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Microbiological and Susceptibility Profile of Clinical Gram Positive Isolates at a Tertiary Pediatric and Maternity Hospital in Ulaanbaatar, Mongolia

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Abstract

Introduction: Information on microbiological and susceptibility profiles of Monoglian bacterial isolates is scarce. Resistance profiles, patient demographics and microbiological work-up of gram positive isolates were analyzed in order to develop infection control activities and policies at the National Center for Maternity and Children's Health (NCMCH) in Ulaanbataar, Mongolia.

Methods: All gram positive isolates of specimens submitted to the microbiology laboratory at NCMCH between January 2014 and August 2017 were included. Data collected included demographic data, specimen type, in-/outpatient status, hospital ward of sample origin, and antimicrobial susceptibility testing profile. Susceptibility testing was performed by trained microbiologists at the NCMCH microbiology laboratory. T-test, Mann-Whitney, Chi-square and Fisher exact tests were used as appropriate.

Results: Of 11,889 isolates, 4012 (33.7%) were gram positive, with most identified as S. aureus (62.6%, n=2512). Rates of methicillin resistance (MRSA) remained stable at a quarter, but was significantly higher among inpatients (inpatients: 630/2002, 31.5%; outpatients 67/290, 23.1%; $p \leq 0.05$) and sterile site isolates (sterile: 83/171, 48.5%; non-sterile: 416/1678, 24.8%; $p \leq 0.01$). The vast majority of S. pneumoniae isolates (12/14; 85%) was found to be penicillin resistant by oxacillin disk diffusion. While identification of Group B streptococci was rare (n=137) due to of lack of diagnostic measures available, the number of enterococcal isolates identified increased signifi-cantly due to implementation of improved microbiological work-up (2015: n=7; 2016: n=26; 2017: n=83).

Conclusion: Compared with published studies from neighboring nations, the rates of antimicrobial resistance among gram positive isolates at NCMCH, particularly with respect to S. aureus and S. pneumoniae, were much higher. Further improvement of microbiological diagnostics and collabo-ration of stakeholders is required to address the pressing infection control and stewardship issues and to ensure reliable identification of relevant pathogens in Mongolia.

Keywords: *Child Health; Women Health; Communicable Diseases; Epidemiology; Maternal and Child Health; Mongolia*

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Research

Introduction

Gram positive organisms (GPO) include some of the most clinically relevant bacteria, such as *S. aureus*, *S. pneumoniae* and enterococci, which can cause a wide array of serious infections among hospitalized and community patients[1].

The WHO estimates that globally, 700,000 deaths each year are directly attributable to antimicrobial resistance (AMR), based on AMR data from Asian countries of the Western Pacific Region of the WHO (WPRO), including China, South Korea, and Malaysia[2,3]. This report emphasizes the need for the development of the national action plans for all nations, while underscoring the importance of the multidimensional One Health approach encompassing health care sector, public, veterinary, agricultural, environmental, and food sectors, as well as financial stakeholders[4]. A National Action Plan for Mongolia was approved in 2017[5]. AMR in Asia is increasing at alarming rates[6-9], with little data availible on the susceptibility patterns of gram positive organisms in Mongolia. Mongolia is a vast country with an area of 1,500 million km^2 and just over three million inhabitants featuring one of the lowest population densities worldwide. Half of the population lives in the capital Ulaanbaatar, while the rest inhabits rural areas, many following the traditional nomadic lifestyle of Mongolian herders[10].

In recent years, Mongolia has experienced rapid economic growth and modernization, especially in Ulaanbaatar. Contrasting this, many parts of the country remain extremely remote and difficult to access. This poses significant challenges to the introduction of antimicrobial surveillance and infection control, staff education and diagnostic tools, enforcement of drug regulation and auditing of prescription practices[10,11]. In a community-based survey, over 70% of children had received antibiotics in the preceding six months, more than half of which had not been prescribed by a healthcare professional[12]. In 2018, the WHO released its first global report on the consumption and use of antibiotics, and Mongolia recorded the highest consumption among the six Western Pacific Region countries that submitted the data. A high burden of infectious diseases, such as respiratory and genitourinary infections, tuberculosis and sexually transmitted diseases, high usage of over-the-counter antibiotics, and widely prevalent antibiotic use based on self-diagnosis are among the contributing factors[12,13]. Multidrug-resistant GPOs are a growing concern in other Central Asian countries[14].

