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Progress on the National Action Plan of Pakistan on Antimicrobial Resistance (AMR): A Narrative Review and the implications

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Abstract

Introduction: The emergence and spread of antimicrobial resistance (AMR) is a threat to public health. In 2015, the World Health Organization (WHO) introduced a global action plan to tackle AMR in World Health Assembly. Pakistan's national action plan (NAP) for AMR was released in May 2017 by the Ministry of National Health Services. Based on the NAP, strategies have been initiated on a national and provincial scale in Pakistan.

Methodology: A narrative review of the five components of the Pakistan NAP has been taken based on the publications known to the co-authors. The suggestions have been made on the basis of that to reduce the burden of the AMR.

Areas Covered: This review discusses some of the challenges in implementation of the NAP for AMR including different opinions and views of key stakeholders, concerns with lack of diagnostic facilities and financial resources and continued wide and suboptimal use of antimicrobials in human and animal health as well as food production.

Expert Opinion: Going forward, healthcare authorities should focus on screening and monitoring of all the objectives of the NAP by establishing proper policies as well as promoting antimicrobial stewardship interventions and Infection prevention and control (IPC) practices. Overall, the comprehensive strengthening of the healthcare system is required to adequately implement the NAP, tackle continued inappropriate antimicrobial use and high AMR rates in Pakistan.

Keywords: Antimicrobial Resistance, AMR, Antimicrobial Utilization, AMU, Antimicrobial Surveillance.

Article Highlights:

- The challenges to the implementation of the National Action Plan (NAP) for antimicrobial resistance (AMR) have been covered in this article including the opinions of the key stake holders who have concerns with the lack of the diagnostic facilities, financial resources and continued excessive use of antimicrobials as prophylaxis in hospitalized patients and sale without prescription at community level.
- The healthcare authorities should focus on screening and monitoring of all the objectives of the NAP by establishing proper policies as well as promoting antimicrobial stewardship interventions and IPC practices.
- The comprehensive strengthening of the healthcare system is required to adequately implement the NAP.

1. Background:

The rising antimicrobial resistance (AMR) is considered one of the most threatening challenges to global public health increasing morbidity, mortality and costs as well as limiting the choice of antimicrobials for potential treatment [1-5]. O'Neill and colleagues published in 2014 that unless addressed AMR could result in over 300 million people dying prematurely and costing up to US$100 trillion globally [6]. Besides, the Organisation for Economic Co-operation and Development (OECD) predicted that between 2015 and 2050, 2.4 million could die across Europe, North America and Australia each year as a result of AMR, with the situation worse in lower- and middle-income countries (LMICs) where up to 60% of infections are already resistant to current antibiotics [7]. The World Health Organization (WHO) has recently reported that up to 45% of the deaths of patients in South East-Asia are due to antimicrobial-resistant infections and resistant

Klebsiella pneumoniae was the major cause in 81% of the deaths [8,9]. Overall, it is estimated that up to US$3.5 billion will be needed every year to combat the consequences of AMR among OECD and European countries [7].

Given increasing concerns with AMR and its impact, the WHO launched a Global Action Plan (GAP) in 2015 with a political declaration made by the United Nation (UN) General Assembly in 2016 reinforcing the GAP [10]. The GAP was supported by all countries including Pakistan which is the world's sixth most populous country and is expected to rise to fourth place by 2050 [11]. In recent years, Pakistan has spent 0.46% of its Gross Domestic Product (GDP) on health care services, and per capita, health spending is US$36 compared to the WHO recommended benchmark of US$86. Out of total spending on medicines, out-of-pocket spending comprises nearly 75% with the majority (80%) of the population utilizing the private health sector utilizing funds additional to the US$36 spent by the government [12]. As a result, there can be catastrophic consequences when family members become ill in Pakistan especially with an appreciable number of citizens currently living below the poverty level [13-15]. In Pakistan, the Provincial Governments are completely autonomous and responsible to outline their health needs, develop and implement strategies and operational plans. However, the Ministry of National Health Services Regulations and Coordination (MNHRC) sets the national framework for establishing policies and fulfils international commitments on health. This includes national policies to tackle AMR.

As mentioned, Pakistan has recently developed its national action plan (NAP) to identify, prevent and control infectious diseases, and to combat the AMR, with the five strategic and operational work plan components aligned with the objectives of the GAP [16]. Ongoing initiatives by the Government of Pakistan to tackle AMR include the National Institute of Health (NIH) in collaboration with different partners deciding to be the custodian of AMR surveillance in Pakistan through participation in Global Antimicrobial Surveillance System (GLASS) [17]. Before this, a few other organizations in Pakistan were already working at a micro level to tackle AMR including the Antibiotic Stewardship Initiative in Pakistan (ASIP) and Pakistan Antimicrobial Resistance Network (PARN) under the umbrella of Medical Microbiology and Infectious Diseases Society of Pakistan (MMIDSP) [18,19]. The Pakistan Global Antibiotic Resistance Partnership (GARP) was also established in the wake of national and international efforts to reduce AMR. However, to date, there are concerns that the implementation on the NAP to tackle AMR in Pakistan has been limited and there continue to be grave concerns regarding the level of AMR in Pakistan [20].

In April 2018, the Chair of GARP-Pakistan launched the Situation Analysis Report on Antimicrobial Resistance in Pakistan: Findings and recommendations for Antibiotics Use and Resistance at the 15th Annual Conference on Infectious Diseases in Pakistan [21]. The major challenges and issues identified in the report include an unnecessary large number of registered antimicrobials, unjustified or misleading advertisements, polypharmacy, untrained professionals (quacks), suboptimal prescribing by physicians, availability of over the counter (OTC) antibiotics without a prescription and bias towards costly broad-spectrum antibiotics [21]. In Pakistan, the inappropriate use of antimicrobials poses a major threat to its healthcare system, contributing to

the increasing burden of infectious diseases due to resistant pathogens whilst leaving limited treatment options for effectively treating current and future infections [22,23]. The indiscriminate and suboptimal use of antimicrobials appears most frequent among general physicians and public sector hospitals by prescribing costly broad-spectrum antimicrobials [24].

Several causes for inappropriate prescribing and dispensing of antimicrobials in Pakistan have been identified to include poor public awareness regarding the rational use of antimicrobials, an insufficient number of trained medical staff, limited time for consultations, patient's self-medication driven by inappropriate requests and profit motives among pharmacists, and the prescribing of antimicrobials by an appreciable number of unlicensed healthcare practitioners [24-30]. The ready availability of OTC medicines, especially antimicrobials, is a common practice in Pakistan including dispensing of Reserve antibiotics from the WHO AWaRe list enhancing AMR rates [31-34]. There are also concerns about inappropriate prescribing of antimicrobials in hospitals in Pakistan exacerbated by concerns with the instigation and effectiveness of Antimicrobial Stewardship Programmes (ASPs) [35,36]. We are also aware that the pattern of AMR has not been well documented in Pakistan with only a few studies and surveys conducted over a decade regarding such issues and microbiology laboratories are currently not standardized [21,37]. Published and unpublished data has also highlighted high mortality among patients with infections associated with multidrug-resistant organisms (MDR) including typhoid, tuberculosis, and malaria [21]. The situation is further compounded by the widespread use of antimicrobials in poultry animals and agriculture in Pakistan without any regulations [30,38,39]. Currently, there is also a lack of collaboration for containment of AMR between human health and other sectors such as the veterinary, poultry and the agriculture sectors. Encouragingly, nationwide coordinated surveillance mechanisms to capture data on antimicrobial use and resistance have started; however, they face difficulties due to inadequate quality assurance systems among microbiology laboratories. There is also a lack of relevant experts on AMR, IPC and ASP in Pakistan. The implementation and enactment of policy legislation are some of the additional challenges.

