ANTIBIOTICS' SUSCEPTIBILITY PATTERNS OF BACTERIAL ISOLATES CAUSING LOWER RESPIRATORY TRACT INFECTIONS IN ICU PATIENTS AT REFERRAL HOSPITALS IN NAMIBIA

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ABSTRACT

Introduction: LRTIs are a particularly important problem in Namibia, as they are rated the second leading cause of death in the country and cause around 300 deaths in children under 5 years in 2016. To reduce the burden of Lower Respiratory Tract Infection (LRTIs) on health systems and ensure appropriate patient management, it is critical to know the most prevalent pathogens leading to LRTIs and the susceptibility patterns of those pathogens in the local setting. **Aim:** To formulate cumulative antibiograms for ICUs of referral hospitals in Namibia for the period studied. **Methods:** This retrospective analytical cross-sectional study was conducted over two years: 2017 and 2018. The cumulative antibiograms were constructed according to CLSI guidelines and the chi-square test was used to compare the changes in susceptibility rates from 2017 to 2018. The data used to develop the cumulative antigrams was obtained from NIP. **Results:** *Klebsiella pneumoniae* (8.8%, 8.1%) was a predominant pathogen in Windhoek Central hospital ICU in 2017 and 2018. In Oshakati intermediate hospital ICU, *Enterobacter sp*. (22.2%) and *Pseudomonas aeruginosa* (37.5%) were the common pathogens in 2017 and 2018. *Acinetobacter baumannii* isolates were > 90% susceptibility to colistin, carbapenems and tigecycline in 2017. In 2028, *Acinetobacter baumannii* isolates were highly susceptibility to amikacin, carbapenems and colistin, but moderately susceptible to tigecyclines. In 2017, *Klebsiella pneumoniae* isolates were more susceptible to carbapenems (imipenem 94% and meropenem 93.8%), amikacin 89.3% and tigecycline 88.7%. In 2018, *Klebsiella pneumoniae* isolates were 100% susceptible to amikacin, colistin and carbapenems. *Stenotrophomonas maltophilia* isolates were more than 80% susceptible to all the tested antibiotics. *Staphylococcus aureus* isolates were 100% susceptible to linezolid, rifampicin, teicoplanin, vancomycin in 2017 and 2018, its susceptibility to these antibiotics did not change. **Conclusion:** The susceptibility patterns of the common isolated gram-negative pathogens were highly variable. Meropenem combined with gentamicin, is now the recommended empiric therapy for patients with LRTIs in Windhoek Central hospital ICU.

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ABBREVIATIONS

CLSI	Clinical and Laboratory Standards Institute
ESKAPE	*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp.*
ICU	Intensive Care Unit
LRTIs	Lower Respiratory Tract Infections
NIP	Namibia Institute of Pathology

DEFINITIONS

Antibiogram- is defined as a laboratory report that shows the susceptibility profile of a bacterial isolate to different usually tested and used antibiotics in a specified period (1,2)

Antibiotic susceptibility pattern- defined as a sequence observed when isolates growth is inhibited by the presence of antibiotics at the recommended doses for that site of infection (3).

Cumulative antibiogram **i**s a cumulative report that lists the percentage of isolates susceptible to different antibiotics using data from the patients receiving care at a particular institution over a defined period of time (2).

Referral hospital- a hospital that provides complex clinical care to patients referred from clinics, health centres and district hospitals

Susceptible is when the growth of micro-organisms is inhibited in the presence of an antimicrobial drug used at the recommended dose to treat that infection (4)

ACKNOWLEDGEMENT

I would like to express my gratitude to my research supervisors for their expert guidance and support in the whole process. I would like to acknowledge the School of Pharmacy academic staff for making time to review my research work, I really value the guidance you provided. Finally, I appreciate the Namibia Institute of Pathology (NIP) staff members giving me the data needed for my research on time.

DECLARATIONS

I, Pia Nashinyeuvo Simeon, hereby declare that this study is my own work and is a true reflection of my research and that this work or any part thereof, has not been submitted for a degree at any other institution.

Pia Simeon	Simeon	September 2022
Name of Student	**Signature**	**Date**

INTRODUCTION

Background

Lower respiratory tract infections (LRTI) are the sixth leading cause of death globally (5). In 2016, the global death toll of LRTIs was about 2.38 million. Of these 47.4% occurred in sub-Saharan Africa (5). LRTIs are a particularly important problem in Namibia, as they are rated the second leading cause of death in the country (6) and cause around 300 deaths in children under 5 years in 2016 (7). In 2015, a third of health funds were spent on infectious and parasitic diseases in Namibia, with respiratory infections accounting for 10% (8). LRTIs deaths can be prevented or their rates reduced with the appropriate use of antimicrobials (9).