The paucity of data on susceptibility patterns of GPOs in Mongolia impacts the development of infection control practices, antimicrobial stewardship, and poses a significant public health concern.

The National Center for Maternal and Child Health (NCMCH), Ulaanbaatar, is the country's largest governmentrun pediatric and maternity hospital, and national tertiary referal center. The pediatric hospital accommodates 19 medical and surgical subspecialties, 320 inpatient beds, and provides treatment for approximately 40,000 inpatients and over 175,000 outpatients per year. The adjacent maternity hospital has 250 inpatient beds providing gynecological and obstetric care, with just under 12,000 deliveries annually[15]. The NCMCH is the first Mongolian center to publish its data on gram positive AMR internationally.

The goal of this study was to identify areas in need of further improvement in diagnostic microbiological work-up, surveillance of resistant organisms, enabling development of antimicrobial treatment guidelines, and improvement of infection control practices.

Methods

Data collection

All gram positive isolates of specimens submitted to the microbiology laboratory at NCMCH between January 2014 and August 2017 were included. Data collection began with the introduction of routine electronic data collection in 2014. Data were collected retrospectively (2014-2017) and prospectively (2017) using WHONET vs. 5[16], an electronic laboratory

Organism	2014	2015	2016	2017	Total
S. aureus	414 (47.0%)	1036 (64.7%)	750 (70.6%)	312 (66.5%)	2512 (62.6%)*
Coagulase negative staphylococci	267 (30.2%)	432 (27%)	252 (23.7%)	45 (8.9%)	996 (24.8%)*
Group B streptococci	19 (2.2%)	116 (7.2%)	3 (0.3%)	0	138 (3.4%)*
Viridans streptococci	102 (11.6%)	8 (0.5%)	10 (0.9%)	3 (0.6%)	123 (3%)*
Enterococcus spp., unidentified	4 (0.5%)	4 (0.2%)	22 (2.1%)	83 (17.7%)	113 (2.8%)*
Group A streptococci	58 (6.6%)	1 (0.1%)	10 (0.9%)	18 (3.8%)	87 (2.2%)
S. pneumoniae	4 (0.5%)	4 (0.2%)	10 (0.9%)	8 (1.7%)	26 (0.6%)
Micrococcus spp.	11 (1.3%)	0	0	0	11 (0.3%)
E. faecalis	1 (0.1%)	0	4 (0.4%)	0	5 (0.1%)
E. avium	0	0	1 (0.1%)	0	1 (0.0%)
Total	880	1601	1062	472	4012 (100%)

*significant differences in annual isolation frequency (P≤0.05), for the five most frequently identified organisms per year

Table 1. Species identification of gram positive isolates.

database made available by the WHO. Data collected included demographic data, specimen type, in-/outpatient status, hospital ward of sample origin, and antimicrobial susceptibility testing (AST) profile. Organisms identified by means other than culture (ie. latex agglutination) were not included (n=13). In cases of an identical organism being isolated from a patient within 30 days, only the first isolate was included.

Susceptibility testing

Susceptibility testing was performed by trained microbiologists at the NCMCH microbiology laboratory.

Instances where NCMCH laboratory AST differed from Clinical Laboratory Standards Institute (CLSI) guidelines are specifically indicated[17-19]. Additions or omissions to standard test panels are indicated separately. Susceptibility interpretation is reported as per CLSI 2016 guidelines[17]. Fully resistant and intermediately susceptible isolates (%I/R) are reported as one category. Only species with a minimum of 30 isolates annually were used to test for antimicrobial succeptability[18]. Reports on isolates with less than 30 isolates per year are explicitly specified. Molecular detection of organisms or susceptibility status was unavailable.