Overall, Pakistan ranked third for antimicrobial consumption among LMICs [40], with a 67% increase in consumption between 2000 and 2015 increasing AMR rates [41]. As mentioned, this has been exacerbated by the appreciable extent of antimicrobials currently being sold OTC in medical stores and pharmacies in Pakistan as well as physicians typically preferring broad-spectrum antimicrobials over narrow-spectrum ones [32,42-46]. Several studies have also reported that prescription rates for antimicrobials are typically higher in Pakistan than among similar countries [47-49]. In addition, most antimicrobials are currently being prescribed without culture sensitivity testing [50]. Consequently, we believe there is an urgent need to describe the current situation regarding the NAP in more detail to provide future direction in an attempt to reduce appreciable rates of AMR in Pakistan.

2. Methods:

We undertook a narrative review of the five strategic and operational components of the Pakistan NAP to tackle AMR and the current status in Pakistan. This was based on publications known to the co-authors rather than a systematic review given the broad nature of the NAP as well as anticipated concerns with the number of publications in well-respected journals. The co-authors have used this approach before when reviewing and discussing key areas for future health authority activities among LMICs in key areas for both infectious and non-infectious disease areas as well as general areas such as fixed-dose combinations [33,51-55].

This will be followed by suggestions for the future for Pakistan to achieve the goals of the NAP to reduce the incidence of infection with antibiotic-resistant pathogens. This will, in part, be based on the considerable experience of the senior level co-authors researching and discussing current utilization patterns and potential ways forward to improve the prescribing and utilization of antimicrobials in their own countries and elsewhere. This scoping review includes editorials, systematic reviews, point prevalence studies (PPS) in hospitals, studies on the extent of hospital-acquired infections especially in LMICs as well as the extent of ASPs, current utilization patterns and the extent of inappropriate prescribing and dispensing of physicians and pharmacists in ambulatory care in LMICs and potential ways forward, knowledge of physicians and pharmacies towards antimicrobials and AMR in ambulatory care and ways to address this, as well as activities undertaken by health authorities across LMICs to improve antimicrobial utilization and their influence [28,33,36,56-75].

3. Results and implications for key stakeholder groups:

The findings were firstly be broken down into the five sections of the Pakistan NAP and the current situation in-country and drawing on evidence and experiences in other LMICs before summarizing potential ways forward for all key stakeholder groups in Pakistan to achieve the NAP goals.

3.1 Five Strategic and Operational Work Plan Components of NAP:

The challenges regarding suboptimal antimicrobial use and AMR in the healthcare system including other sectors such as agriculture in Pakistan are serious and hamper the success of the NAP at the national level. Notwithstanding that the NAP holds responsible various stakeholders from the animal, human, agriculture and environment sectors for each of the designated strategic priority, the lack of coordination mechanisms between the various sectors and a current segregated approach towards strategy development delays the processes. The existing surveillance models for other vertical programs and communicable diseases including health information system (HIS) can be adapted and integrated for strengthening the AMR surveillance. In Japan, Government of Japan established new surveillance platform (Japan Surveillance for Infection Prevention and Healthcare Epidemiology) to closely assess and monitor the IPC and ASPs (e.g. antimicrobial use, antibiogram, hand hygiene, the incidence of hospital-acquired infections), resulting in the reduction of antimicrobial use (15.0%) over last 5 years [76]. Few foundation materials including laboratory biosafety policies have been developed to guide policy-making. In August 2020, a comprehensive fully-funded AMR and IPC program has been approved by the government that

will solely work on NAP. However, the development of execution mechanisms by the program will take time.

To minimize the emergence and spread of AMR, it is important that the Government in Pakistan fully implements the NAP on AMR in its true spirit. If proper steps for preventing and controlling infectious diseases are not implemented, it will become more difficult and expensive to cope with AMR, and the ability to control infectious disease will continue to decline. Current strategies with objectives for countermeasures on AMR are discussed in Table 1 [77]. Consequently, this scoping review was performed to check the progress of the NAP to reduce AMR rates in Pakistan and discuss potential further activities to achieve desired goals

Table 1. Five strategies with objectives for countermeasures on AMR

Sr. No.	Strategies	Objectives
1.	Awareness	To improve public awareness and understanding of AMR through effective education and training of healthcare professionals.
2.	Surveillance	To promote the knowledge of antimicrobial use and its resistance through surveillance, monitoring and research.
3.	Infection Prevention and Control (IPC)	To minimize the incidence of infection by implementing appropriate Infection Prevention and Control practices.
4.	Rational use of antimicrobials	To optimize the judicious use of antimicrobials in human and animal health.
5.	Investment	To promote the investments for AMR activities, research and innovations.

3.1.1 Awareness:

The AMR crisis across countries led to the development of the global action plan compelling countries with continued high rates of antimicrobial misuse and AMR, including Pakistan, to develop strategies to counter this threat. The strategy initiated by the NIH in Pakistan to cope up with the challenge was firstly to create awareness by organizing seminars and training sessions among the general public, physicians and the pharmacists regarding appropriate antimicrobial use, their specificity and the importance of the issue regarding the threat humanity could face if antimicrobial misuse is not reduced in countries such as Pakistan [20,21]. The strategy emphasized nation-wide measures necessary to promote public awareness and understanding of antimicrobial use and AMR. This is because sufficient knowledge, communication and training regarding antimicrobial use and AMR is necessary to raise awareness and understanding among key stakeholder groups including the general public, physicians, pharmacists and other paramedical staff, to improve future prescribing and dispensing [33]. Consequently, there is a need within countries to identify behavioral drivers among the general public and healthcare professionals as well as develop national guidelines for key stakeholder groups to improve future antibiotic

prescribing [33,78,79]. However, most of the studies conducted to date regarding antimicrobial prescribing and resistance, and potential ways to address concerns, have been conducted with healthcare professionals including physicians and pharmacists with currently limited data around potential strategies with the general public especially around the cost-effectiveness of educational initiatives in LMICs (Table 2) [33].

In Pakistan, published studies have reported that the general physicians and pharmacists in Pakistan typically have insufficient knowledge and training regarding the rational use of antibiotics and AMR [28,47,69,80]. Pharmacology is taught at the undergraduate level; however, there is currently little or no training in clinical therapeutics at a post-graduate level or for general physicians, nurses, pharmacists and other paramedical staff [81]. Other triggering factors include the level of education of patients, the lack of health facilities in the public sector, low health literacy, poor infrastructure of healthcare settings in rural areas, prescriber's experience and lack of knowledge among healthcare professionals with often the internet and pharmaceutical companies a principal source of information, high consultation fees of private practitioners and presence of more than 600,000 unprofessional quacks [82-84]. The Government of Pakistan has ceased more than 20,000 quacks outlets in the Province of Punjab and has decided to closely monitor the sale of antimicrobials in Islamabad [85]. All unqualified quacks without authorization must be addressed strictly through governmental interventions and control policies.