To reduce the burden of LTRIs on health systems and ensure appropriate patient management, it is critical to know, 1). the most prevalent pathogens leading to LRTIs; and 2). the susceptibility patterns of those pathogens in the local setting (10). Studies on respiratory tract infections revealed that bacterial susceptibility differs locally and changes with time (11,12). To effectively manage LRTIs, adequate, updated, and good quality data about susceptibility patterns of the causative organisms are needed (11).

Little is known about the prevalence and susceptibility of pathogens causing LRTIs in ICU patients in Namibia. Therefore, this study will reveal the common pathogens that caused LRTIs and formulate the requisite cumulative antibiogram for intensive care units (ICU) in Namibia's referral hospitals for the period studied.

Statement of the problem

The emergence of antimicrobial resistance in ICUs poses a massive challenge in managing LRTIs, as it has been associated with treatment failure (13,14). Infections caused by *P. aeruginosa* are challenging to manage due to the organism's intrinsic resistance (15), yet *P. aeruginosa* became the most frequent (35.3%) cause of infections in ICU in Nepal (16). In that regard, understanding the epidemiology of the most prevalent bacterial infections is critical for designing the appropriate empirical antibiotic regimens (17). In Namibia, pathogens' epidemiology and susceptibility patterns causing LRTIs in hospitals have not been comprehensively studied. Neither literature about the pathogens responsible for LRTIs in ICUs nor their susceptibility patterns were found. Therefore, the need for a hospital antibiogram, a tool used to guide antibiotic empiric therapy and monitor trends in antibiotic resistance, motivated this study.

Objectives

General objectives

To formulate the requisite cumulative antibiograms for ICUs in referral hospitals in Namibia for the period studied.

Specific objectives

i. To identify the common pathogens causing LRTIs in ICU at a referral hospital in Namibia.
ii. To describe antibiotic susceptibility patterns of each of the pathogens commonly causing LRTIs.
iii. To formulate a cumulative antibiogram against the pathogens commonly causing LRTI in the ICUs in referral hospitals in Namibia.

Significance of the study

The results of this study will determine the need for and possibly generate interest in conducting similar studies and/or encourage active surveillance of antibiotic susceptibility in Namibia. The knowledge gained can be used to build the capacity at local levels to allow hospital-based decisions on the appropriate empiric antibiotic use. The application of this study's results may positively benefit therapeutic outcomes by avoiding inappropriate empirical use of antibiotic therapy, which may advertently reduce the emergence of antimicrobial resistance and associated health costs.

Limitation of the study

This study used secondary data for analysis, hence some demographic information was missing. There might have been multiple samples of the same strain of bacteria from the same patient in the database. However, only one sample per isolate species per patient was included in the analysis.

Delimitation of the study

Only the lower respiratory specimens from ICU patients at referral hospitals in Namibia were considered therefore, the findings of this will not be generalised to other hospitals or wards.

LITERATURE REVIEW

The research articles that are included in the literature review of this study were found in the following databases: PubMed, Cochrane and Google Scholar. The search terms that were used included: "antibiogram research studies AND Namibia", "lower respiratory tract infections in ICU Africa OR developed countries", "susceptibility patterns of pathogens causing lower respiratory infections in ICU", "cumulative antibiograms", "empiric antibiotic therapy", "WHONET", "antimicrobial resistance in ICU".

Common pathogens and lower respiratory bacterial susceptibility

The Global Burden of Disease Study evaluated the evidence for the global, regional, and national morbidity and mortality associated with LRTIs reported that more than half of the LRTIs were caused by bacteria in Africa (5). The respiratory pathogens causing LRTIs and their susceptibility to antibacterial agents may differ by geographical area.

A multi-centred retrospective study conducted in the United States of America (USA) found that *P. aeruginosa* (36.2%) was the most common pathogen, followed by *K. pneumoniae* 12% and *E. coli* 11% (18). In this study 21.6% of *P. aeruginosa* isolates were multidrug-resistant and a quarter of *K. pneumoniae* isolates were resistant to carbapenems (18). Laboratory results were the source of the susceptibility data.

A study that was conducted in Romania recorded similar prevalence findings. The authors studied the resistance profiles of nosocomial ESKAPE (*E. coli, S. aureus, K. pneumoniae, P. aeruginosa, A. baumannii, E. faecium, Enterobacter spp*.) pathogens by assessing all the antibiograms of the ESKAPE pathogens from healthcare records. In this study, *A. baumannii,* at 77%, was the most common pathogen. The second most frequent pathogen was P. aeruginosa: 60%, of which a third of the isolates were from ICU and surgery wards (19), followed by *Klebsiella spp.* at 35%, *S. aureus* 29%, and *Enterococcus spp*. Of the *P. aeruginosa* isolates from ICU 95% were susceptible to colistin, while around 40% of its isolates were susceptible to other antibiotics (19). *A.baumannii,* was poorly susceptible to all tested antibiotics (<30%) except colistin, to which the organism was 98.5% susceptible (19). Around 50% or more of the *K. pneumonia* isolates were susceptible to carbapenems and only 1.86% were susceptible to ampicillin (19).

