, therefore decreasing the occurrence of antibiotic resistance. Another major issue is a lack in surveillance, which in turn allows resistance development, poor quality of available antibiotics, and clinical misuse or extensive use of antibiotics.[54] To counter this, the WHO has tried to increase surveillance through the Global Antimicrobial Resistance Surveillance System (GLASS) in developing countries like Pakistan.[55] Moreover, the National Action Plan of Pakistan against antimicrobial resistance aims to establish an integrated national AMR surveillance system and implement a national awareness raising campaign to educate people about the risks of resistance.[52]

In Pakistan, much of the health sector is privatized or unregulated, allowing physicians to prescribe antibiotics as they wish. There is also a lack of diagnostic resources which promotes self-medication, therefore, the implementation of a framework in which physicians are monitored would correct these issues.[54] The implementation of surveillance and regulations for antibiotic use would greatly reduce resistance development as physicians would be held accountable for their prescriptions. This would decrease the overprescription of antibiotics, clinical misuse and lower their accessibility to the general public, encouraging people toward alternatives. Currently, many alternative treatment methods are being rediscovered such as phage therapy or developed such as lysin therapy and antimicrobial peptide therapy.[53] Phage therapy uses phages, viruses which infect bacteria, to breakdown the bacteria or make it more susceptible to antibiotic treatment.[53] Lysin therapy uses lysin enzymes,

TABLE 1 Summary of recommendations, describing the intervention (recommendation column), its scientific basis and potential impact (evidence column), and the feasibility of implementing the intervention and what that would entail (feasibility column).

Challenge	Recommendations	Evidence	Feasibility
Unregulated prescription of antibiotics Lack of diagnostic resources Self-medication	Implementation of systemic framework of surveillance/monitoring for physicians Implementation of regulations on antibiotic use and availability	Reduces resistance development by reducing risk of misuse, over prescription of antibiotics, and lowers accessibility to general public[51]	Would require government involvement from the healthcare sector
Overuse of antibiotics	Use of alternative therapies like phage, peptide, and lysin therapy Use of traditional medicine	Have shown effects that increase susceptibility to antibiotics or treat antibacterial infections[52] Effective against many antibiotic resistant bacteria based on study in 2018[53]	Would require development, research, clinical testing, and government funding
Existing ABR	Changing drug regime by limiting prescription of one or two antibiotics per class, and so on[51] Research and development of new antibiotics	Limits occurrence of ABR and would resolve current ABR[51]	Would require development, research, clinical testing, and government funding
Relatively weak policy framework	Incorporating elements of more comprehensive NAP-AMRs to address the issue holistically, while liaising with all stakeholders	A multifaceted approach with private sector engagement, and which addresses ABR at all levels, can provide a more robust defense against ABR	Would require a concerted parliamentary and bureaucratic effort to effectively liaison between concerned parties

which are produced by bacteria and have a antimicrobial effect, to selectively hydrolyze the bacterial cell wall and can be further developed to clinically treat antibiotic infections.[53] Another alternative method is to turn to traditional medicine, as many in Pakistan use traditional techniques to solve urinary tract infections, skin disorders, diarrhea, cholera, and many more.[56] Pakistan has a plethora of different flora, which based on a study done in 2018, can be used as anti-infectives against many antibiotic-resistant bacteria.[56] The study found modest antibacterial activity in five of the nine species of flora tested and no significant cytotoxicity.[53] Thus, this method could provide a potentially safe and alternative solution to antibiotic use, upon further development and clinical testing.[19] In circumstances, where antibiotics are necessary, limiting prescribing options to one or two antibiotics per class or changing the drug being used with another of its class can help reduce incidences of resistance development.[54] Promoting research and development of new antibiotics would also help minimize the existing ABR.

