EVALUATION OF CURRENT PRACTICES OF ANTIMICROBIAL USE AMONG NEONATES AND CHILDREN IN SELECTED HOSPITALS OF PUNJAB, PAKISTAN

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by

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AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship
AWaRe	Access, Watch and Reserve
ASP	Antimicrobial stewardship program
HIC	High income country
LMIC	Low-middle income country
HAI	Health-care associated infection
PPS	Point prevalence survey
URTI	Upper respiratory tract infection
LRTI	Lower respiratory tract infection
PHC	Primary healthcare facility
BHU	Basic Unit Health
RHC	Rural Health Center
SDG	Sustainable Development Goal
HCW	Heath Care Worker
ICU	Intensive Care Unit
SSI	Surgical Site Infection

LIST OF APPENDICES

PENILAIAN AMALAN SEMASA PENGGUNAAN ANTIMIKROB DALAM KALANGAN NEONAT DAN KANAK-KANAK DI BEBERAPA HOSPITAL TERPILIH DI PUNJAB, PAKISTAN

ABSTRAK

Penggunaan antibiotik yang berlebihan dan tidak sesuai merupakan salah satu pemacu utama kepada rintangan antimikrob (AMR), termasuk dalam kalangan kanak-kanak. Oleh itu, penggunaan agen antibakteria yang rasional dan optimum adalah satu keperluan yang utama dalam program pengawasan antimicrobial (ASP) berorientasikan kanak-kanak. Terdapat kebimbangan yang ketara terhadap penggunaan antibiotik yang tinggi dan tidak sesuai di semua sektor di Pakistan dan implikasinya terhadap AMR. Walau bagaimanapun, bagi mencapai sasaran masa depan, maklumat yang lebih lanjut diperlukan, terutamanya selepas pandemik COVID-19. Oleh itu, objektif kajian ini adalah untuk menentukan amalan semasa penggunaan antimikrob dalam kalangan neonat dan kanak-kanak di hospital di Punjab, Pakistan, serta menilai pengetahuan semasa mengenai ASP dan pelaksanaannya dalam kalangan pakar pediatrik bagi memberikan panduan kepada semua pihak berkepentingan utama di Pakistan. Pertubuhan Kesihatan Sedunia (WHO) telah membangunkan metodologi standard bagi menilai amalan preskripsi antibiotik di hospital yang dikenali sebagai "kajian prevalens titik (PPS)", yang telah diadaptasi untuk kajian PPS dalam kajian PhD ini. Dalam fasa pertama kajian ini, PPS pelbagai pusat telah dijalankan dalam kalangan hospital kanak-kanak utama dalam sektor awam di Pakistan yang merawat bayi dan kanak-kanak serta di wad kanak-kanak di 14 hospital penjagaan tertiari di wilayah terbesar, Punjab. Hasil kajian menunjukkan bahawa hampir semua (>95%) neonat dan kanak-kanak diberikan sekurang-kurangnya

satu antibiotik pada hari kajian, dengan purata 1.57-1.90 antibiotik setiap pesakit. Sebanyak 56.9-58.7% antibiotik telah dipreskripsikan secara terapeutik, manakala 27.2-31% diberikan secara profilaktik, dengan 75.2-77.9% daripada kanak-kanak yang dikaji menerima profilaksis yang berlanjutan (> satu hari). Kebanyakan antibiotik telah dipreskripsikan secara empirik (92.2-96.6%) dan diberikan melalui laluan parenteral (85.6-92.3%). Antibiotik yang paling kerap dipreskripsikan termasuk ceftriaxone (25.8-28.8%), cefotaxime (8-13.2%), amikacin (9.2-9.5%), vancomycin (5.1-7.9%) dan meropenem (4.1-8%), dengan majoriti daripadanya tergolong dalam kategori 'Watch' WHO (75.2-76.6%) di bawah klasifikasi antibiotik AWaRe. Dalam fasa kedua, PPS mengenai jangkitan berkaitan penjagaan kesihatan (HAI) telah dijalankan di wad kanak-kanak di 19 hospital sektor awam di seluruh Punjab mengikut garis panduan Pusat Pencegahan dan Kawalan Penyakit Eropah (ECDC). Prevalens HAI dalam kalangan neonat dan kanak-kanak adalah 13.3%, dengan jangkitan aliran darah (26%) dan jangkitan saluran pernafasan bawah (21.6%) merupakan jenis HAI yang paling biasa dilaporkan. Spesies bakteria yang paling kerap dikenal pasti sebagai penyebab HAI ialah *Staphylococcus aureus* (31.7%), diikuti oleh *Klebsiella pneumoniae* (22.9%) dan *Escherichia coli* (17.4%). Faktor yang dikaitkan dengan HAI termasuk tempoh kemasukan hospital yang lebih lama, kemasukan ke ICU, pesakit dengan prognosis "fatal secara cepat" mengikut kriteria McCabe dan Jackson, penggunaan kateter pusat dan periferi, serta ventilasi mekanikal invasif ($p < 0.001$). Dalam fasa ketiga, satu kajian retrospektif melalui semakan rekod perubatan telah dijalankan di empat hospital di Punjab bagi menilai penggunaan antibiotik dalam kalangan kanak-kanak yang dimasukkan ke hospital akibat COVID-19. Kajian mendapati bahawa majoriti pesakit (>85%) menerima preskripsi antibiotik, terutamanya daripada kategori 'Watch' (>80%), walaupun prevalens jangkitan bakteria sekunder atau koinfeksi