A study conducted in a similar treatment setting in Egypt discovered a different prevalence pattern from that of Romania. This study found that *K. pneumonia* (33.5%), *Staphylococcus spp*. (23.2%) and *E. coli* (19.3%) were the commonest bacteria isolated from different specimens (20). *K. pneumoniae* was highly susceptible to colistin (96.2%) and had a susceptibility of less 50% to all other tested antibiotics(20). *E. coli* was more susceptible to colistin (94.7%) and tigecycline (86.9%) and poorly susceptible to all other tested antibiotics(20).

In the ICU of a Turkish hospital, it was reported that *A. baumannii* was the most common agent: 43.4%; followed by *P. aeruginosa* (32%) and *Enterobacter spp*. (8.6%) (21). The study demonstrated the annual change in susceptibility of the isolated pathogens from 2004 to 2011. *A.baumannii* susceptibility to carbapenems reduced: from 78.1% in 2004 to 7.1% in 2011 for imipenem and 76.6% in 2004 to 5.8% in 2011 for meropenem (21). Fluctuations in susceptibility were observed for *P. aeruginosa* to piperacillin-tazobactam 52.2% in 2000 to 51.8% in 2005 to 64.3% in 2006 to 57.8% in 2007. Regarding *Enterobacter spp.* they have been 100% susceptible to carbapenems over the years, and the susceptibility to ciprofloxacin increased from 79.4% in 2004 to 84.7% in 2010 and then decreased to 70.7% in 2011(21). The susceptibility findings for isolates in this study are not categorised according to an anatomical source of specimens. This makes it difficult to report susceptibility results for respiratory bacteria due to differences in susceptibility rates of organisms from different anatomical sources (22).

An increase in the susceptibility rates of certain bacteria to certain antibiotics was observed in a retrospective analytical study conducted in Johannesburg, South Africa. The study compared the cumulative antibiograms of 2013 and 2017 of blood specimens. This study spotted an increase in the susceptibility rates of certain

antibiotics from 2013 to 2017 that could not be explained (4). In Switzerland, a study conducted on stratification of cumulative antibiograms in hospital units, specimen type, isolate sequence and duration of hospital stay reviewed all the diagnostic antibiograms that were recorded during the clinical patient care. The study found that the respiratory *E. coli* isolates were 92.1% susceptible to ciprofloxacin. Isolates from respiratory specimens were more resistant to imipenem, 64.4% (22). A different study aimed at studying the hospital-acquired infections and their susceptibility patterns in Uganda found that *K. pneumoniae* (22.03%) followed by *Acinetobacter spp.* (18.6%), *and P. aeruginosa* (8.5%) were the common bacteria isolates from the respiratory specimens (23). These organisms were more susceptible to amikacin except *P. aeruginosa* and imipenem.

The choice of the best appropriate antimicrobial agents is guided by the knowledge of local epidemiology of most frequent causative agents as well as their antibiotic susceptibility patterns (24–27). Increasing antibiotic resistance in frequently isolated respiratory tract pathogens has posed the need for suitable selection of the antimicrobial agents (28).

Development of Antibiogram

Cumulative antibiograms may be different within and across hospitals and this may be due to different patient populations attended to at different times within the hospital and at different hospitals (29). The cumulative antibiogram may include all isolated bacteria or may be infection site-specific (1). The cumulative antibiogram guides antibiotic empiric therapy and it is suitable for detecting and monitoring antibiotic resistance trends provided that the susceptibility data is summarised annually (30). On the other hand, the cumulative antibiogram may not be used to monitor the emergence

of antibiotic resistance during treatment or guide therapy for recurrent and prolonged infections (30).

Annual cumulative antibiograms may be a useful tool for discovering changes in the susceptibility rates overtime (31). Changes discovered in the cumulative antibiograms may guide antibiotics prescribing (31). The differences in susceptibility rates between annual cumulative antibiograms may be due to true changes in susceptibility, sample sizes, changes in the patient population, sample collection practices, laboratory testing or data reporting (31).

The Clinical and Laboratory Standards Institute (CLSI) recommended the following, when preparing antibiogram to guide empiric therapy (32): 1) The data should be compiled, analysed and presented annually; 2) only final verified results and diagnostic isolates should be included; 3) only the first isolate per patient per reporting period is included; 4) only species with testing data for ≥ 30 isolates per reporting period are included and 5) only antimicrobial agents routinely tested (not agents selectively tested) are included.

RESEARCH METHODS

Research design

This retrospective analytical cross-sectional study described the susceptibility patterns of commonly isolated bacteria over 2 years from 01 January 2017 to 31 December 2018. Only the bacterial isolates from lower respiratory tract specimens collected from the ICUs of the referral hospitals were considered. Only the lower respiratory tract specimens (sputum, bronchial aspirate, pleural fluid) were included in the analysis.