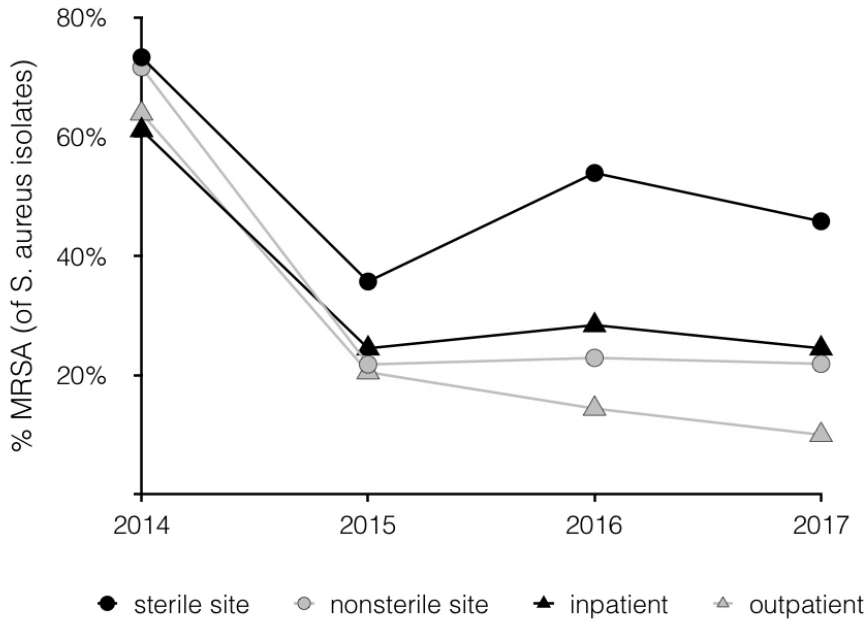

Figure 1. The prevalence of Methicillin-resistant Staphylococcus aureus in 2014-2917

While both CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) now recommend induction of the mecA gene with cefoxitin[19-23], the NCMCH relies on Oxacillin disk diffusion (DD) for diagnosis of methicillin resistant *S. aureus* (MRSA); hence these results were interpreted as per CLSI 2006 guidelines[22]. Vancomycin resistance testing was done by DD. As no broth microdilution data was available, organism rates with DD diameters ≥15 mm on a 30 mcg Vancomycin disk were reported as susceptible (VSSA), the remaining as vancomycin resistant *S. aureus* (VRSA)[22-23]. In *S. pneumoniae* isolates, penicillin susceptibility was tested on 1 mcg Oxacillin disks. As no broth dilution was done, meningitis breakpoints and cephalosporin susceptibilities are not reported[20,22,24]. The ethics committee at NCMCH approved this study.

Statistical analysis

Quantitative variables were reported as absolute numbers and percentages. For continuous variables, comparisons between groups to test equality were performed using the t-test or Mann-Whitney test when appropriate. Tests of association between categorical variables were based on Chi-square and Fisher Exact Tests. All *P* values reported are two-sided and were considered statistically significant if $P<0.05$. Statistical computations were performed using SPSS 22.0 (SPSS Inc. Chicago, Illinois).

Results

Of 11,889 isolates, 4012 (33.7%) were gram positive (Table 1). Neonatal samples accounted for n=951 (23.8%); pediatric samples for n=2,010 (50.2%), and adult samples from patients ages ≥18 years for n=1,043 (26.0%) of isolates. Three quarters of specimens originated from wound and surface swabs (26.3%), genital swabs (28.2%), urine (21.2%); and 598 (5%) from blood cultures. The remaining samples (7.6%) were obtained from respiratory secretions, cerebrospinal fluid,

S. pneumoniae (n, non-meningitis breakpoints)			2014	2015	2016	2017	Total
Oxacillin 1mcg disk, zone diameter in mm	not done		3	4	3	2	12
	resistant	8	0	0	0	1	1
		10	0	0	0	1	1
		14	0	0	1	0	1
		≤19	1	0	5	3	9
	susceptible	23	0	0	0	1	1
		25	0	0	1	0	1
	Total		4	4	10	8	26
Vancomycin 30mcg disk, zone diameter in mm	not done		2	2	0	0	4
	resistant	16	0	0	1	0	1
		17	0	0	1	0	1
	susceptible	≥17	2	0	0	0	2
		18	0	0	0	1	1
		20	0	0	2	3	5
		22	0	0	0	3	3
		25	0	0	3	1	4
		26	0	2	2	0	4
		29	2	0	1	0	3
	Total		4	4	10	8	26

Table 2. Interpretation of susceptibility data by non-meningitis breakpoints of S. pneumoniae isolates.