bakteria adalah sangat rendah (3.7%). Faktor yang dikaitkan dengan peningkatan preskripsi antibiotik termasuk tahap keterukan COVID-19, tempoh kemasukan hospital, keperluan untuk ventilasi mekanikal, serta paras WBC, CRP, D-Dimer dan ferritin yang tinggi ($p < 0.001$). Dalam fasa keempat, satu kajian keratan rentas telah dijalankan di enam fasiliti penjagaan kesihatan ambulatori di Punjab bagi menilai tahap rasional preskripsi antibiotik dalam kalangan kanak-kanak berumur sehingga 12 tahun. Hanya 35.8% daripada antibiotik yang dipreskripsikan adalah sesuai mengikut buku AWaRe WHO. Dalam fasa kelima, satu kajian keratan rentas telah dijalankan menggunakan instrumen kajian yang disahkan bagi menilai tahap pengetahuan, persepsi, kesiapsiagaan, penglibatan, serta halangan yang dihadapi oleh pakar pediatrik dalam pelaksanaan program ASP. Terdapat kebimbangan yang ketara apabila hanya 7.6% daripada pakar pediatrik yang mengambil bahagian menyatakan bahawa mereka mempunyai ASP yang berfungsi di hospital mereka. Namun, mereka yang pernah menerima latihan ASP dan mempunyai ASP yang berfungsi di hospital mereka menunjukkan kesiapsiagaan yang lebih baik terhadap ASP berbanding mereka yang tidak menerima latihan ASP ($p = 0.008$). Dalam fasa akhir, satu kajian keratan rentas telah dijalankan di tiga daerah di Punjab menggunakan instrumen kajian yang disahkan untuk menilai amalan penggunaan sendiri antibiotik, serta tahap kesedaran dan amalan ibu bapa terhadap penggunaan antibiotik dalam kalangan anak mereka yang dimasukkan ke hospital. Keputusan menunjukkan bahawa 63% ibu bapa menyatakan mereka mengamalkan penggunaan sendiri antibiotik untuk anak-anak mereka, dengan antibiotik yang paling biasa digunakan ialah amoxicillin (33.6%), co-amoxiclav (18.1%), dan azithromycin (15.2%). Peserta dengan tahap pendidikan yang lebih tinggi dan mereka yang mengenali nama antibiotik dikaitkan dengan penggunaan antibiotik tanpa nasihat perubatan ($p < 0.001$). Pelbagai kajian ini menunjukkan

bahawa penggunaan antibiotik yang berlebihan dan tidak sesuai adalah sering berlaku dalam kalangan neonat, kanak-kanak serta dalam kalangan ibu bapa di hospital sektor awam di Punjab, Pakistan. Oleh itu, langkah segera perlu diambil untuk memperbaiki amalan semasa dalam penggunaan antibiotik di kedua-dua sektor penjagaan kesihatan ambulatori dan penjagaan hospital di Pakistan di bawah naungan ASP, terutamanya apabila kini buku *AWaRe* telah diterbitkan bagi memberikan panduan preskripsi untuk pelbagai jenis jangkitan.

EVALUATION OF CURRENT PRACTICES OF ANTIMICROBIAL USE AMONG NEONATES AND CHILDREN IN SELECTED HOSPITALS OF PUNJAB, PAKISTAN

ABSTRACT

Excessive and inappropriate use of antibiotics are one of the principal drivers of antimicrobial resistance (AMR) including children. Consequently, the judicious and optimal use of antibacterial agents is an urgent need under pediatric oriented antimicrobial stewardship program (ASP). There are considerable concerns with current high levels of inappropriate antibiotic use across all sectors in Pakistan and the subsequent implications for AMR. However, more information is needed, especially following the COVID-19 pandemic, to achieve future targets. Consequently, the objectives of the study were to ascertain the current practices of antimicrobial use among neonates and children across hospitals in Punjab, Pakistan, combined with the current knowledge of ASPs and their implementation among pediatricians, to provide future guidance to all key stakeholder groups in Pakistan. The World Health Organization (WHO) developed a standardized methodology to ascertain current antibiotic prescribing practices in hospitalized settings named “point prevalence survey (PPS)”, which was adopted for the PPS studies in this PhD. In the first phase of this study, a multicenter PPS was conducted among leading children’s hospitals in the public sector in Pakistan treating infants and children as well as in the children wards of fourteen tertiary care health settings in the largest province, Punjab. Our findings showed that nearly all (> 95%) neonates and children were prescribed at least one antibiotic on the day of survey, with an average of 1.57-1.90 antibiotics per patient. 56.9-58.7% antibiotics were prescribed therapeutically with 27.2-31% administered

prophylactically, with extended prophylaxis (> one day) i.e. 75.2-77.9% of surveyed children. Most of the antibiotics were prescribed empirically (92.2-96.6%) and via the parenteral route of administration (85.6-92.3%). Frequently prescribed antibiotics included ceftriaxone (25.8-28.8%), cefotaxime (8-13.2%), amikacin (9.2-9.5%), vancomycin (5.1-7.9%) and meropenem (4.1-8%) with the majority of them from WHO 'Watch' category (75.2-76.6%) under the AWaRe classification of antibiotics. In the second phase, a PPS of health-care associated infections (HAIs) was performed in the childrens' wards of nineteen public sector health facilities across Punjab according to European Centers for Diseases Prevention and Control (ECDC). The prevalence of HAIs among neonates and children was 13.3%, with blood stream infections (26%) and lower respiratory tract infections (21.6%) commonly reported HAIs. Commonly identified bacterial species causing HAIs were *S. aureus* (31.7%) followed by *K. pneumoniae* (22.9%) and *E. coli* (n = 28, 17.4%). Identified factors associated with HAI were increased length of hospital stay, being admitted to the ICU, "rapidly fatal" patients under the McCabe and Jackson criteria, central and peripheral catheterization, and invasive mechanical ventilation ($p < 0.001$). In the third phase, a retrospective, medical records review study was conducted in four health facilities of province Punjab to evaluate antibiotic use among children hospitalized due to COVID-19. We found that the majority of admitted patients (>85%) prescribed antibiotics, principally from Watch' category (>80%), despite very low prevalence of bacterial co-infections or secondary bacterial infections (3.7%). Factors associated with increased antibiotic prescribing were COVID-19 severity, length of hospital stay, patients requiring mechanical ventilation, and high levels of WBCs, CRP, D-Dimer and ferritin levels ($p < 0.001$). In the fourth phase, a cross-sectional study was conducted in six ambulatory health care settings of province Punjab to assess the extent of rational

antibiotic prescribing among children up to 12 years age. Only 35.8% of prescribed antibiotics were appropriate according to the WHO AWaRe book. In the fifth phase, a cross-sectional study was conducted using a validated study tool to assess pediatricians' knowledge, perception, preparedness, involvement and perceived barriers towards ASPs. There were considerable concerns with only 7.6% of participating pediatricians stated they had functional ASPs in their hospitals. Encouragingly, those study participants who had received ASP training, and had functional ASPs in their hospital, showed better preparedness towards ASP compared to those who had not ($p = 0.008$). In the final phase, self-medication with antibiotics, as well as their awareness and practices towards antibiotics, were assessed among parents of hospitalized children through a cross-sectional study in three districts of Punjab using a validated study tool. Of concern is that 63% parents stated they practiced self-medication with antibiotics among their children, and the most commonly used antibiotics by parents included amoxicillin (33.6%), co-amoxiclav (18.1%), and azithromycin (15.2%). Participants with increased education levels, and those who were familiar with antibiotics names, were associated with higher antibiotics use without medical advice among their children ($p < 0.001$). The various studies demonstrated that excessive and inappropriate use of antibiotics is frequent among neonates and children across public sector hospitals in Punjab, Pakistan, as well as among parents. Consequently, urgent measures are needed to improve current practices regarding antibiotic use across both ambulatory and hospital care in Pakistan under the umbrella of ASPs, especially now that the AWaRe book has been published providing prescribing guidance across a range of infection.