Population

The study included ICU lower respiratory tract specimens of three out of four referral hospitals (Oshakati intermediate, Onandjokwe, and Windhoek central hospital) in Namibia. Oshakati intermediate and Onandjokwe hospitals are regional referral hospitals, whereas Windhoek Central hospital is a national referral hospital. These hospitals provide tertiary and more specialized health care, specifically for critically ill patients. There were eight ICU beds, six ICU beds and four ICU beds at Windhoek Central hospital, Oshakati Intermediate hospital and Onandjokwe hospital, respectively. ICU patients are more prone to infections due to their underlying diseases and diagnostic, interventional or therapeutic procedures they undergo at the hospital(33).

Sample

All lower respiratory clinical specimens from patients in ICU submitted to NIP from 01 January 2017 to 31 December 2018 for susceptibility testing made up the sample of this study (22). The CLSI M39 guidelines for cumulative antibiogram development recommended a minimum of 30 isolates per species per reporting period for a cumulative antibiogram, therefore, all lower respiratory clinical specimens were included to reach the recommended target. As part of the routine clinical practice, the specimen is taken from a patient with suspected infection and send to NIP for culture and sensitivity testing. Specimen is collected before administration of antibiotics or after the commencement of antibiotics to monitor the effectiveness antibiotics therapy.

Research instruments

The data was provided in excel by NIP. WHONET software, version 5.6 was downloaded from https://whonet.org/. WHONET is a free windows-based database software for the management and analysis of microbiology laboratory data, focused on the analysis of antimicrobial susceptibility test results (34). The data was saved in BacLink data conversion software, then transferred to WHONET for analysis.

Culture and Sensitivity Standard Operating Procedures: NIP

At NIP, pathogen identification and antibacterial susceptibilities are performed using Wellcogen® Bacterial Antigen Kit, Gram stain, and methylene blue stain. Antibiotic susceptibility testing was performed according to the CLSI guidelines. NIP performed standard bacterial culture and sensitivity tests using horse blood agar (5%) or chocolate agar. Culture results were read after 24 hours of incubation. Plates were re-incubated for 24 hours further and re-examined for additional organisms (35). The results are recorded on a worksheet and entered in Meditech®. Meditech® is a laboratory information system healthcare software that records, stores as well as manages the patient results related to laboratory testing.

Research Procedures

The data was accessed in an Excel format. Firstly, the database was checked for missing susceptibility information. Patient demographic data with a full record of isolated bacteria species and susceptibility data were retrieved from Excel database received from NIP. In addition, the database was cleaned by removing and adding the data fields which were deemed necessary by the researcher. Lastly, the data was transferred to WHONET for analysis.

Data analysis

WHONET strategies for handling multiple patient isolates, including CLSI recommendations, were used to include one isolate per species per patient in the analysis. The susceptibility data was analysed using '% Resistance, Intermediate, Susceptible (RIS) and test measurement' feature in WHONET to formulate a cumulative antibiogram which is presented as the percentage of susceptible isolates in a table. Intermediate susceptibility was considered resistant. The WHONET 'isolate listing and summary' feature was used to determine the commonest pathogens. The Chi-square test was used to compare the changes in susceptibility from 2017 to 2018, where p-values < 0.05 were considered statistically significant.

Validity and reliability of the study

NIP is an accredited laboratory that provides antimicrobial susceptibility testing services to all state hospitals in Namibia. Standard operating procedures (SOPs) entail stepwise instructions and provide a full description of the activities performed in the lab (36). Hence, the existence of the SOPs in the lab guarantee consistency, quality and reliability of the lab data (36). Periodic quality control reports (both internal and external), ensure reliability and repeatability of the lab results (36). LRTIs are caused by specific bacteria and the data (specimens) of this study were collected overtime, which ensured validity of this study.

RESEARCH ETHICS

This study was approved by the University of Namibia, Ministry of Health and Social Services and NIP's research and ethical committees. No participants were directly involved as the study was based on retrospectively collected data available from NIP. The data was de-identified to ensure anonymity and confidentiality as it was

transferred from Meditech ® to Excel and was secured on a password protected computer.

RESULTS

Analysis of the first isolate cultures per patient

A sum of 976 first isolate cultures was obtained in 2017 (Table 1). Of these, 0.1% (n=1); 1.8% (n=18); and 98.1% (n=957) were from ICUs of Onandjokwe Hospital, Oshakati Intermediate Hospital, and Windhoek Central Hospital, respectively. Of the 1128 isolate cultures obtained in 2018, only 0.9% (n=10); 1.4% (n=16); and 97.7% (n=1102) were from ICUs of Onandjokwe Hospital, Oshakati Intermediate Hospital, and Windhoek Central Hospital, respectively.