joint and pericardial aspirates, and stool samples. The source of specimen could not be determined in 11.7% of cases. Two thirds of isolates (n=2,512; 62.6%) were identified as *S. aureus;* mostly from inpatients (86%, 2,171/2,478). Oxacillin susceptibility was available in 92.5% (2,320/2,512) of isolates; two thirds (69.8%, 1,620/2,320) were methicillin susceptible (MSSA), the remainder resistant (MRSA). Whilst in 2014 high rates of MRSA (60%, 224/377) were observed, they remained stable thereafter at approximately one quarter (Figure 1). MRSA was significantly more common among inpatients compared to outpatients (MRSA inpatients: n=630/2,002, 31.5%; outpatients: n=67/290, 23.1%; P=0.04). MSSA predominated on surface swabs (78.3%, 875/1,117) and other non-sterile site cultures (82.0%, 128/156); whereas *S. aureus* positive blood cultures grew

MRSA in 44.5% (23/53). The MRSA rate among sterile samples was overall higher (sterile: n=83/171, 48.5%; non-sterile: n=416/1,678, 24.8%; *P*=0.01; Figure 1) and increased significantly over the study period (*P*=0.02). The exception were swabs taken from burns, where MRSA accounted for 78% (40/51) of staphylococcal isolates.

Vancomycin susceptibility was available for 88.1% (n=661/750) of *S. aureus* isolates in 2016 and 97.4% (n=304/312) in 2017. Resistance was reported in six instances, originating from the maxillofacial (n=4/6) and pediatric intensive care units (n=2/6). Non-reliable vancomycin susceptibility was more frequently documented in 2014/15 when staff had just started to undergo training, and quality control was being established for vancomycin susceptibility testing. Hence, vancomycin susceptibilities from 2014-2015 were not used for clinical management and are therefore not reported. Teicoplanin and daptomycin were not included in the test panel. Susceptibilities to clindamycin, rifampicin, or cotrimoxazole were only tested in a minority of isolates.

Isolates of coagulase negative staphylococci (CoNS) (n=996) were comprised of *S. epidermidis* (85.5%, n=851), *S. xylosus* (n=12), *S. saprophyticus* (n=1), *S. auricularis* (n=1), *S. sciuri* (n=4), *S. hominis* (n=1), *S. hemolyticus* (5.3%, n=53), *S. lugdunensis* (n=1), *S. warneri* (n=1) and other, not further identified CoNS spp. (6.7%, n=71). Sample origin was available for 75% (744/996) of isolates. Of those, 9% (n=67/744) were sterile sites isolates, mostly (n=52/67) from blood cultures. Most originated from pediatric patients (75.8%), mainly from wound swabs. A substantial proportion (16.8%, n=167/996) did not undergo susceptibility testing. Cefazolin susceptibilities were available for 88.8% (n=884/996), 10.9% of which were resistant. Vancomycin susceptibilities were available for 83.2% (n=829/996), of which 11% (n=12/829) were resistant, all identified between 2014 and 2015. Since 2016, no vancomycin resistant CoNS were identified.

Despite identification of Group B Streptococci (GBS) being mostly outsourced to another facility, 137 GBS isolates were identified; 66 in children, 47 in adults, only twelve from neonatal isolates. In adults, GBS was mostly isolated from respiratory tract or wounds. Among n=716 urinary and n=3,313 genital tract samples from adults, only three uterine and one urinary sample were identified as GBS, the majority of isolates from these sites were gram negatives.

Group A streptococcus (GAS) isolates were mainly found in nasopharyngeal specimens (59.8%; n=52/87); a quarter (n=10/46) of pediatric GAS isolates had been sampled from burns. All GAS isolates tested (n=48/60) were penicillin susceptible.

Viridans streptococci or not further identified *Streptococcus spp*. originated mainly from respiratory and oral specimens. Penicillin susceptibility was tested by oxacillin disk diffusion, which is not recommended for viridans streptococci and hence not reported. However, disk diffusion is acceptable for testing of cephalosporin susceptibilities: 16.5% (n=15/91) were reported as not susceptible to cefotaxime, 0.7% (n=6/86) as not susceptible to ceftriaxone.