CHAPTER 1

INTRODUCTION

1.1 Background to antibiotics

Since the discovery of penicillin in the 1940s, antibiotics have always been acknowledged as one of the most significant therapeutic entities of 20th century (Bulman et al., 2022). Antibiotics were recognized as a magic bullet that selectively targeted pathogens that were involved in disease causation. The period between 1940-1970 is often regarded as a golden era of antibiotics in terms of the discovery of nearly all present-day antibiotic classes along with an appreciable reduction in mortality due to infectious diseases (Bulman et al., 2022). Antibiotics not only saved lives but also played a pivotal role in achieving significant advances in the field of medicine and surgery (Ito et al., 2019; Saleem et al., 2022a). Moreover, infections associated with complicated surgeries, including joint replacement, cardiac surgery and organ transplantation, have benefited from antibiotics (Surat et al., 2021; Ventola, 2015). A global reduction in mortality in children under five years from 216 per live 1000 deaths in 1950 to 39 deaths per 1000 live births in 2017, along with an increase in life expectancy from 48 years to 71 during the same duration, happened as a result of antibacterial therapy coupled with others initiatives (Burstein et al., 2019; Dicker et al., 2018). Consequently, antibiotics are considered as an essential component of treatment regimens especially in low- and middle-income countries (LMICs) where the prevalence of infectious diseases is typically higher than seen in high-income countries (HICs) (Nepal & Bhatta, 2018; Sachdev et al., 2022; Sulis et al., 2020). However, there have been considerable concerns with their over-use increasing antimicrobial resistance (AMR).

1.2 Antimicrobial resistance and its causes

Infections caused by resistant bacterial agents are spreading, compromising efforts to treat them with available antibiotics. AMR occurs when bacteria, viruses, fungi and parasites change themselves in such a way that that available antimicrobials are no longer effective thereby making infections difficult to treat (Prestinaci et al., 2015). Moreover, due to AMR there are greater chances of infection spreading as well as increasing the severity of illnesses and ultimately death (Serwecińska, 2020; Uddin et al., 2021).

Whilst AMR affects every country, the greatest burden of AMR is currently seen among LMICs due to numerous political, economic, socio-cultural and environmental factors (Ahmad et al., 2021; Ayukekbong et al., 2017; Collignon et al., 2018; Iskandar et al., 2021; Sharma et al., 2022; Sulis et al., 2022). Key factors enhancing AMR include poor surveillance/research regarding antibiotic use patterns exacerbated by a lack of electronic prescribing and monitoring systems, insufficient hygiene practices including a lack of regular hand washing, a lack of awareness in the general population about the risks of AMR, lack of sufficient diagnostic facilities to differentiate bacterial from viral infections, inappropriate prescribing and dispensing of antibiotics including extensive use of broad-spectrum antibiotics for essentially self-limiting conditions, insufficient staff capacity and their training, as well as communication gaps among healthcare professionals (HCPs) (Ahmad et al., 2021; Ayukekbong et al., 2017; Godman et al., 2021; Godman et al., 2022; Godman et al., 2020).

Alongside this, the higher prevalence of infectious disease outbreaks, including malaria, dengue fever, typhoid, tuberculosis and Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS), places an additional burden on the poorly developed health infrastructures of LMICs (Vos et al., 2020). These additional infectious diseases, and their impact on limited available resources, further compromise initiatives to improve the rational use of antimicrobials among LMICs.

AMR is a natural phenomenon; however, the over use and misuse of antibiotics, i.e. inappropriate choices, improper doses, duration, frequency and route of administration, as well as poor compliance with standard treatment guidelines, appreciably enhances the development of AMR (Ayukekbong et al., 2017; Bell et al., 2014; Laxminarayan et al., 2013; Llor & Bjerrum, 2014; Riedel et al., 2007; Uddin et al., 2021). Hospital settings particularly in LMICs, are highly vulnerable sites for AMR development due to excessive and inappropriate antibiotic use (Otaigbe & Elikwu, 2023; Sartelli et al., 2020). Nearly, 20-50% antibiotics prescribed among hospitalized patients in LMICs are currently reported to be inappropriate (Castro-Sánchez, Moore, Husson, & Holmes, 2016). Alongside this, there is considerable over-prescribing of antibiotics to treat principally viral infections in LMICs (Godman et al., 2021; Godman et al., 2020; Mittal et al., 2020). A systematic review and meta-analysis reported from 27 LMICs showed that the prevalence of antibiotic prescribing at primary healthcare centers (PHCs) was 52% and the proportion of inappropriate antibiotic (in terms of indication, dose, duration, frequency and route of administration) prescribing ranged from 8% to 100% (Sulis, Adam et al., 2020). A previous multi-national study revealed that antibiotics were inappropriately prescribed among 28.3% patients in China 49.9% in India and 50% in Kenya in primary health care centers (PHCs) (Sulis, Daniels et al.,

2020). Alongside this, more than half (51.5%) of patients received antibiotics during their visits to PHCs among six in African countries (Ofori-Asenso & Agyeman, 2015).

In addition, antibiotics are among the most commonly purchased medicines globally often without a prescription especially among LMICs (Auta et al., 2019; Belachew et al., 2021a; Belachew et al., 2021b; Nepal & Bhatta, 2018; Sono et al., 2023; Torres et al., 2021). Self-medication (SM) is defined as the consumption of medicinal products, including over the counter (OTC) or non-prescription medicines as well as prescription only medicines (POM) including antibiotics, to treat self-diagnosed illness without consultation from a physician, pharmacist or other HCPs. This also includes the continuous or intermittent use of a medication previously prescribed by a physician for chronic or recurring symptoms or diseases and without any medical supervision (Mustafa et al., 2023; Nepal & Bhatta, 2018). Various factors contributed to SM in LMICs. These include a lack of financial resources for medical consultations, distant health facilities, desire for self-care, information received from family, friends and neighbors, advertisements in print and electronic media, previous drug prescriptions, previous success with antibiotics, limited knowledge among patients and the ready availability of antibiotics from drug sale outlets without valid prescriptions (Belachew et al., 2021b; Belachew et al., 2021a; Godman et al., 2020; Hoxha et al., 2018; Raza et al., 2022; Shoaib et al., 2021; Sono et al., 2023). However the purchasing of antibiotics without a prescription may lead to undesirable outcomes including unnecessary consumptions of medicines including antibiotics and financial constraints, adverse drug reactions (ADRs) related to these drugs, drug-drug and drug-food interactions, delay in attaining professional services, drug dependence and abuse as well as AMR (Elayeh et al., 2021; Quincho-Lopez et al., 2021; Sono et al., 2023).