A study conducted in Pakistan found that community pharmacists typically have poor knowledge regarding antimicrobial use and its resistance and do not involve in any ASPs resulting in high prevalence rates of self-medication [28]. Several studies have also reported high rates of antimicrobial prescribing in hospitals of Pakistan, with concerns about their rational use although positive attitudes towards ASPs [1,49,71,86,87]. Rational prescribing of antimicrobials can be achieved by education and other interventions to change prescribing behaviour of physicians [33,88,89]. Community pharmacists can play an important role in the development and implementation of ASPs in the community [86].

Studies conducted among the various regions of Pakistan have documented that patient-related problems including low socioeconomic status, previous experience, lack of knowledge and training, and ease of purchasing antimicrobials from medical stores and pharmacies without prescriptions, were the major cause of suboptimal use of antimicrobials resulting in the emergence and spread of AMR [90-93]. In addition, patients do not always comply with prescribed or dispensed regimens, which can eventually increase their healthcare costs. Pharmacists and others can play an important role in the development and implementation of ASPs in both the community and hospitals to address current concerns [36,86,94-96]. Identification of knowledge and attitudes related to inappropriate antimicrobial prescribing will permit specific interventions to be designed targeting areas of concern to improve future antimicrobial use in Pakistan and reduce AMR [69,97].

Lack of resources, poor healthcare infrastructure, and inadequate training of healthcare professionals are though major barriers to the implementation of ASPs in Pakistan, similar to other LMICs [24,67,98]. A multidisciplinary framework is typically needed to rationalize antimicrobial use and minimizes AMR in Pakistan. Consequently, healthcare professionals should be motivated to follow national as well as international guidelines associated with antimicrobial use and AMR, starting with training in pharmacy schools and continued with further educational strategies [1,33,99-101]. ASPs can minimize inappropriate use of antimicrobials, reduce healthcare costs and decrease hospital stay [102,103]. This is in line with the objectives of the Pakistan NAP to help reduce AMR; however, as mentioned there are currently concerns with implementation [20].

As part of this, there is a dynamic need for training initiatives to improve antibiotic prescribing behavior among general practitioners assisted by the development of local guidelines, with the majority of the physicians in favor of such training if offered [84]. This can be accompanied by the dissemination of information about local resistance rates alongside encouraging great knowledge about antimicrobials [69,104,105]. Encouragingly, physicians in Pakistan have shown a positive attitude towards the introduction of ASPs including teaching hospitals [24,106]. Introduction and monitoring of prescribing against standard treatment guidelines can improve future prescribing [107-109]. Important strategies going forward include prospective audits with feedback and regular educational sessions as part of local ASPs within Pakistani hospitals [1].

Table 2: Knowledge, Attitude/Perception and Practice Studies from Pakistan

Reference	Author & Year	Study Design	Population	Objectives	Knowledge	Attitude/ Perception	Practice	Inference
[69]	Saleem et al. 2019	Qualitative	Physicians	Factors influencing antibiotic use and resistance	Poor knowledge so need improvement	Positive to change	Need improvements especially in IPC practices	Need to work on specific approaches and initiatives.
[84]	Maira et al. 2019	Quantitative	Physicians	To assess KAP of physicians about antimicrobial prescribing and AMR	More likely to know about the appropriate use of antimicrobials	Positive attitude towards training program to be initiated	No cultural sensitivity test was performed before prescribing	Training sessions are required to improve antimicrobial prescribing through the development of local guidelines
[110]	Hassan et al. 2019	Quantitative	Physicians, Pharmacists, Community members	To assess KAP among 3 stakeholders	Physicians well aware about AMR than other community members	Physicians showed positive attitude than other community members	Physicians received training on antimicrobial use whereas mostly qualified pharmacists were not present on pharmacies	Regular monitoring and auditing of prescription is required to minimize the antimicrobial consumption
[88]	Saleem et al. 2019	Quantitative	Physicians	To assess perception concerning antimicrobial use and factors influencing antibiotic use and AMR	Most of the physicians well aware of antimicrobial use and its resistance	Positive attitude concerning inappropriate use of antimicrobials	Over prescribed antimicrobials	Educational sessions are needed and IPCs programs should be initiated and implemented to reduce inappropriate use
[99]	Salman et al. 2018	Quantitative	Physicians, Nurses and Technicians	Assess KAP associated with Hand Hygiene among HCWs	Nurses are more likely to know about hand hygiene guidelines than other HCWs	Nurses showed positive attitude	HCWs has poor hand hygiene practices. HCWs had received training	Education and training of HCWs associated with hand hygiene knowledge is required
[97]	Ullah et al. 2020	Quantitative	Physicians	To assess prescribing pattern of antimicrobials	Less likely to know about prescribing guidelines	Mostly believed AMR is caused by self-medication	Mostly prescribed antimicrobials for fever	Establishing educational activities, ASPs and interventions can improve prescribing behavior

[1]	Hayat et al. 2020	Quantitative	Physicians, Nurses and Pharmacists	To evaluate attitudes of HCWs towards ASPs and AMR	Physicians are more aware about AMR than pharmacists and nurses. All HCWs are not well aware of ASPs.	HCWs showed positive attitude to become a part of ASP team	Need to improve prescribing behavior, formulary restriction, regular education activities	Initiation and development of local ASPs in Pakistani hospitals is required
[24]	Hayat et al. 2019	Qualitative	Physicians	To explore physician's views about ASPs	Diminished understanding of hospital ASPs	Positive response towards enforcement of ASPs in all healthcare settings	Insufficient resources, poor healthcare infrastructure, and inadequate training programs are major hurdles	Initiation and development of ASPs in hospitals is required.
[111]	Saleem et al. 2019	Qualitative	Pharmacists	To explore determinants of AMR and antimicrobial dispensing	Did not know about the guidelines for antimicrobial use and ASPs	Inappropriate use of antimicrobial is the major cause of AMR	Dispense antimicrobials with or without prescription	Multidisciplinary framework is needed to reduce suboptimal use of antimicrobials and AMR
[47]	Rehman et al. 2018	Quantitative	Pharmacists	To assess the knowledge and practices of pharmacists towards ASPs	Well-aware of their roles in ASPs	Adopted positive attitude towards ASPs	Need to reduce the transmission of infections and antibiotic dispensing without prescription	HCWs should collaborate to reduce problem of AMR and improve the patient's QOL
[86]	Rehan et al. 2018	Quantitative	Pharmacists	To assess the knowledge, perception and practices towards antimicrobial use	Majority have good knowledge regarding antimicrobials use	Believed that they played an important role in AMS and infection control programs	Mostly dispensed antimicrobials without prescriptions and never took a part in any awareness campaigns	Development of customized interventions are needed to improve perception and practices of regarding ASPs
[93]	Atif et al. 2019	Qualitative	Public	To assess KAP regarding antimicrobial use and resistance	Have satisfactory knowledge about antimicrobials and its resistance	Very poor and mostly believed that antimicrobials treat all type of infections	Mostly did not complete their antimicrobial course	Seminars, campaigns should be organized to improve awareness and understanding of antimicrobial misuse & AMR
[82]	Khan et al. 2020	Quantitative	Public	To assess KAP towards antimicrobial use and resistance among consumers	Poor to moderate knowledge as mostly unaware of even the word AMR	Positive attitude noted, but the storage of antibiotics at home was preferred	Did not actually follow the actual dosage regimen as prescribed	Educational sessions should be arranged for awareness about antimicrobial misuse