In 2017, the isolated culture from Onandjokwe Hospital ICU was obtained from one specimen, which was negative. In 2018, ten isolate cultures were obtained from five specimens, of which 50% were negative (Table 1). Isolates from Oshakati intermediate hospital's ICU were obtained from 17 and 15 specimens in 2017 and 2018, respectively (Table 1). All the isolated cultures from Oshakati intermediate hospital ICU were positive. Isolates from Windhoek Central hospital ICU were obtained from 421 and 465 specimens in 2017 and 2018, respectively. Almost half (45.7%) of the isolate cultures from WCH were negative in 2017 and 2018, alike (Table 1). Sputum was the most typical specimen type (Table 1).

Table 1: Characteristics of lower respiratory tract specimens and isolates of ICUs of the referral hospitals

Location	Windhoek Central Hospital ICU		Oshakati intermediate hospital ICU		Onandjokwe hospital ICU	
Reporting period	2017	2018	2017	2018	2017	2018
Number of specimens	421	465	17	15	1	5
Sputum, n (%)	376 (89.3)	443 (95.5)	16 (94.5)	13 (86.7)	1 (100)	5 (100)
Pleural fluid, n (%)	41 (9.7)	19 (4.1)	-	1 (6.7)	-	-
Bronchial aspirate, n (%)	4 (1)	3 (0.65)	1 (5.9)	1 (6.7)	-	-
Number of isolate cultures	957	1102	18	16	1	10
Gram positive, n (%)	61(6.4)	70 (6.4)	-	2 (12.5)	-	-
Gram negative, n (%)	328 (34.3)	425 (38.5)	14 (77.8)	12 (75)	-	1 (10)
Fungal, n (%)	89 (9.3)	80 (7.3)	3 (16.7)	2 (12.5)	-	4 (40)
No growth, n (%)	437 (45.7)	504 (45.7)	-	-	1 (100)	5 (50)
Others, n (%)	42 (4.3)	23 (2.0)	-	-	-	-

Key: n (%) = Number (percentage)

Others = Mycobacterium tuberculosis, contaminated isolate cultures and no anaerobes found

Pathogens causing LRTIs in ICUs of referral hospitals

In 2017, *K. pneumoniae* (8.8%) was a predominant pathogen in Windhoek Central hospital ICU, followed by *P. aeruginosa* (7.5%), *E. coli* (4.3%), *S. aureus* (4.0%), *S. maltophilia* (3.8%) and *A. baumannii* (3.2%) (Figure 1). In 2018, the most bacteria isolates were *K. pneumoniae* (8.1%), followed by *A. baumannii* (6.8%), *P. aeruginosa* (5.8%), *E.cloacae* (5.0%), *S. aureus* (5.2%) and *S. maltophilia* (4.9%) (Figure 1).

The most common bacterial isolates in Oshakati intermediate hospital ICU were, *Enterobacter sp*. (22.2%), *K. pneumoniae* (16.7%) and *E. coli* (11.1%) in 2017 (Figure 2). In 2018, *P. aeruginosa* (37.5%), *Enterobacter sp*. (12.5%) were the most common bacteria isolates (Figure 2). *K. aerogenes* was the only bacteria isolate in 2018 for Onandjokwe hospital ICU.