1.3 Negative consequences of antimicrobial resistance

Overall, AMR is one of the principal global health threats, compromising food security, economic growth and development (Gautam, 2022; Jee et al., 2018; WHO, 2023). AMR itself is associated with prolonged hospitals stays and economic loss alongside increased morbidity and mortality (Ait Ouakrim et al., 2020; Cassini et al., 2019; Dadgostar, 2019; Hofer, 2019; Huemer et al., 2020). Nearly 5 million (4.95) deaths were associated with AMR globally in 2019, with 1.27 million deaths directly attributable to AMR, with the greatest burden currently in sub-Saharan Africa and Asia (Murray et al., 2022). According to the Centers for Disease Control and Prevention (CDC), AMR is currently responsible for the annual loss of USD 55 billion in the United States of America (Dadgostar, 2019). If no immediate measures are taken to address AMR, AMR could result in more than 10 million deaths annually, and economic loss of more than 5% of GDP per country per year, by 2050 (Bank, 2019; Laxminarayan et al., 2020; O'Neill, 2016). This needs to be avoided through extensive efforts collectively. Consequently, it is important to improve the understanding in Pakistan regarding current antibiotic utilization and resistance patterns to develop appropriate targeted interventions across all key stakeholder groups to reverse current trends.

1.4 Global initiatives to combat AMR

As a result of ongoing concerns with rising rates of AMR and their consequences, many international and national initiatives have been undertaken (Bank, 2022; OECD, 2018; WHO, 2016). This includes, the development of ‘Global Action Plan’ (GAP) on AMR by the World Health Organization (WHO) in 2015 in accordance

with 68th World Health Assembly recommendations (WHO, 2016). The core objectives of the GAP include:

i) Improvement in the awareness and understanding of AMR through effective coordination education and training among HCPs
ii) Enhanced knowledge through surveillance and research
iii) Reduction in the incidence of infection through appropriate sanitation, hygiene and infection prevention measures
iv) Optimize the use of antimicrobial agents in human and animal health
v) Financial arrangement for sustainable investment to increase investment in new medicines, diagnostic tools, vaccines and other interventions

These objectives stressed the need for rational antibiotic use along with infection awareness, education and preventive measures. The first steps being improved understanding of current antibiotics utilization and resistance patterns across the sectors. In addition, ongoing programs to improve future utilization including instigating antimicrobial stewardship programs (ASPs) and their impact (Cox et al., 2017; Godman et al., 2021; Dilip Nathwani et al., 2019; Pierce et al., 2020). The GAP also emphasized that each country should develop its own National Action Plan to combat AMR building on the GAP.

The WHO Expert Committee on Selection and Use of Essential Medicines also recently developed the AWaRe classification of antibiotics whereby all available antibiotics have been classified into Access, Watch and Reserve groups (Mike Sharland et al., 2018). The primary objective of this classification was to restrict the use of antibiotics belonging to ‘Watch’ and ‘Reserve’ categories in order to reduce

AMR (Mike Sharland et al., 2019; Sulis et al., 2022). The 'Access' group of antibiotics includes those antibiotics that act on a wider range of causative bacterial organism along with lower potential of developing of AMR compared to antibiotics in the 'Watch' and 'Reserve' groups. These antibiotics include trimethoprim and sulfamethoxazole, ampicillin, amoxicillin, amikacin, metronidazole and doxycycline (Mike Sharland et al., 2019). The 'Watch' group include antibiotics with a greater potential to develop resistance; consequently, they should be used in severe infections. Examples include third generation cephalosporins, fluroquinolones and carbapenems. Antibiotics in the 'Reserve' Group are last-resort antibiotics and should be reserved for the life-threatening conditions including MDR cases (Mike Sharland et al., 2019). Examples of 'Reserve' antibiotics include linezolid, ceftazidime/avibactam, colistin and meropenem/vaborbactam. The WHO has currently set a target of 60% utilization of 'Access' antibiotics across settings (Klein et al., 2021; Michael Sharland et al., 2022; Sulis et al., 2022). It is increasingly likely that quality targets linked to the AWaRe categories will be introduced as part of future ASPs to improve prescribing (Chigome et al., 2023; Haseeb et al., 2023; Saleem et al., 2022c)

1.5 Infectious diseases burden and targets in children

Appropriate management of children is a priority across countries especially LMICs with more than 5.2 million deaths globally recorded in children under the age of five years in 2019 (WHO, 2020). According to age distribution, neonates (0-28 days) accounted for 2.4 million deaths. There were 1.5 million deaths among children age 1-11 months and 1.4 million deaths among children aged 1-4 years in 2019. More than 80% global deaths among child under five age were reported in two regions, sub-Saharan Africa and Central and Southern Asia (Organization, 2020). This is an

improvement with a 61% decrease in mortality from 1990 to 2019 in children in the age group 5-9 years (WHO, 2020). However, more needs to be done to further reduce morbidity and mortality in this age group. The Sustainable Development Goals (SDGs) were formulated to promote healthy lives and well-being for all children around the globe. The SDG Goal 3.2.1 deals with the deaths of newborns and under-5 children by 2030. In this regards, two targets were set to be achieved by 2030: one is to reduce newborn mortality to 12 per 1000 live births in every country and the second is to reduce under-5 mortality to 25 per 1000 live births in every country (Sustainable Development Goals).

The critical countries include Nigeria, India and Pakistan, who were the top three countries in 2019 with the highest mortality burden in children under five years of age (Organization, 2020). Overall, Pakistan has a high rate of mortality among neonates and children under the age of five years, which needs to be addressed going forward. Respiratory tract infections (RTIs) are responsible for 20-30% child deaths in Pakistan (Naz et al., 2019).