Among 26 isolates of *S. pneumoniae*, five were blood stream- and six Cerebrospinal Fluid (CSF) isolates, the remainder originated from wound and eye swabs, all in children. Approximately half (n=14/26) underwent pencillin susceptibility testing by oxacillin disk diffusion. The majority 85.7% (n=12/14) were identified as resistant by this method, confirmation by Minimum inhibitory concentrations (MIC) testing was not available. Nearly all *S. pneumoniae* tested for vancomycin (n=20/22) were found to be susceptible with the exception of a neonatal eye swab and a pediatric wound isolate. Among CSF isolates, susceptibilities could not be retrieved in 4/6 instances, the remaining two were penicillin resistant per oxacillin disk when considering non-meningitis break points. Vancomycin susceptibilities however were available for all, and

vancomycin susceptibility with zone diameters exceeding 17 mm was universal.

While in 2014 and 2015 only ten enterococcal isolates were identified, there were 26 in 2016 and 83 in 2017, reflecting that standardized diagnostic measures for enterococcal identification were introduced in October 2016. Most (n=113/119) were reported as *Enterococcus spp*. and not further identified, five as *E. faecalis*, and one as *E. avium*. They originated equally from children (n=64) and adults (n=52). Six of 97 isolates that underwent vancomycin susceptibility testing were resistant, all of them sampled from adult outpatients. Ampicillin susceptibility was not documented even though it constitutes the antibiotic of choice. Gentamicin susceptibility was universal for all available (n=25/119), though specific testing for high-level enterococcal resistance was not done.

Discussion

This study is the largest report on the susceptibility profile of gram positive isolates from clinical specimens in Mongolia to date. The results highlight important points on the epidemiology of gram positive pathogens in Mongolia. Rates of MRSA remained stable at approximately one quarter overall. Methicillin resistance in S. aureus isolates from inpatients and sterile site specimens howvere increased. Hence, MRSA spread appears to be mainly nosocomially driven. The isolation of enterococci increased dramatically, reflecting improved diagnostic means. *S. pneumoniae* was frequently identified as penicillin resistant, a finding that bears important clinical relevance.

In addition to the large sample size and a patient cohort representing patients of all ages and given the NCMCH is a tertiary referral center for patients from across all of the Mongolia, data were collected consecutively over several years, thereby enabling an observation over time. During the data collection period, several changes were implemented in order to improve diagnostic processes, quality control, and staff training. However, this also means that the study has important limitations. Adjustments made to microbiological diagnostics are reflected in a changing species and susceptibility profile over the study period. Susceptibility panels remained dependent on locally available equipment and antimicrobials used in clinical practice[18,20]. It is recognized that this will require ongoing adjustments, which are often subject to financial constraints.

The study identified a need for further implementation of improved diagnostics through modernized equipment and staff training, in order to enable accurate identification of a wider range of gram positive pathogens. This need is currently being addressed.

As a country at the threshold of developing into a modern state, Mongolia's health care system has a unique opportunity to apply modern technology and therapeutic options, while facing new challenges in surveillance, governance, and stewardship policies. This situation is exemplified by the increasing use of antimicrobial agents for nosocomial infections in intensive care settings and the resulting spread of multidrug resistant organisms. Clinicians are increasingly confronted with the complications of modern intensive care medicine, expansion of intensive neonatal care, and surveillance of changing epidemiology of childhood infections as vaccination schedules are changing. An important gram positive vaccine preventable pathogen, *S. pneumoniae*, was not commonly identified. However, the majority of isolates available for analysis were penicillin resistant on oxacillin disk testing. This method may underestimate non-reliable penicillin susceptibility[18,24]. MICs to penicillin and vancomycin were unavailable, and while reliable conclusions regarding penicillin susceptibility cannot be drawn based on this data alone, the results should caution Mongolian clinicians against the use of

beta-lactam monotherapy in pneumococcal meningitis, especially in the absence of universal and reliable cephalosporin susceptibilities [24,25]. These findings are in agreement with recent reports from the Russian Federation, where a survey identified 28% of pneumococcal isolates as penicillin resistant[26]. By contrast, among *S. pneumoniae* isolates in Kazakhstan[27], penicillin susceptibility was almost universal.

Pneumococcal vaccination of infants has recently been introduced to targeted populations in Mongolia but is not universal yet[28]. In the coming years, more widespread pneumococcal vaccination is likely to change the epidemiology of pneumococcal infections in Mongolia. Therefore, reliable identification, susceptibility testing and serotyping of S. pneumoniae in order to monitor vaccination impact must be ensured.