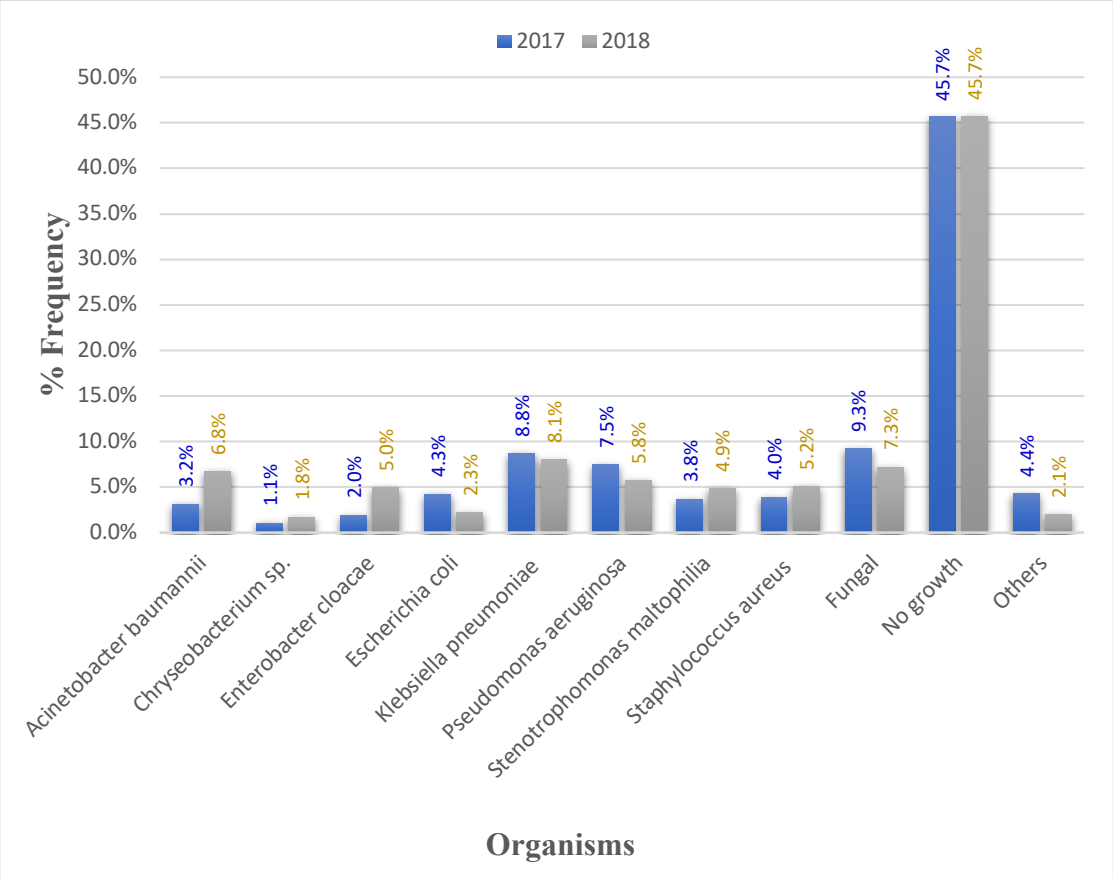

Figure 1: Common pathogens causing LRTIs in Windhoek Central hospital ICU in 2017 and 2018

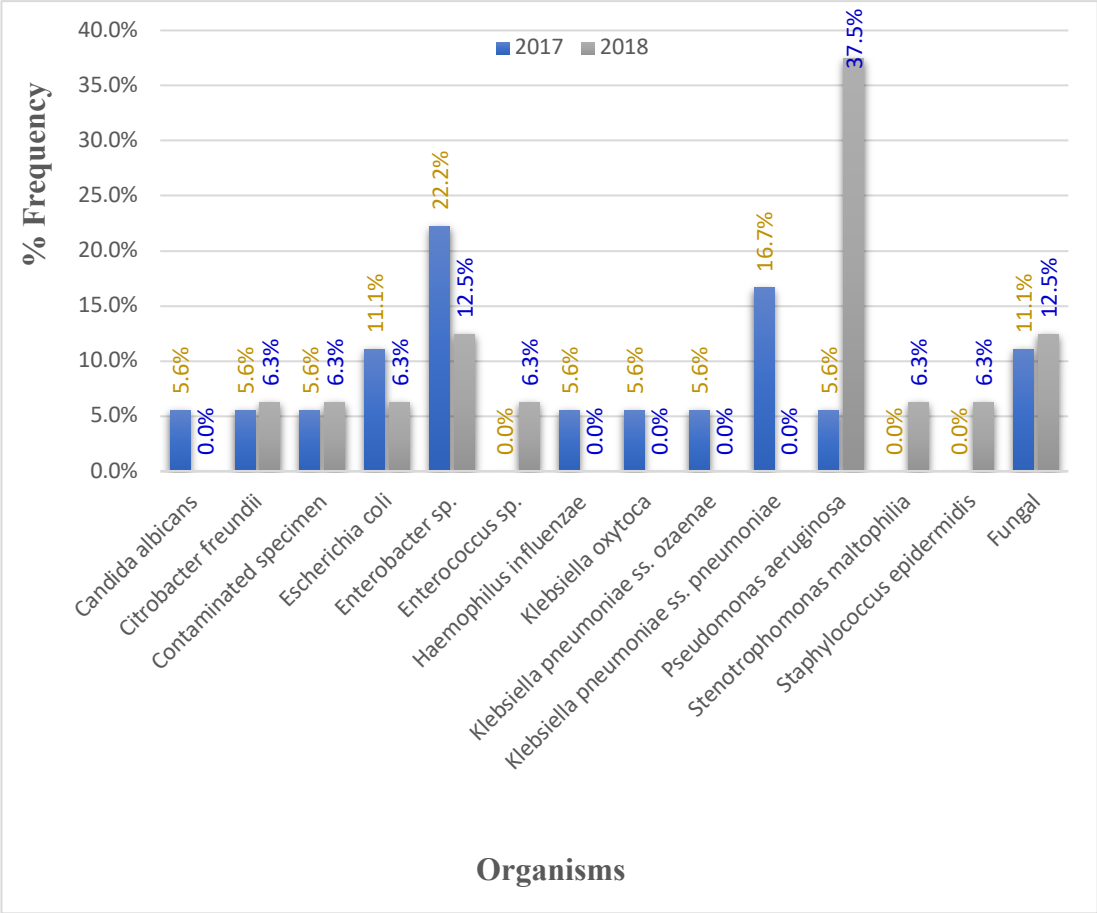

Figure 2: Common pathogens causing LRTIs in Oshakati intermediate hospital ICU in 2017 and 2018

Analysis of susceptibility patterns

The analysis of susceptibility patterns was conducted for WCH ICU isolates, but not for Onandjokwe and Oshakati intermediate hospital ICUs, since the number of isolates from the latter two hospitals was not enough (< 30).