[100]	Saleem et al. 2019	Quantitative	Pharmacy and Medical students	To assess KAP concerning antimicrobial use and resistance.	Pharmacy students have better knowledge of antimicrobial use and resistance than medical students	Most of the participants believed that inappropriate use of antimicrobials cause resistance	Poor infection control practices by HCWs cause spread of AMR	Efforts should be undertaken to ensure that future pharmacists and physicians are well educated in practices of rational use antimicrobials and ASP
ASPs: Antimicrobial stewardship programs, AMR: Antimicrobial resistance, KAP: Knowledge, attitude and practices, IPC: Infection Prevention and Control, HCWs: Healthcare workers, QOL: Quality of life								

3.1.2 Surveillance:

Surveillance of any type of infection is a key element of an effective infection control strategy to identify issues, analyze possible intervention programs, and prioritize resources. Surveillance includes various factors incorporating susceptibility reporting, standardized and reliable laboratory practices, as well as data management and analysis, and is integral for the development of AMR surveillance [112]. Prospective surveillance is one of the most recommended methods for screening multi-resistant bacterial infections to provide future direction [113,114]. However, one of the major challenges in Pakistan to help reduce AMR is a current lack of surveillance systems at the institutional level. Inadequate utilization of Laboratory Information Systems (LIS) and low participation in AMR surveillance are the primary issues that need to be addressed in order to intensify data collection, validation and aggregation of regional as well as national resistance data within countries [112]. However, in resource-limited countries such as Pakistan, insufficient standardized laboratories hinder the development of effective surveillance systems [112,115]. In addition, due to the lack of following standard practices, there is currently a question regarding the quality of data from the laboratories. The role of key stakeholders and donors need to be elucidated to avoid duplication in efforts towards AMR. Well defined collaboration is needed within government sectors to help address key issues relating to AMR in Pakistan including improved surveillance [116].

Poor access to reliable susceptibility testing results in the emergence and spread of AMR within the population. Consequently, the building of standardized and reliable microbiology laboratories is needed for implementing antimicrobial conservation practices in LMICs. Encouragingly, Pakistan is enrolled in the GLASS and is in the process of implementing it [16,117]. However, it is recognized that urgent action is needed to strengthen the infrastructure of diagnostic microbiology laboratories in Pakistan [20]. Knowing the microbes and their antimicrobial susceptibility patterns via monitoring and understanding trends at a national level is of great importance to design and modify subsequent treatment guidelines, with, as mentioned, adherence to standard treatment guidelines (STGs) seen as a key indicator to assess the quality of prescribing [45,79,116,118,119]. With the help of Ministry of National Health Services Regulations and Coordination (NHSR&C), the NIH has taken many important steps to initiate and implement NAP and is currently collaborating with all key stakeholders from the public sector, especially tertiary care hospitals and their microbiology laboratories, the veterinary sector, and environment sectors in all provinces to reinforce the national capacity for community awareness, laboratory diagnosis and AMR surveillance [120]. Based on the recommendations of Joint External Evaluation (JEE) of International Health Regulations and Global Health Security Agenda (IHR-GHSA), AMR is now included as a key area in the Pakistan NAP for Health Security, and we will be monitoring this in the future [120].

Table 3 summarizes the current surveillance of antimicrobial use among the different regions of Pakistan based on published studies. Most of the studies have been undertaken in Lahore, reporting the highest use of antimicrobials, with findings leading to the initiation and implementation of ASPs for appropriate use. The most commonly used antimicrobials were penicillin and cephalosporins. Among 13 hospitals in different regions of Punjab, the reported use of antimicrobials among patients was 77.6% where the ceftriaxone was the most frequently used antimicrobials followed by metronidazole and ciprofloxacin [35]. A recent study was conducted in Islamabad where antimicrobial use was 100% of in-patients, reporting the highest use of ceftriaxone [121]. Another study regarding self-prescribing of antimicrobials among students of the University of Lahore reported a high rate at 79.2% of students with beta-lactams the most commonly purchased antibiotic class, suggesting the initiation of educational programs and training sessions among medical and pharmacy students is urgently needed to promote the rational use of antimicrobials mirroring other countries [33,122,123].

Table 4 summarizes the surveillance of AMR within Pakistan. The majority of studies were undertaken in Karachi, Pakistan. All of the studies were published between 2002 and 2019. Nine out of 21 studies isolated organisms from the blood and some of the studies collected samples from multiple sites such as sputum, pus, urine, nasal swab and fluids. Different studies reported that E. coli was the most causative pathogen followed by MRSA and showed high resistance to beta-lactams antimicrobials; consequently, regular screening and surveillance of these organisms should now be undertaken among healthcare facilities in Pakistan [124-127]. High susceptibility to vancomycin was reported for MRSA [124]. S. enteriditis was resistant to bacitracin, erythromycin and novobiocin but high susceptible to chloramphenicol and ampicillin [128]. Resistance to isoniazid, pyrazinamide and streptomycin were observed for MDR-TB suggesting an urgent review of national treatment and prevention guidelines [129]. Shigella species showed high resistance to co-amoxiclav, ampicillin and chloramphenicol [130]. These studies emphasize the routine need and use of antibiograms within hospitals to help guide future empiric use.

Table 3. Surveillance of antimicrobial use									
Reference	Author & Year	Location	Healthcare Setting	Study Duration	Antimicrobial use rate (%)	Top 3 Commonly Used Antimicrobials			Inference
						Antibiotic-1 (%)	Antibiotic-2 (%)	Antibiotic-3 (%)	
[35]	Saleem, 2019	7 cities of Punjab	13 hospitals	October 2017 and February 2018	77.6	Ceftriaxone (35.0)	Metronidazole (16.0)	Ciprofloxacin (6.0)	ASPs should be initiated to preserve future effectiveness of antimicrobial use, to improve prescribing practices and minimize the patient harm due to AMR.
[131]	Saleem, 2019	Punjab	Cancer care hospital	2017-2018	84.7	Piperacillin, enzyme inhibitor (31.8)	Meropenam (7.8)	Ceftriaxone (6.2)	Intervention programs should be developed addressing the appropriate use of antimicrobials and its resistance.
[97]	Kalimullah, 2020	Lahore	3 public and 3 private hospitals	June 2018-December 2018	100	Amoxicillin (30.0)	Ceftriaxone (15.4)	Cefixime (11.6)	Broad spectrum antimicrobials were given to patients for UTIs. Therefore, proper treatment guidelines should be established to reduce suboptimal use of antimicrobials.
[132]	Ahsan, 2020	Karachi	5 public and tertiary care institutions	November 2018 – May 2019	19.7	Amoxicillin (91.8)	Penicillins (44.5)	Clindamycin (16.6)	Continuing medical education of healthcare professionals and regular updates regarding treatment protocols may improve the prescribing behavior or dentists.
[122]	Saleem, 2016	Lahore	University of Lahore	9 months	79.21	Beta-lactams (43.6)	Quinolones (16.5)	Macrolides (18.9)	Educational and training programs should be designed to counsel the students regarding rational use of antimicrobials.
[121]	Khan, 2020	Islamabad	Tertiary care hospital	December 2016-February 2017	100	Ceftriaxone (28.0)	Metronidazole (22.5)	Amikacin (13.6)	To reduce spread and emergence of AMR, continuous educational training, availability of proper treatment guidelines and ASPs are required for appropriate utilization of antimicrobials