It is pertinent to note that since Pakistan is just one in a host of LMICs with issues arising from ABR, it can learn from, implement wholly, or retrofit native policies with elements from existing plans of action in countries which are in somewhat comparable or worse situations. As stated above, China registered as having one of the highest rates of ABR in the developing world and a rapid growth rate of resistance at 22% average growth from 1994 to 2000.[57] However, recognition and remediation efforts at the national and district level has brought about a hopeful and favorable trend. The WHO reported a reduction in antimicrobial use across health facilities from 59.4% in 2011 to 36% in 2019. It credited this to a robust implementation of China's OneHealth National Action Plan carried out by 14 concerned ministries.[55] Additionally, neonate resistance levels also dropped, with susceptibility of *E. coli* improving by 30.4%, 39.4%, and 21.4% to ampicillin, cefotaxime, and ceftriaxone respectively. The prevalence of ESBL-producing *E. coli* saw a remarkable dent with an 80% decrease from 2012 to 2019.[58] How did China achieve a downward trend in resistance? An effective prescription monitoring regimen, coupled with an unpairing of physicians' pays from pharma sales and a 'zero mark-up' policy to divorce profit from sales might have played a part.[8] Policies akin to these have been, to an extent, outlined in the Pakistani National Action Plan (NAP), however, implementation is of dubious efficacy as is shown by a 2021 systematic review which concluded that there were major gaps in surveillance and an increasing trend of ABR in Pakistan.[19] The NAP, though well-intentioned, seems to be on the backburner of government priorities, with constant political upheaval and instability leading to rapid changes in appointments within the Ministry of National Health Service. This lack of unified, lasting leadership could be a determinant of lax implementation.

8 | LIMITATIONS

Our review held some limitations, as the literature search yielded a plethora of studies that differed in methodology and clinical outcomes. Analyzing studies with different study designs, interventions, sample size, and outcome measures, we chose to analyze the data with a narrative method, rather than trying to perform a quantitative and statistical analysis. Since there were no explicit criteria for article selection and no meta-analysis or systemic review was performed, selection bias could be observed. The studies also differed in their methodological quality, which may have had an impact on the results, and biased our findings and limited our interpretations. Depending on their relevance, the included studies were compared, and factors associated with antibiotic resistance in Pakistan were determined. The conclusion was also subjective of the authors' interpretation of the sensitivity of the factors.

9 | CONCLUSION

This study focuses on antibacterial resistance and its impact on the spread of infectious diseases in Pakistan. The findings of this study categorize the causes of ABR into lack of regulation and medical stewardship as well as self-medication. Through the evaluation of factors resulting in drug-resistant infections, these findings provide insights for healthcare practitioners as well as policy-makers to emphasize the burden of growing ABR within the public. Although the effects of ABR are reflected in the increased mortality rates, insufficient data toward current morbidity and mortality numbers is suggestive of pertinent gaps in surveillance. This study highlights the importance of implementing surveillance and regulation for antibiotic use to maintain a check and balance on drugs being prescribed which will enhance physician accountability as well as limit drug accessibility. As emphasized in this study, mitigation of ABR is essential and thus alternative treatment methods such as phage or lysin therapy should be encouraged in instances where antibiotics are not necessary. By establishing stronger surveillance as well as promoting existing programs, the reversal of ABR will benefit the healthcare system by increasing effectiveness of standard treatments and decreasing morbidity and mortality rates as a result of preventable infections.

AUTHOR CONTRIBUTIONS

Hania-Tul Mirha: Conceptualization; writing—original draft. **Syed H. Ali**: Methodology; writing—original draft. **Humna Aamar**: Resources; writing—original draft. **Mahnoor Sadiq**: Supervision; writing—original draft. **Zoaib H. Tharwani**: Supervision; writing—original draft. **Zehra Habib**: Writing—original draft; writing—review and editing. **Abdullah Malikzai**: Writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors (Hania T. Mirha, Syed H. Ali, Humna Aamar, Mahnoor Sadiq, Zoaib Habib Tharwani, and Abdullah Malikzai) confirm that the data supporting the findings of this study are available within the article (and/or) its Supporting Information. All authors have read and approved the final version of the manuscript (corresponding author

or manuscript guarantor: Abdullah Malikzai) had full access to all the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The lead author Abdullah Malikzai affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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