Analysis of the susceptibility pattern of 2018 bacteria isolates revealed a susceptibility pattern like the 2017 pattern for all gram-negative isolates except *E. cloacae* (Table 3). Organism specific results are provided below:

- *A. baumannii* isolates exhibited > 90% susceptibility to colistin, carbapenems and tigecycline (Figure 3) in 2017. In 2018, *A. baumannii* isolates were highly

susceptible to amikacin, carbapenems and colistin, but moderately susceptible to tigecycline (Figure 3).

- *E. coli* isolates were 100% susceptible to Amikacin, carbapenems (imipenem and meropenem) and tigecycline in addition to colistin (Figure 4) but were less than 60% susceptible to 3rd and 4th generation cephalosporins and penicillins.
- According to the 2018 results, *E. cloacae* isolates were 100% susceptible to amikacin and colistin, and highly susceptible to carbapenems (ertapenem 94.4%, imipenem and meropenem 98.1%), tigecycline 97.5% and piperacillin/tazobactam 83% (Figure 9).
- In 2017, *K. pneumoniae* isolates were more susceptible to carbapenems: ~94%, amikacin: 89.3%, and tigecycline: 88.7% (Figure 5). These isolates were less susceptible to penicillins and all cephalosporins tested except cephamycin, cefoxitin (94.4%). *K. pneumoniae* was less than 100% susceptible to colistin (98.7%). In 2018, *K. pneumoniae* isolates were 100% susceptible amikacin, colistin and carbapenems (Figure 5).
- In 2017, *P. aeruginosa* isolates were highly susceptible to aminoglycosides (amikacin 94.4% and gentamicin 90.1%), 3rd and 4th generation cephalosporins (cefepime 83.1% and ceftazidime 85.9%), ciprofloxacin 83.1%, carbapenems (74.3%) and piperacillin/tazobactam 84.5% (Figure 6). In 2018, The susceptibility of *P. aeruginosa* isolates to amikacin, gentamicin, piperacillin/tazobactam, ciprofloxacin, 4th generation cephalosporins and ceftazidime ranged from >85% to 100% (Figure 6).
- *S. maltophilia* isolates were more than 80% susceptible to all the tested antibiotics (Figure 8).

- *S. aureus* was the only gram-positive bacteria with >30 isolates in 2017 and 2018. Its isolates were 100% susceptible to linezolid, rifampicin, teicoplanin, vancomycin in 2017. In 2018, its susceptibility to these antibiotics did not change (Figure 7). *S. aureus* isolates' susceptibility was >85% for the following antibiotics: ciprofloxacin, moxifloxacin, clindamycin, cloxacillin, erythromycin, oxacillin, and tetracycline (100%). In 2018 a decrease in susceptibility was observed: ciprofloxacin 71.9%, moxifloxacin 71.9%, clindamycin 72.7%, cloxacillin 72.7%, erythromycin 66.7%, oxacillin 88.9% and tetracycline 96.4%.

The statistically significant susceptibility changes in cumulative antibiograms from 2017 to 2018 were observed in *A. baumannii, K. pneumoniae, P. aeruginosa* isolates and *S. aureus* (Table 4). It is noteworthy that the statistically significant changes in susceptibility were improvements *A. baumannii, K. pneumoniae, and P. aeruginosa,* while for *S. aureus* they were declines (Table 4).