Infectious diseases including pneumonia, diarrhea, malaria, tuberculosis and measles, are the leading cause of death among neonates and children (Perin et al., 2022). Infectious diseases can be prevented or treated with appropriate antibacterial therapy alongside immunization, clean water supply and appropriate care from HCPs. (Ellwanger et al., 2021)

1.6 Global antibiotic use/consumption in children

As a result of the fragile physiologic system, greater bacterial exposure, lack of appropriate immunity and recurrent episodes of infections in neonates and children, effective antimicrobial therapy is essential to reduce morbidity and mortality in this

population (Woll et al., 2018). Antimicrobial agents are one of the most common classes of medicines prescribed among neonates and children globally (Youngster et al., 2017). Of concern though is that there has been an appreciable increase in the consumption of antimicrobial agents in last two decades, including among children, which raises concerns with their appropriateness and associated increase in AMR. Browne et al. reported a 46% increase in global antibiotic consumption among child under five years age from 2000 to 2018 from 9.8 (9.2–10.5) DIDs in 2000 to 14.3 (13.2–15.6) DIDs in 2018 (Browne et al., 2021). In another study conducted among sick children below the age of five years among 73 LMICs, there was also an increase in antibiotic use from 36.8% in 2005 to 43.1% in 2017 (Allwell-Brown et al., 2020).

1.7 Global burden and determinants of healthcare-associated infections (HAIs)

Healthcare-associated infections (HAIs) are also a concern globally alongside rising rates of AMR, increasing morbidity, mortality and costs (Saleem et al., 2019a). However, they are a potentially preventable adverse consequence of healthcare delivery, threatening the health of both patients and HCPs (Cassini et al., 2016). HAIs are defined as an infection neither present nor incubating at the time of hospital admission and reported after 48 hours or more of hospital admission (Haque et al., 2018; Maki & Zervos, 2021). Whilst the hospital environment including poor hand hygiene, a lack of isolating high-risk patients and insufficient infection prevention and control measures, contribute to the development of HAIs. HAIs also develop following the use of invasive devices including intravascular and urinary catheters and ventilators as well as those related to antimicrobial use (Bennett et al., 2018; Zaidi et al., 2016). Common types of HAIs are ventilator-associated pneumonia, central line-associated bloodstream infections, catheter-associated urinary tract infections, surgical

site infections (SSIs) and *Clostridiodes difficile* infections (CDC, 2014; Mwita et al., 2021; Saleem et al., 2019a).

HAIs are typically 2-5 times more likely in LMICs versus higher income countries (Abubakar et al., 2022; Zaidi et al., 2016). For instance, it is estimated that one in 31 (3%) hospitalized patients in the USA experience at least one HAI (Konnor, 2022), which is down from approximately 4.5 to 5% previously (Haque et al., 2020). Overall, the prevalence of HAIs decreased by approximately 16% between 2011 and 2015, largely due to reductions in SSIs and urinary tract infections (Magill et al., 2018). In Europe, 6.5% of patients in acute hospitals have at least one HAI (Kärki et al., 2019).

However in Africa, the prevalence of HAIs have recently been estimated at 12.8% of hospitalized patients, with a high degree of heterogeneity across countries and settings (Abubakar et al., 2022). The highest rates of HAIs were found in intensive care units (ICUs) in Africa (25.2%–100%), followed by neonatal ICUs/wards (7.0%–53.6%) and pediatric medical wards (2.7%–33.0%) (Abubakar et al., 2022). SSIs are the most common recognized HAI in the African region, accounting for 41.6% of all HAIs (Allegranzi et al., 2011).

With respect to ICUs, the prevalence of HAIs also varies considerably between countries. The prevalence has been reported to be as low as 5.2% in the USA, 6.8% in Australia and 8.4% among European ICUs (Blot et al., 2022). However, in LMICs, a higher prevalence of HAIs has been reported. This was 45.1% in Nigeria, 50.0% in India and > 50% in South Africa (Blot et al., 2022). Key factors associated with high prevalence rates for HAIs in LMICs include a lack of policies to reduce HAIs, poor adherence to infection prevention and control guidelines, inadequate hand hygiene and

a lack of ASPs to improve future antibiotic use (Phu et al., 2016; Salman et al., 2018; Sengupta et al., 2019; Shahida et al., 2016; Weinshel et al., 2015).

HAIs are also seen among children across countries associated with high morbidity, economic lose, increased length of hospital stay and readmission as well as increased mortality. For instance, in the USA, the economic loss associated with central line-associated bloodstream infections (CLABSI) cases among children was $55,646 along with increased length of stay up to 19 days compare to non CLABSI cases (Goudie et al., 2014). HCPs as well as parents and family members are enlisted to practice appropriate hand hygiene and other preventive practices to minimize HAIs in children (Gilbert & Cartwright, 2021). Zipursky et al reported that the prevalence of HAIs among 30 neonatal units in Canada was 11.7% (Zipursky et al., 2019). A Dutch study revealed that the prevalence of HAIs among children was 12.8% along with readmission of 5.8% compare to non-HAIs cases (Bekhof et al., 2019). Pneumonia, sepsis and gastroenteritis were frequent HAIs reported in a study among neonates in Vietnam (Peters et al., 2019). Singh et al concluded that hospital related diarrhea was reported in 37% children admitted in hospitals in India (Singh et al., 2022). In Brazil, the cost of hospitalization and length of hospital stay of HAIs cases reported in children was 4.2% and three times higher respectively compare to non HAIs cases (Leoncio et al., 2019). Rising AMR and hospital-associated drug-resistant infections (HARIs) are of great concern in terms of their impact on morbidity, mortality and economic loss (Cassini et al., 2016; Hofer, 2019; Murray et al., 2022). Consequently, need to be avoided where possible.

1.8 Antibiotics use/consumption in Pakistan

Excessive use of antibiotics has been reported throughout Pakistan with an increase of 67% from 2000 to 2018, similar to other South Asian countries (Browne et al., 2021). Pakistan's situation analysis report on AMR in 2018 also illustrated appreciable antibiotic consumption even in well-established public sector hospitals across the country (Global Antibiotic Resistance Partnership. The Center for Diseases Dynamics, 2018). According to this report, antibiotics sales/consumption of commonly used antibiotics, including amoxicillin-clavulanate and piperacillin-tazobactam, cephalosporins, carbapenems, vancomycin and tigecycline, fluroquinolones and macrolides, has increased in recent years. Published studies have revealed that > 70% (70.3%) of prescribed antibiotic among hospitals in Lahore, the capital city of Punjab, were inappropriate (Saleem, Saeed et al., 2019), with a similar high use of broad-spectrum antibiotics among cancer and other patients in hospitals in Pakistan (Saleem, Hassali, Hashimi et al., 2019; Saleem, Hassali, Versporten et al., 2019). Khan et al also reported high use of antibiotics among hospitalized patients in Islamabad, the capital city of Pakistan, where 100% prescriptions contained antibiotic (Khan et al., 2019). There have also been concerns regarding the prophylaxis use of antibiotics among hospitalized patents (> 64%) (Salman Khan et al., 2013), as well as extended prophylaxis adding to AMR (Butt et al., 2019; Khan et al., 2020; Mwita et al., 2021; Saleem, Hassali, Versporten et al., 2019). Alongside this, there has been excessive and inappropriate prescribing of antibiotics in ambulatory care in Pakistan, along with appreciable dispensing of antibiotics without a prescription including those from the 'Watch' and 'Reserve' category of antibiotics (Alam et al., 2023; Saleem et al., 2020; Saleem, Hassali, Godman, Hashmi & Saleem et al., 2019). In Lahore, more than 54% HCPs believed to dispense antibiotics in children in sore throat and 48.9%