[133]	Sarwar, 2018	Punjab	16 rural and 16 basic healthcare units	January 2017- June 2017	81.5	Penicillins (23.6)	Cephalosporins (20.1)	Fluroquinolones (19.4)	Continuing education and training of medical staff and cost-effective policies could play significant role in promotion of appropriate use of antimicrobials.
[134]	Riaz, 2011	5 cities	Primary care facilities	August 2008 – April 2009	46.04	-	-	-	Managerial and regulatory interventions are proposed to improve prescribing and dispensing practices
[135]	Khan, 2010	Peshawar	Hyderabad Medical Complex	July 2006- June 2007	100	3rd Generation Cephalosporins (28.3)	1st Generation Cephalosporins (24.5)	Penicillin (19.1)	The available resources are needed to be effectively utilized, to minimize the hospital stay due to appropriate use of antimicrobial.
[46]	Elahi, 2017	Lahore	Cancer specialty hospital	-	-	Piperacillin/Tazobactam	-	-	Piperacillin/Tazobactam was used inappropriately in cancer hospital, calling for urgent action.
[39]	Mohsin, 2019	Faisalabad	Broiler farm	2013-2017	100	Colistin	Tyrosin	Enrofloxacin	In Pakistan, antimicrobials are being overused in broiler production, thus, urgent action plan is required to reduce the overuse of antimicrobials.
[136]	Ahmed, 2005	Rawalpindi	4 tertiary care hospitals	-	88.35	-	-	-	Better surveillance techniques, changing prescribing behavior of physicians, educating public regarding rational use of antimicrobials can be beneficials.
[50]	Atif, 2017	Bahawalpur	Bahawal Victoria Hospital	January 2016 – June 2016	82.3	Ceftriaxone (39.6)	Metronidazole (23.4)	Cefotaxjme (23.1)	Continuous education and training of healthcare professionals could play a significant role in promoting the appropriate use of antimicrobials.

[137]	Riaz, 2015	Punjab and KPK	Private and public healthcare facilities	January 2011-December 2012	50.3 (outpatients) 96.7 (inpatients)	-	-	-	Educating public regarding rational use of antimicrobials and training of healthcare professionals is needed to address this issue. There is also need to ensure low prices for generics and enhance their utilization.
[138]	Khan, 2019	Islamabad	Two tertiary care hospitals	August 2015-August 2016	100	Ceftriaxone (46.5)	Cefazolin (26.5)	Metronidazole + Cefazolin (15.6)	Multi-centered studies should be performed to assess the prescribing practice in different regions of Pakistan.
[139]	Khan, 2019	Islamabad	2 hospitals	January 2017 – December, 2017	97.5	Ceftriaxone (59.5)	Amoxicillin + Clavulanic acid (10.5)	Cefazolin (6.1)	Awareness among surgeons continuous educational training, implementation of international or local guidelines, availability of appropriate antimicrobials, and ASPs are required.
[140]	Khan, 2019	Islamabad	2 hospitals	January 2018-March 2018	100	Cephalosporins (95.3)	Aminoglycosides (1.9)	Penicillin (1.7)	Overprescribing of antimicrobials, low generic prescribing, lack of patient's knowledge and short consultation and dispensing times were the major identified problems.

Table 4. Surveillance of antimicrobial resistance

Ref	Author & Year	Location	Healthcare Setting	Sample	Microbes	Most Resistant Antibiotics	Most Sensitive Antibiotics	Inference
[125]	Jabeen, 2005	Karachi	Tertiary care hospital laboratory	-	Enterobacter 50%, E. coli 41%, K. pneumoniae 36%	Beta-Lactam antibiotics	Fluoroquinolones, Aminoglycosides, co-trimoxazole	This study supports urgent need for regular screening and surveillance for these organisms.
[124]	Hafiz, 2002	Major Cities	8 Different Laboratories	Pus, blood, urine, aspirates, ear and eye swabs	MRSA	Methicillin, oxacillin	Vancomycin	No vancomycin resistant Staphylococcus has been isolated from any of the major cities.
[128]	Akhtar, 2010	Faisalabad	Human and Poultry Sources	Poultry eggs & meat, bakery products and human stool	S. enteritidis	Bacitracin, erythromycin, novobiocin	Ampicillin (92.85%), chloramphenicol (100%)	The prevalence of highly susceptible S. enteritidis strains suggests the limited use of antibiogram as an epidemiological marker.
[141]	Mansoor, 2009	Karachi	Department of ENT, Karachi Medical and Dental College & Abbasi Shaheed Hospital	Pus from discharging ears	S. aureus, Pseudomonas aeruginosa	Ceftriaxone	Amikacin, Ceftazidime, Ciprofloxacin	Ceftriaxone resistance is very high.
[142]	Kumarasamy, 2010	Pakistan, India, UK	NA	Blood	E. Coli, Klebsiella, Pneumonia	Beta-Lactam Antibiotics	Tigecycline, Colistin	Co-ordinated international surveillance is needed to address the issue.

[143]	Hasan, 2008	Karachi	Patients under age 15 years	Blood	S. Typhi and S. Paratyphi	Quinolones and Fluroquinolones	-	The rapid increase in quinolone resistance in S. Paratyphi A when compared to S. Typhi is concerning.
[144]	Ching, 2019	Lahore	Hospital and Diagnostic facility	-	Not specified	Not specified	Not specified	To identify emerging resistance, increased AMR surveillance is required.
[145]	Samad, 2017	Peshawar	Northwest General Hospital and Research Centre	Sputum	Pseudomonas aeruginosa	Cefoperazone, sulbactam (16.9%)	Amikacin (92.86%), Meropenem (91.55%),	P. aeruginosa is one of the commonly isolated organisms and it is becoming more resistant to commonly used antimicrobials.
[146]	Latif, 2009	Lahore	Microbiology Section, Department of Pathology, Services Institute of Medical Sciences (SIMS)	Blood	Staph. Aureus, Klebsiella Spp. and E. coli, Pseudomonas Spp. and Acinetobacter Spp	Oxacillin, 3rd generation Cephalosporins, Carbapenems	Not Specified	The multidrug resistant pathogens lead to longer hospital stay, more expensive/ toxic drugs and higher mortality thus, requiring action plan.
[147]	Khan, 2010.	Karachi	Department of Pathology/Microbiology, Aga Khan University Hospital, Stadium Road	Blood, urine, wound, respiratory, sterile fluids CVP.	ESBL and MDR ESBL producing K. pneumoniae	Carbapenem, aminoglycoside, fluoroquinolone and co-trimoxazole.	Not specified	Continuous surveillance and use of appropriate screening tests for laboratory detection is required.