A GBS screening program is not currently performed in Mongolia, hence the data presented is not representative of GBS carrier or infection prevalence among women or neonates in Mongolia. The lack of laboratory exposure to GBS diagnostics may explain the unusual susceptibility patterns, including the report of seven cephalosporin resistant isolates. Misidentification cannot be ruled out, however it should be noted that penicillin and cephalosporin susceptibility is no longer universal for GBS, particularly in Asia[29,30]. More data on GBS epidemiology in Mongolia is currently being assimilated and molecular testing will become part of the NCMCH's laboratory strategy by the end of 2019. Once in place, a guideline for risk stratification of fetomaternal and neonatal management will be introduced.

Enterococcal identification was introduced in 2016, and universal testing for aminopenicillin, gentamicin, and vancomycin susceptibility is currently being introduced. The increase in enterococcal identification underscores the significant impact of improved diagnostics on the accuracy of institutional species composition and treatment considerations.

In previous years, limited data available on *S. aureus* in Mongolia identified a rate of 9% of methicillin resistance and of 28% of multidrug resistance in 2007 and 2011[31]. Sample origin was only known for 21% of isolates in this study. Our data shows a much higher rate of MRSA, possibly as a result of a greater number of sterile samples from hospitalized patients, though a comparison of the two studies is difficult. Our findings may also be indicative of a significant rise in the proportion of MRSA among *S. aureus* isolates in Mongolia over time. Comparison with a similar institution in the neighboring nation of Kazakhstan shows that rates of MRSA in Mongolia are strikingly higher. In Kazakhstan, 95 to 100% of S aureus isolates were reported as oxacillin susceptible[32], of our isolates, one third were methicillin resistant. In Russian Siberia, nosocomial MRSA rates among *S. aureus* are more comparable at a rate of 22%, though community rates of MRSA in Siberia were reportedy much lower (2.9%) than we identified in outpatients attending the NCMCH.

In relation to the community acquired infections, Mongolia's unique position as country where animal husbandry and nomadic herders' lifestyle applies to much of the population remains to be investigated. Over 700 drugs are registered and commonly used in livestock production. AMR monitoring in the livestock and food supply is critical in order to control AMR development. Laboratories routinely examine food for food borne pathogens, however AMR testing is not yet systematically conducted throughout the food chain[32]. A Mongolian Food Chain AMR monitoring system piloted in 2016 with WHO support revealed that food borne pathogens found in animal products and animal production facilities were commonly resistant to antimicrobials with a high proportion of multidrug-resistance. In another study, almost half of food items tested MRSA positive[33]. This highlights that in addition to infection control in the hospital environment, AMR is an issue that requires an integrative and collaborative approach of multiple agencies[34]. Susceptibility testing for gram positive isolates at NCMCH is now performed

following a more standardized approach, and staff training is ongoing. Cefoxitin disk testing for MRSA identification has been introduced at NCMCH and follow-up data is being collected. Vancomycin susceptibility testing has been included from 2016. Of the six *S. aureus* isolates exhibiting non-reliable vancomycin susceptibility, all but one were methicillin susceptible, contrasting the fact that most studies have identified that the majority of vanA or vanB positive *S. aureus* isolates to be also methicillin resistant. VanA/B/C acquisition is increasingly recognized to occur irrespective of methicillin susceptibility[33,35]. In the future, isolates found to be vancomycin resistant will be tested for extended antimicrobial susceptibilities. Susceptibility testing will aim to include vancomycin susceptibility by MIC into testing of all invasive *S. aureus* isolates, with an implementation deadline by the end of 2019.

Our study constitutes the largest published record of clinical gram positive isolates in Mongolia. The results emphasize the importance of consequent surveillance and urgent attention to strategies that that allow rapid diagnosis of gram positive infections; a difficult task Mongolia shares with other countries in the area experiencing rapid and profound societal and economic change. Compared with studies from neighboring nations, the rates of AMR among gram positive isolates at NCMCH, particularly *S. aureus* and *S. pneumoniae*, were much higher. As a nation with significant livestock populations, AMR monitoring must be embedded in an approach that involves both the public and veterinary sector as well as healthcare facilities. International collaboration is critical to address these issues.

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