in diarrhea (Rakhshani et al., 2022). A study from Quetta, Pakistan revealed that 69.8% upper respiratory tract infections (URTI) prescriptions contained at least one antibiotic and 18.2% contained macrolide group (Hashmi et al., 2021). Moreover, the sale of antibiotics without a valid prescription from a register medical practitioner is also frequent leading to excessive antibiotics use across communities. More than 90% antibiotics were dispensed without prescription in Hazara division in a recent study with commonly dispensed antibiotics being ciprofloxacin (46.5% of all antibiotics dispensed) followed by azithromycin (29.4%) (Ahmad et al., 2022).

1.9 Antibiotics use/consumption in children in Pakistan

Studies from different regions of Pakistan indicated high use of antibiotics in children across different indications. Hafeez et al. (2020) reported that 99.2% children were prescribed antibiotics in a six month longitudinal study in Lahore, the capital city of Punjab province (Hafeez et al., 2020). Another study conducted among six health facilities in Punjab revealed all hospitalized children under the age of 12 years were prescribed at least one antibiotic for common URTIs and only 11% of the study population were prescribed antibiotics appropriately (Mustafa et al., 2020). A further study from Punjab also demonstrated considerable prescribing (90%) of antibiotics among hospitalized children lower than five years age for lower respiratory tract infections (LRTIs) (Mustafa, Salman, Aslam et al., 2022). Sara et al. also found a high prevalence of antibiotic prescribing among hospitalized children at 94.6% of in-patients among five hospitals in the capital city of Punjab, Pakistan (Arif et al., 2021). Another study reported from Karachi, Pakistan, also showed high antibiotic prescribing rates among hospitalized neonates at 92.8% (Khalid et al., 2022). These published studies in well-respected Journals demonstrate considerable inappropriate

prescribing of antibiotics among neonates and children, which need to be addressed going forward to meet the goals of the National Action Plan (NAP) in Pakistan to reduce AMR.

1.10 Antimicrobial resistance situation in Pakistan

Pakistan is located in South-Asia with population of 240 million (5th largest country in the world in terms of population) and third largest consumer of antibiotics globally followed by India and China among LMICs (Aziz & Fang, 2019). As a result of the overuse of antibiotics, there is appreciable AMR in Pakistan, which is increasing (Saeed et al., 2021). Published studies from Pakistan have revealed that 91% of *E. coli*, 91.7% of *S. Typhi*, 90.9% of *Acinetobacte*r species, and 100% of *Klebsiella* species, were reported to be resistant to amikacin, fluoroquinolone, imipenem, and third generation cephalosporins, respectively (Qamar et al., 2014; Sohail et al., 2015; Sohail et al., 2016). Another systematic review revealed that that 90% *Salmonella* species in Pakistan were resistant to ciprofloxacin, > 70% of *Pseudomonas spp*. were resistant to ceftazidime and 96% of *Enterococcus spp*. were resistant to erythromycin (Bilal et al., 2021). Both multi-drug-resistant (MDR) and extensively drug-resistant (XDR) bacteria have been documented in different cities across Pakistan adding to mortality and rising costs (Atif et al., 2022; Butt et al., 2022; Ullah et al., 2016; Zakir et al., 2021). A recent study reported that throughout public and private sectors hospitals of Punjab, there was appreciable prevalence of MDR bacterial infections, i.e. *E. coli*, (74.44%), *P. aeruginosa*, (68.2%) *K. pneumoniae,* (71.37%), *S. aureus*, (51.38%) (Saleem et al., 2023). Another study from Lahore, Pakistan, showed that *A. baumannii* isolates had high levels of resistance to all antibiotics even to carbapenems (Altaf et al., 2023) .The first series of cases of XDR typhoid were reported in Pakistan in 2016

in the second largest province Sindh (Akram et al., 2020; Rasheed et al., 2019). Following this, 14,360 cases of XDR typhoid fever were reported in Karachi, the largest city of Pakistan in 2021 (Butt et al., 2022). These rising rates of resistant organisms need to be urgently addressed to reduce future morbidity, mortality and costs in the country.

Currently, in LMICs, up to 95% of antibiotics used in humans are being utilized in ambulatory care; consequently, their appropriate use in these facilities including PHCs is vital to address AMR (Duffy et al., 2018; Michael Sharland et al., 2022). This includes their appreciable prescribing for self-limiting conditions including for acute respiratory infections (ARIs) and URTIs (Alam et al., 2023; Godman et al., 2020; Massele et al., 2023; Mustafa et al., 2020). Consequently, it is important to concentrate on current antibiotic utilization patterns in PHCs in Pakistan and their impact to guide future policy and other initiatives to reduce AMR in the country. This starts with an understanding current utilization pattern across all sectors of care including PHCs, including neonates and children.

1.11 National initiatives in Pakistan to combat AMR

In line with the recommendation of the WHO, the Ministry of National Health Services Regulations & Coordination, Government of Pakistan formulated its National Action Plan (NAP) against AMR in 2017 (MoNHSRCG, 2017; Saleem et al., 2018) with the strategic priorities including,

i) Formulation and implementation of national awareness campaign and behavioral change strategy against AMR

ii) Establishment of an integrated national AMR surveillance system to document antibiotics use in human and animal.

iii) Improve infections prevention & control measures in health care, community, animal, food, agriculture and environment.

iv) Enforce regulations to ensure appropriate antimicrobial use in human and animal health

v) Discourage the use of antimicrobial agents for growth and suggest alternatives like prebiotics and probiotics for such purposes

vi) Integration of AMR in all public health research strategies

vii) Estimation of health and economic burden of AMR for policy and decision making

However, there are challenges in the implementation of NAP in Pakistan. These include the lack of robust healthcare delivery systems and policies in the country to ensure appropriate use of antibiotics, insufficient resources and trained personnels (Saleem, Godman, Azhar et al., 2022), which is similar to other LMICs (Charani et al., 2023; Godman et al., 2022; Iwu & Patrick, 2021).