[148]	Hussain, 2019	Karachi	Department of Medicine and Department of microbiology and Immunology, Pakistan Navy ship, Shifa Hospital.	Blood	S. Typhi and S. Paratyphi.	Ampicillin, Chloramphenicol, Ciprofloxacin	Ceftriaxone, meropenem, azithromycin	The emergence of exensively drug-resistant S. typhi and S. paratyphi is alarming and highlights the significance of strict antimicrobials susceptibility surveillance.
[127]	Anwar, 2004	Lahore	Pathology Laboratory	Nasal swab	MRSA	Methicillin	Not specified	The nasal S. aureus carriage as well as methicillin resistance among these isolated are more common in urban community.
[149]	Ali, 2017	Punjab	43 centers	Throat swab, sputum, bronchial wasing, tracheal secretion	Not specified	Not specified	Imipenem, meropenem, cefipime	Imipenem is a broad-spectrum antimicrobial used as empiric therapy in respiratory tract infections
[150]	Ghanchi, 2011	Karachi	Aga Khan University Hosptial	Blood	P. falciparium	Chlorquine, Sulfadoxine-pyrimethamine	Not specified	High prevalence to invivo resistance to chlorquine was observed, therefore, effective measures are required.
[126]	Rehman, 2016	Peshawar	North West General Hospital and Research Center	Blood	MRSA, cephalosporinase producing E.coli	Piperacillin/tazobactum, ceftoxime, amoxicillin+clavulanic acid	Amikacin, meropenem, imipenem	Useful protocol for empiric therapy selection of patient with systemic

								infections should be designed.
[151]	Hafeez, 2004	Lahore	Chughtai Lab	Pus, urine, semen, ear & nasal swab, tissue, sputum, fluids, urethral discharge and endotracheal secretion	MRSA	Ciprofloxacin, Erythromycin and gentamicin	Fusidic acid, clindamycin and ofloxacin	Healthcare authorities must introduce more effective measure to control its spread.
[152]	Saeed, 2015	Lahore	Microbiology department, Allama Iqbal Medical College/ Jinnah hospital	Blood	Enterobacteriaceae, Staphylococcus	Cephalosporins, Carbapenems	Vancomycin, linezolid and piperacillin/tazobactum	Linezolid were most effective drug among gram positive pathogens and Piperacillin/tazobactum was most potent antimicrobial against P. aeruginosa
[153]	Zafar, 2016	Islamabad	Pathology Department, Al Nafees Medical College	Urine	E. coli, K. pneumoniae, P. aeruginosa	Not specified	Quinolones, aminoglycosides, cephalosporins	Quinolones, aminoglycosides and cephalosporin are drug of choice for treatment of urinary tract infections.
[130]	Zafar, 2009	Karachi	4 urban slums	Stool	S. flexneri, S. sonnei, S. dysentriae	Co-amoxiclav, ampicillin, chloramphenicol	Not specified	Surveillance at national level to facilitate the control of shigellosis is urgently required.

[154]	Butt, 2003	Rawalpindi	Department of microbiology, Ahmed Force Institute of Pathology	Sputum, pus, endometrium, pleural fluid, lymph node, urine, CSF, ascitic fluid, synovial fluid, semen, bone marrow	Not specified	Not specified	Not specified	Increased awareness of magnitude of the problem posed by extrapulmonary tuberculosis is required so that appropriate control measure can be adopted.
[129]	Ayaz, 2012	Karachi	Marie Adelaide Leprosy Center	Sputum	MDR-TB	Isoniazid, Pyrazinamide, streptomycin	Not specified	A r\eview of national treatment an\d prevention regimens relying on INH is suggested.
[155]	Ayesha, 2014	Abbottabad	Ayub Medical Complex	Vaginal swab	Staphylococcus, streptococcus, E.coli.	Not specified	Macrolides	To determine the susceptibility of those species, future studies are needed.

In addition, as a preliminary action, purchasing of non-prescribed drugs should be appreciably curtailed where pertinent alongside educational activities among all key stakeholders especially regarding the need to conserve Reserve and other antibiotics [33,59,116,156].

3.1.3 Infection Prevention and Control:

In Pakistan, infectious diseases are considered to be one of the most concerning public health issues and the major cause of morbidity and mortality in the country [157-159]. However to date, healthcare authorities in Pakistan are not to be fully prepared to fully tackle infectious diseases with pertinent funding; however, strategies undertaken by healthcare professionals might prompt policymakers towards re-appraisal of available resources [160]. The lack of a cohesive infrastructure currently, increased workload, shortage of trained staff, as well as language difficulties among public and healthcare professionals, appear to be the major barriers for initiating and implementing effective infection control programs that need to be urgently addressed [158].

The highest child mortality rates around the world are due to vaccine-preventable diseases [161,162]. Pakistan initiated its Expanded Program on immunization (EPI) in 1978; however, the program's performance is currently unsatisfactory [163]. Pakistan is still struggling with polio despite the polio eradication initiative launched in 1994, which was subsequently modified in 2000 with additional activities including national immunization days multiple times in a year. However, the programme still faces many challenges in delivering routine immunization. The joint efforts of local, national and global stakeholders can help with improving the country's immunization system, global health security and accomplishment of sustainable goals [163]. However, there are concerns across LMICs including Pakistan that lockdown and other activities associated with the current COVID-19 pandemic will have appreciable consequences on immunization programmes and subsequent morbidity and mortality associated with vaccine-preventable diseases [15,51,164,165]. Community pharmacists and others can play a vital role during the current pandemic to help address such concerns [15,166,167].

The first national infection guidelines in Pakistan were developed in 2006, with the collaboration of the National Aids Control Program at the Ministry of Health. These guidelines were established to restrain the transmission of various infections by educating and training healthcare professionals. These guidelines were further classified into standard precautions and additional (transmission-based) precautions. In 2019, the second National IPC Guidelines were developed with the collaboration of WHO [168]. The guidelines provide a comprehensive strategy to develop IPC programs at federal, provincial and institute level. Standard precautions should be practised for all patients regardless of disease, diagnosis or infection status [168]. For instance, hand washing, and the use of personal protective equipment (PPE) including, masks, gown and gloves are vital in the prevention and management of serious infectious diseases including COVID19

[169]. Precautionary measures should also be taken in hospitals such as keeping infected patients in isolated rooms [168]. However, there are concerns with the robust implementation of National guidelines in Pakistan, which itself needs further defining. To date, most healthcare settings in Pakistan have not developed any institutional policies or SOPs to follow the national guidelines on hospital infection control and prevention, which is a concern going forward that needs to be urgently addressed [170].

Medical professionals must have adequate knowledge, skills and attitudes towards infection prevention control programs. Effective infection prevention and control measures including good hygiene practices, initiation of ASPs, and appropriate use of indwelling devices and screening. Such measures should be adopted among hospitals in Pakistan to reduce the risk of healthcare-associated infections (HAIs) [35,99]. IPC committees should also be routinely established in hospitals in Pakistan starting in all tertiary and major secondary hospitals if not already implemented. Committee members should include infection control practitioners, physicians trained in infectious diseases, nurses, heads of clinical departments, hospital pharmacists, medical superintendent, Chairman of Board of Governors, Chief Engineers and heads of housekeeping [171]. This committee should be able to assess the training needs of medical staff and provide training, organize regular training for effective infection control practices, review the impact of training and provide re-training if needed [117,168]. Strong support from top-level stakeholders, the dedication of medical staff members, and active participation among all groups are needed for effective implementation of such programs.

3.1.4 Appropriate use of Antimicrobials:

Antimicrobials are powerful and effective medicines to treat infectious diseases. As mentioned, the rational use of antimicrobials is extremely important to reduce morbidity, mortality and costs [172,173]. Self-medication with antimicrobials is also very common among the populace in many LMIC including Pakistan [174,175]. The use of antimicrobials in paediatrics is also high due to several reasons including community-acquired sepsis, HAIs, postoperative prophylaxis, and inappropriate dosage forms [176,177]. This results in toxicity, medication errors, administration errors, development of AMR, and increasing treatment costs which needs to be addressed going forward [178-180].

The use of surgical antimicrobial prophylaxis and pre-operative antimicrobial prophylaxis is a recognized evidence-based practice in Pakistan and other countries to minimize the incidence of surgical site infections (SSIs) [139,181,182]. However currently in Pakistan, there are no proper prophylactic guidelines, with cephalosporins the most common antibiotic class given inappropriately for prophylaxis for patients to prevent SSIs [183,184]. In hospital settings, conventional antimicrobial therapy is usually prescribed for 7-10 days to post-surgically as well as postnatal patients with episiotomy, which is a concern as prolonged prophylaxis can increase AMR as well as adverse events [75,185-189].

Rational use of restricted antimicrobials can be achieved by changing the prescribing behaviour of physicians across sectors [88,133,190]. Regular screening and monitoring of prescriptions can help in minimizing inappropriate prescribing [81]. In this respect, ASPs can play an important role with optimizing the use of antimicrobials in hospitals; however, there can be concerns with manpower and competency in LMICs although this is not universal [36,98,103,181,191-194]. The focus of ASPs should be to reduce inappropriate antimicrobial prescribing, to rationalize the use of antimicrobials, to promote clinical outcomes, as well as reduce increasing rates of AMR and associated healthcare costs with managing resistant infections [195,196]. However, different healthcare professionals will have different opinions as well as different training needs, which may affect implementing ASPs [66,67]. Consequently, the success of implementing ASPs in hospital settings is highly dependent on the joint efforts of healthcare professionals, including physicians, nurses, clinical pharmacists and other paramedical staff, which is a key issue in Pakistan going forward [24]. Healthcare practitioners working in the community as well as in hospital settings should have adequate knowledge regarding the rational use of antimicrobials and strategies needed to cope with AMR [197-200]. Implementation of ASPs and standard guidelines/protocols is required so that the quality of care and patient safety goals can be achieved [108,118,119,182]. Additional benefits include reduced workload of medical staff as well as decreased length of stay in hospital and costs.

OTC sales of antimicrobials is another contributing factor to the misuse as well as abuse, making this issue a multifaceted one to address going forward [81,156,201]. Implementation of ASPs and standard guidelines/protocols is required including only allowing the community pharmacists to dispense selected list of antimicrobials if required. It may resolve the co-pay issues especially when the patient cannot afford physician fees, and other issues including access to physicians during normal working hours, alongside monitoring, dispensing via mobile and other technologies so that quality care and patient safety goals can be achieved [56,59,156,182]. We have seen different categories of pharmacy stores in Tanzania only allowed to dispense certain antimalarials and this practice could be extended along with guidelines and other interventions among different pharmacy stores [202]. In addition, ensuring a minimum level of knowledge among dispensers given concerns in some countries [61]. Education and training modules should also be designed for university students to disseminate targeted information regarding the potential hazards of antibiotic self-use and importance of consultation with qualified and registered medical doctors/pharmacists before starting with antibiotics [33,122].

3.1.5 Investment:

Pakistan currently has a mixed public-private healthcare system. The public health sector is currently classified into three sectors; primary (basic healthcare facilities), secondary (district and tehsil hospitals) and tertiary (tertiary hospitals) care [203]. Currently, key stakeholders in Pakistan have expressed lesser concern with monitoring of drug prices alongside a sustainable and adequate procurement system to enhance the affordability of medicines over other domains of the

framework [204,205]. This may reflect current high rates of patient co-payments for healthcare services in Pakistan including medicines reflected by the fact that when family members become ill in Pakistan this can potentially have catastrophic consequences [13-15]. Greater control over the price of medicines in Pakistan could help address concerns as seen recently with appreciable prices for antibiotics and antimalarials among some community pharmacies in Pakistan following the COVID-19 pandemic [15]. We are aware that the instigation of price controls for medicines among several Asian countries including India helped to limit price increases for recommended medicines early in the COVID-19 pandemic [15]. There also need for investment in pharmacy and physician education in Pakistan to reduce inappropriate prescribing and dispensing of antimicrobials, along with ensuring that costs are not a barrier to patients receiving appropriate antimicrobials to alleviate their bacterial infection.

Funding from the government and other non-government organizations is also required to develop and maintain standardized and reliable laboratory practices. This is the first step in hospitals to develop accurate antibiograms for empiric use alongside other measures in hospitals including the instigation of IPC committees and ASPs to reduce AMR.

3.1.6 Suggested activities for all key stakeholder groups in Pakistan to attain NAP goals to reduce AMR:

As we reviewed progress in Pakistan towards implementing the NAP, we have included suggested activities for all key stakeholder including, the general public, policymakers, healthcare practitioners, pharmacists and other paramedical staff associated with the use of antimicrobials and AMR. Suggested activities include awareness raising by developing local training and educational programs on AMR and assisting with their implementation, initiating debates about the rational use of antimicrobials, enhancing equitable access to antimicrobials and affordable drug pricing; development of appropriate policy, institutional and regulatory frameworks and networks to address AMR, and minimizing the need for antimicrobials by supporting better infection prevention standards including the promotion of good hygiene practices in hospitals as well as reduce inappropriate dispensing of antimicrobials in ambulatory care.

Consequently, activities going forward should primarily focus on three areas; (1) assisting with the establishment of NAP to address key issues surrounding AMR, (2) promoting the development and strengthening of laboratory capacity, (3) preservation of existing therapies through enhancing appropriate prescribing and dispensing as well as collaboration to promote sustainable launches of any new antimicrobials and methods.

4. Discussion:

This narrative review suggests that the implementation of the NAP in Pakistan is a challenging task due to several factors. These include poor awareness of AMR among policymakers, general public and healthcare professionals, insufficient financial and institutional resources to implement

strategies to combat AMR, unavailability of national surveillance system to monitor the emergence of AMR and concerns with the extent of infection prevention and control groups within hospitals. Also, continued concerns with the extent of self-purchasing of antibiotics within community pharmacies. To combat these challenges, measures such as mainstreaming of AMR containment process in the different fields, inter-sectoral partnership for infection prevention and control and appropriate resourcing via national budgets and annual development strategies are needed. The major factor contributing to the spread and emergence of AMR arising from our study includes poor awareness regarding the rational use of antimicrobials. We are aware patients or caregivers pressurize physicians and pharmacists to prescribe and dispense antimicrobials especially in urban areas without any proper diagnosis. In many instances, antimicrobials are used as a 'quick & cheap' alternative by both physicians and the patients or caregivers including use for self-medication. In the Drug Act 1967 of Pakistan, it is clearly stated that dispensing of antimicrobials without prescription is illegal [32,206]. However, dispensing of antimicrobials to the general public without prescription is common. It may be due to the absence of licensed and qualified pharmacists, which is a concern as the presence of qualified pharmacists can reduce suboptimal dispensing of antimicrobials [68]. This is exacerbated by the fact that healthcare professionals and students in Pakistan appear unaware of any guidelines or policies regarding the use of antimicrobials. The poor knowledge about antimicrobial guidelines by medical and pharmacy students have also been reported in other LMICs [207-209]. There are also aggressive marketing strategies by pharmaceutical companies aimed at enhancing the use of antibiotics especially broad-spectrum antibiotics at the expense of patients. This is similar to other regions of the world including India, Indonesia, Malaysia and Nepal [210-213].