1.12 Antimicrobial stewardship programs including in Pakistan

ASPs have been instigated across countries and sectors, including LMICs, to improve future antibiotic prescribing (Chigome et al., 2023; D'Arcy et al., 2021; Massele et al., 2023; Dilip Nathwani et al., 2019; Sono et al., 2023). There were concerns that ASPs were more difficult to perform in LMICs versus high income countries (HICs) due to concerns with available personnel and finances (Cox et al., 2017). ASPs are a coherent set of coordinated activities with the following objectives (Dyar et al., 2017; Kakkar et al., 2020; Mendelson et al., 2020).

i) Optimize the use of antibiotics

ii) Ensure appropriate behavioral changes in antibiotic prescribing and dispensing practices

iii) Improve quality of care and patient outcomes

iv) Save on unnecessary health-care costs

v) Reduce further emergence, selection and spread of AMR

vi) Prolong the lifespan of existing antibiotics

vii) Limit the adverse economic impact of AMR

viii) Build the best-practices capacity of HCPs regarding the rational use of antibiotics

ASPs ideally have three components. First, the system prerequisites include a defined structure of an ASP team, availability of guidelines, appropriate diagnostic facilities as well as necessary human and information technology resources (Mendelson et al., 2020). Secondly, to define what are the goals of ASPs including any targeted improvement in antibiotic use in a given health care setting. This includes the objectives of any ASP team such as encouraging appropriate use of antibiotics in terms of their optimal duration, frequency and route of administration in accordance with prevailing guidelines. Thirdly, how to achieve the predefined objectives of any ASP. This includes determining the quality improvement protocols that will be monitored during audit and feedback sessions performed by the team of professionals to improve the prescribing of antibiotics in the given sector and facility (Mendelson et al., 2020).

Core members of hospital ASPs typically include prescribers, pharmacists, infection preventionists, epidemiologists, quality improvement and safety staff, microbiology staff, nurses and information technology staff to optimize the use of antibiotics (WHO, 2019). A number of studies have shown that hospital-based ASPs have resulted in a reduction in antibiotic consumption, improvement in antibiotic

susceptibility, reduction in AMR and reduced costs (Nathwani et al., 2019; Al-Omari et al., 2020; Donà et al., 2020; Huang et al., 2022; Huebner et al., 2019; Onorato et al., 2020). According to the Organization for Economic Co-operation and Development (OECD), implementing ASPs together with other policies to reduce excessive antibiotics use, along with improving hygiene in hospitals settings, could save up to 1.6 million lives by the year 2050 and up to USD 4.8 billion per year among the 33 OECD countries (Co-operation & Staff, 2019). Consequently, ASPs need to be actively considered and implemented in hospitals across LMICs, including Pakistan, especially given rising AMR rates.

However, as mentioned, there have been concerns about implementing ASPs in LMICs due to financial and personnel constraints (Cox et al., 2017). This though is now changing with an increasing number of ASPs being undertaken in LMICs including Pakistan (Aiesh et al., 2023; Mahmoudi et al., 2020; Akpan et al., 2020; Gebretekle et al., 2021; Haseeb et al., 2023; Otieno et al., 2022; Saleem, Godman, Cook et al., 2022; Siachalinga & Mufwambi, 2022), with the numbers likely to continue growing.

Among hospitals in Pakistan, Mubarak et al. (2021) found that among public and private sectors hospitals in Punjab, nearly half of the hospitals surveyed had poor implementation of the Core Elements of Hospital Antibiotic Stewardship Programs (CEHASP) (Mubarak et al., 2021). None of the study participant hospitals out of fifty-three public and private hospitals in another study reported 'perfect' adherence towards CEHASP in tertiary care hospitals of Punjab (Raheem et al., 2020). A qualitative study among medical doctors in Punjab, Pakistan, also revealed that they possessed insufficient knowledge about ASP and its implementation (Atif et al., 2021b). Barriers to implementing ASP among study participants included a lack of workshops/training

session to improve antibiotics use and audit systems, insufficient updated knowledge about antibacterial therapy and lack of institutional infectious diseases treatment guidelines (Atif et al., 2021b). Insufficient support from hospital administration, lack of coordination among HCWs and training were also common barriers reported by nurses to implement ASP in hospitals in Punjab (Mustafa, Manzoor et al., 2022).

There is also currently a lack of national or institutional infectious diseases treatment guidelines across health facilities in the country adding to concerns about the potential to instigate appropriate ASPs to improve future prescribing (Khalid & Ali, 2020). As a result, there is misuse and over use of antibiotics across facilities and sectors. Moreover, diagnostic facilities, particularly the availability of culture and sensitivity testing facilities, is currently lacking in many public sector hospitals of Punjab (Hasan et al., 2022) increasing the rates of empiric prescribing. Appropriate activities surrounding the instigation of ASPs can potentially help address these concerns, starting with initiatives to enhance culture and sensitivity testing and documenting the rationale for any antibiotics prescribed.

A scoping review conducted by Berbieri et al. revealed the impact of pediatric ASPs from different regions including the USA, Europe and Asia (Donà et al., 2020). The majority of the studies (79.6%) showed that successful implementation of pediatric ASP led to reduction in inappropriate antibiotic prescribing (Donà et al., 2022).

However, overall, pediatric based ASPs are scarce among LMICs. These are urgently needed due to the differences in antimicrobial need and use among this patient population especially in LMICs including Pakistan, along with unique considerations of this population in terms of antimicrobial dosing, vulnerability for recurrent

infections and resistance due to a lifetime of antibiotic exposure (Nichols et al., 2017). This is beginning to happen (Donà et al., 2020, Klatte, 2020). Long term, children are vulnerable to develop life threatening adverse events from antimicrobial therapy including myelosuppression, renal impairment and hepatic impairment. Moreover, the prescribing of broad-spectrum antibiotics, particularly as empiric therapy in children, is common in conditions where narrow-spectrum can be used, adding to AMR (Melander et al., 2018). These issues need to be addressed to improve the care of children with infectious diseases to help meet the goals of the SDGs. In addition, the NAP goals.