We are aware that many initiatives are ongoing across LMICs to address gaps in knowledge and use of antimicrobials, which have implications for Pakistan. For instance, Pakistan is a recipient of the Fleming Fund, whose main objective was to develop a work plan for AMR and antimicrobial usage (AMU) along with strengthening One Health approach and strengthening AMR and AMU surveillance in Pakistan. Currently, the project is active in Pakistan along with the coordination of the contributing ministries including the Ministry of National Health Services Regulation and Coordination, and the Ministry of National Food Security and Research [214]. GARP-Nepal is working to highlight the components of a national plan for the prevention of AMR in the country [210]. Malaysia and Indonesia also now have national-level committees to monitor antimicrobial prescribing and promote rational use [211,212]. The Indian Council of Medical Research has also Implementation of ASPs and standard guidelines/protocols are required including only allowing a selected list of antibiotics to be dispensed if essential, especially if community pharmacists are the principal healthcare professional available, there are co-pay issues especially if patients cannot afford medicines alongside paying physician fees, and there are issues of access to physicians during normal working hours, alongside monitoring, dispensing via mobile and other technologies so that quality care and patient safety goals can be achieved brought together qualified groups of prescribers in a workshop to enhance their knowledge on AMR and related issues [213]. These countries have also hosted a dedicated website for consumer awareness and education regarding

the rational use of antimicrobials and included schools in the campaign. The ASEAN countries have also developed STGs, problem-based pharmacotherapy and pharmacovigilance in their core medical curriculum [215]. We are also aware that several Central and Eastern European countries as well as former Soviet Union Republics have instigated multiple educational activities among all key stakeholder groups including activities to reduce self-p1urchasing of antibiotics to successfully reduce antibiotic utilization in recent years providing direction to Pakistan [58,62,63]. This compares with Poland with limited demand-side measures where utilization rates continue to rise [104].

Overall, the issue of AMR is multi-disciplinary, multi-sectoral and multi-institutional. Consequently, the adoption of a comprehensive approach across all sectors such as that of One Health is required. For instance, among 16 Asian countries where typhoid is most frequent, inhabitants of Sindh and Punjab provinces of Pakistan were at the highest risk of developing typhoid [216]. In 2018, the outbreak of typhoid in Hyderabad, Pakistan, exposed the vulnerability of the country to the transmission of infection due to poor hygiene practices which increases the effects of unsafe water and sanitation [217]. To support IPC measures, it is critical to promote the implementation of hygiene and IPS as well as strengthen IPC policies and standard operating procedures in all healthcare settings. Consequently, IPC guidelines will need to define and communication best practice standards, as well as follow this up. However, the current review identifies essential policy and implementation gaps that Pakistan should address over the coming years to reduce high AMR rates by incorporating AMR in the curriculum of medical, pharmacy and vet schools, implementing of IPC practices, optimizing use of antimicrobials across all sectors and promoting research and innovation to reduce future rates.

5. Conclusion:

The Pakistan NAP for AMR is a well-designed, comprehensive plan that includes all key objectives of GAP to address future strategies and regulatory issues regarding antimicrobial use according to a “One Health approach”. The implementation of this plan requires the constant engagement of all key stakeholders as well as separate funding for identified activities to reduce AMR with the collaboration between central and state governments to achieve the goals and outcomes contained in the NAP. The commitment of Pakistan on AMR global action plan (WHO) and recent involvement in GHSA at country level provides a basis for moving towards AMR containment plans. However, many gaps and concerns have been identified that urgently need addressing to reduce future AMR rates. The private sector, civil society and the media play a vital role in developing pertinent policies to combat AMR. Healthcare authorities should focus on monitoring and evaluation of all key objectives, develop appropriate governance mechanisms and accountability to design how well these outcomes can be attained in the particular settings. Healthcare professionals should support initiatives to promote antimicrobial stewardship and IPC measures as these strategies are completely under their control. This includes measures to reduce self-purchasing of antibiotics given the likely impact on reducing overall utilization. A strong

political devotion and support from all stakeholders are required for successful implementation to of NAP. We will be following this up in the future.

6. Expert Opinion:

This review suggests that the Pakistan National Actional Plan for the antimicrobial resistance is well laid and is comprehensive as it covers all the main objectives of the GAP. These objectives are needed to address all the future strategies and the regulatory issues regarding antimicrobial use according to 'One Health Approach'. The engagement of all the key stakeholders is required to implement this plan. Along with this separate funding of identified activities to reduce AMR with the collaboration between central and state governments to achieve the goals and outcomes contained in the NAP. Our study suggests that there are many gaps which have been identified and there is an urgent need to address them. The first basic issue is regarding the awareness of this threat. The published studies in Pakistan have reported that general physicians and pharmacists practicing in Pakistan have insufficient knowledge and training regarding the rational use of antibiotics and AMR. The important subject in this case 'Pharmacology' is taught at the undergraduate level; however, there is little training in clinical therapeutics at the postgraduate level for all the essential healthcare workers including general physicians, nurses, pharmacists and other paramedical staff. The factors which trigger the AMR include the level of education of patients, the lack of health facilities in the public sector, low health literacy, poor infrastructure of healthcare settings in rural areas, prescriber's experience. Other issues regarding the implementation of the AMR is the proper surveillance if any type of infection. It is a key element of an effective infection control strategy to identify the issues and analyze the possible intervention programs. However, in the third world countries like Pakistan, insufficient resources and standard laboratories hinder the development of the effective surveillance system. The infection prevention and control strategies are the most significant in controlling the AMR; however, to date, healthcare authorities in Pakistan are not to be fully prepared to fully tackle infectious diseases with pertinent funding. The rational use of antimicrobials is extremely important to reduce morbidity, mortality and costs. However currently in Pakistan, there are no proper prophylactic guidelines, with cephalosporins the most common antibiotic class given inappropriately for prophylaxis for patients to prevent SSIs. The rational use of antimicrobials is also a compelling factor in controlling the AMR. However currently in Pakistan, there are no proper prophylactic guidelines to prescribe the rational antimicrobials. Rational use of restricted antimicrobials can be achieved by changing the prescribing behavior of physicians across sectors which is still a challenge for the healthcare authorities. There is also need for investment in pharmacy and physician education in Pakistan to reduce inappropriate prescribing and dispensing of antimicrobials, along with ensuring that costs are not a barrier to patients receiving appropriate antimicrobials to alleviate their bacterial infection. Antimicrobial stewardship and IPC measures should be supported and initiated by the healthcare professionals as these strategies are completely under their control. This includes measures to detain self-purchasing of antibiotics which will result in reducing overall utilization.

For successful implementation of NAP, strong political devotion and support from all stakeholders are required.

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11. References

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