1.13 Global antibiotics use/consumption and antimicrobial resistance during COVID-19 pandemic

During the pandemic caused by COVID-19, the threat of AMR has been further escalated due to excessive prescribing of antibiotics among patients with COVID-19 across all sectors, often with limited evidence of secondary bacterial infections and bacterial co-infections, with greater emergence and transmission of pathogens particularly Gram-negative organisms in hospital settings (Alshaikh et al., 2022; Sidra Khan et al., 2022; Langford et al., 2020; Langford et al., 2022; Nandi et al., 2023; Rothe et al., 2021; Ul Mustafa et al., 2021). This was particularly the case among LMICs across both primary and secondary care (Chowdhury et al., 2022; Elsayed et al., 2021; Iwu et al., 2020; Santosh Kumar et al., 2022; Sefah et al., 2021; Sulis et al., 2021). Another systematic review revealed that 74% hospitalized COVID-19 patients were prescribed at least one antibiotic during their hospital stay (Chedid et al., 2021).

A significant number of neonates and children hospitalized due to COVID-19 have also been inappropriately prescribed antibiotics across countries. A systematic

review conducted during the early phase of COVID-19 indicated that between 19.4% to 100% in children had been prescribed antibiotics during their hospitalization due to COVID-19 (Wang et al., 2020). The prevalence of antibiotic prescription among neonates and children in Latin America hospitalized with COVID-19 was reported to be >25% (Yock-Corrales et al., 2021), with similar high rates in Bangladesh and India often empirically (Chowdhury et al., 2022; Santosh Kumar et al., 2022). However, in Serbia, less than half (47.2%) of children hospitalization due to COVID-19 received antibacterial therapy (Prijić et al., 2022) providing guidance going forward. The over use of antibiotics in patients with COVID-19, including azithromycin, needs to be avoided to reduce the chances of resistance development with important antibiotics from the Watch list (Seabra et al., 2021)

1.14 Antibiotics use/consumption in Pakistan during the early stages of the COVID-19 pandemic and the implications

Various studies were conducted since the emergence of COVID-19 pandemic, which all showed an appreciable number of hospitalized COVID-19 patents had been prescribed antibiotics (Akhtar et al., 2021; Mustafa, Saleem et al., 2022; Ramzan et al., 2022; Ul Mustafa et al., 2024).

High levels of inappropriate prescribing need to be addressed going forward in Pakistan to reduce AMR (Rana et al., 2021; Zeshan et al., 2021). This includes during COVID-19 and subsequent pandemics. Consequently, suitable ASPs are needed to reduce excessive antibiotic prescribing in future pandemics, and thereby AMR (Sattar et al., 2021; Shaikh, 2021). Alongside this, strategies to enhance uptake of suitable vaccines, such as the COVID-19 vaccine, that can appreciably reduce the extent of

infectious diseases and subsequent over use of antibiotics, with a resultant positive impact on AMR.

1.15 Study Rationale

In view of identified concerns with high levels of inappropriate prescribing and dispensing of antibiotics in Pakistan, including during the first waves of the COVID-19 pandemic, it is critical for all key stakeholder groups in Pakistan to gain a greater understanding of current antibiotic utilization patterns and potential next steps to improve future antibiotic use in the country. This is a crucial step in reducing AMR as outlined in the WHO GAP and the NAPs including the NAP of Pakistan. There have been many issues and challenges with implementing the NAP in Pakistan (Saleem, Godman, Azhar et al., 2022); however, greater knowledge regarding current antibiotic utilization patterns across sectors coupled with knowledge and extent of AMR and ASPs among all key stakeholder groups, will help with the development and implementation of suitable ASP strategies. This is critically important among neonates and children in Pakistan especially given limited knowledge of antibiotic use in Pakistan for this and other age groups during the COVID-19 pandemic. Key issues surrounding the uptake and barriers associated with COVID-19 vaccinations are also important going forward to further reduce unnecessary antibiotic prescribing.

Consequently, the objectives of the PhD were firstly to assess current practices of antimicrobial use among neonates and children in hospital, as well as HAIs, across Punjab province. Subsequently, to assess the extent and knowledge of ASPs among pediatricians in Punjab province. Following this, assess antibiotic utilization patterns among children in ambulatory care, and key factors increasing inappropriate use, since this is where an appreciable proportion of children with infectious diseases are treated

in Pakistan. The pediatric population was chosen for this PhD as they currently account for an appreciable proportion of the population in Pakistan (UNICEF, 2020). In addition, they are a priority group given concerns with currently high mortality rates among neonates and children in Pakistan (Memon et al., 2023). Alongside this, we were aware that a considerable proportion of antibiotics prescribed and dispensed in children are for self-limiting conditions including ARIs/URTIs. The COVID-19 pandemic also took place during the PhD. Consequently, the initial concept of the PhD was adapted to also include studies of antibiotic use during the pandemic given concerns with the possible overprescribing of antibiotics with suspected or proven COVID-19 and the subsequent implications for AMR. This included a breaking down antibiotic use into the different AWaRe categories to assess current use, especially antibiotics from the Watch category, against WHO targets.

As mentioned, it was important to assess pediatricians' awareness, perception, preparedness and involvement in pediatric ASPs given their crucial role with influencing current and future antibiotic prescribing and dispensing in ambulatory care. Aspects of self-medication with antibiotics, as well as awareness and practices of antibiotic use among parents of the hospitalized neonates and children, were also assessed during the PhD as parents can also appreciably influence antibiotic prescribing in ambulatory care in LMICs. These interconnecting themes, and their outputs, provide the basis for this PhD.

This will be an iterative process given the paucity of information regarding Pakistan prior to starting the PhD, especially surrounding COVID-19 as well as classifying antibiotics by the AWaRe classification, as outlined in the Introduction. Alongside this, a number of secondary studies were also conducted during the PhD in view of critical issues surrounding COVID-19, its management and prevention, in

view of the considerable impact on antibiotic use and AMR in Pakistan and other LMICs. Again, this was an iterative process.

1.16 Study Objectives

The following primary studies were undertaken in Punjab as primary studies during the course of the PhD in line with rationale of the PhD. The objective was to provide future direction to all key stakeholder groups in Pakistan. The ultimate aim is to improve antibiotic utilization among neonates and children, thereby helping to reduce AMR in the country:

1.16.1 To determine antimicrobial use among neonates and children in selected public sectors hospitals of Punjab

1.16.1(a) To determine antimicrobial use through point prevalence survey in public sector children's hospitals

1.16.1(b) To determine antimicrobial use through point prevalence survey in the children's wards of public sector tertiary care hospitals

1.16.2 To assess prevalence and factors associated with the development of HAIs among hospitalized neonates and children in public sector hospitals in Punjab

1.16.3 To determine antibiotics prescribing practices among neonates and children hospitalized due to COVID-19 among health care facilities in Punjab