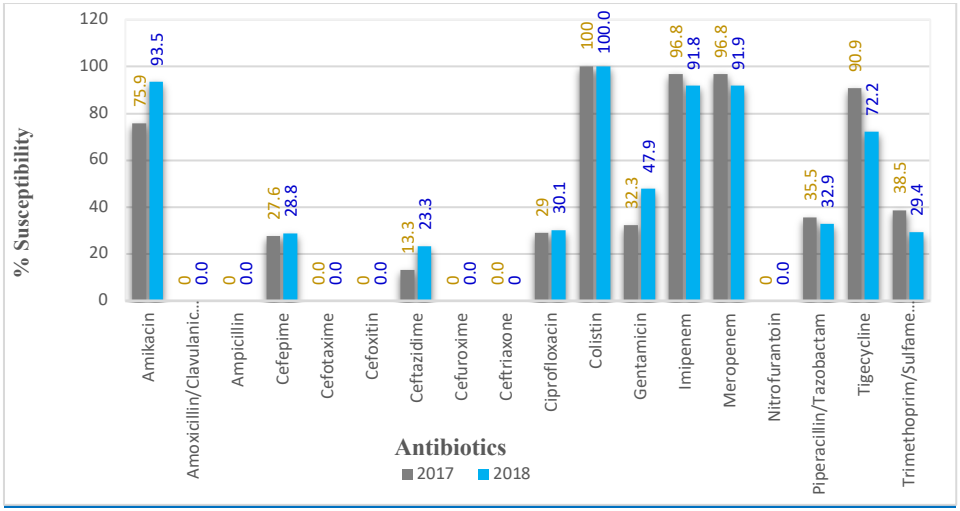

Figure 3: *A. baumannii* antibiotic susceptibility pattern in 2017 and 2018

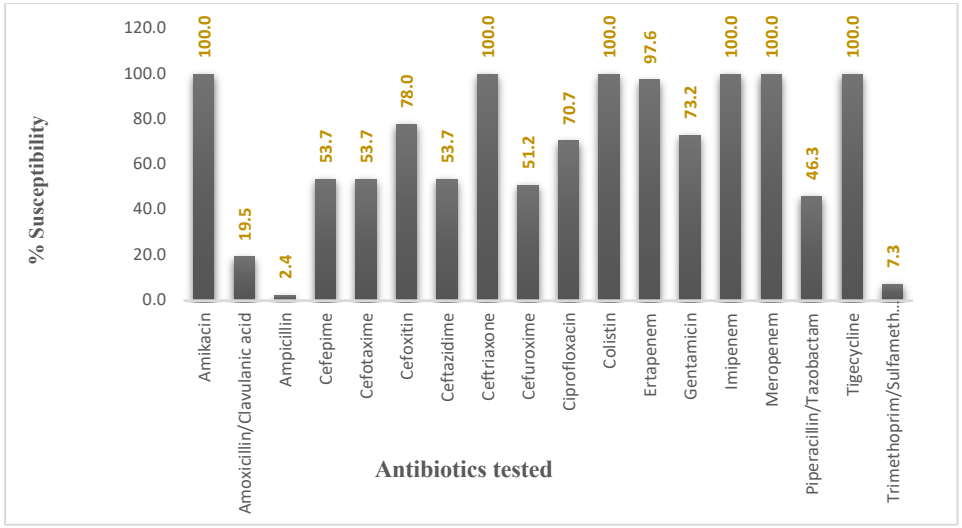

Figure 4: *E. coli* antibiotic susceptibility pattern in 2017

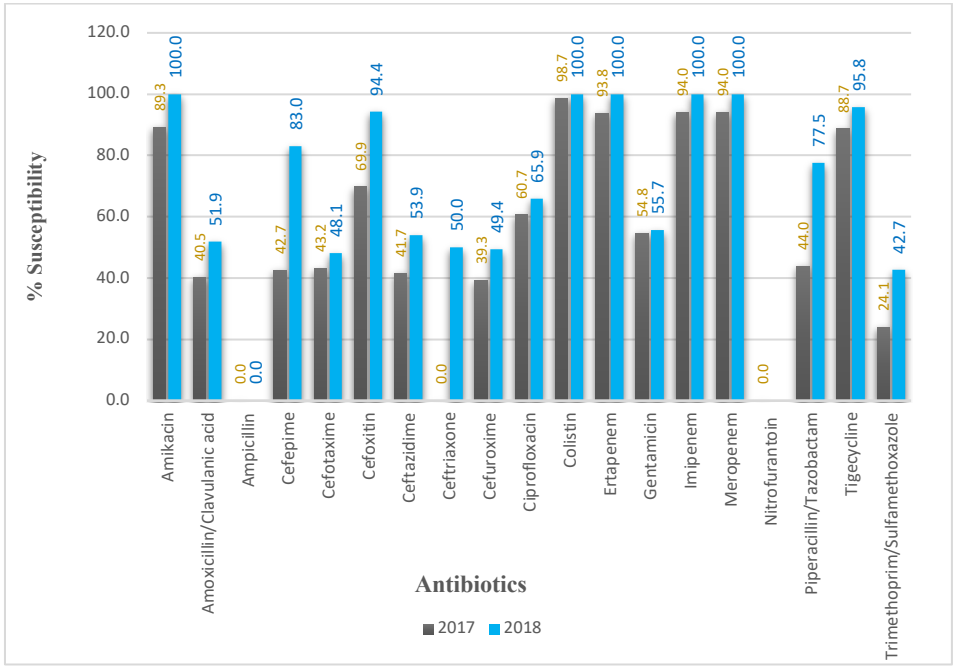

Figure 5: *K. pneumoniae* antibiotic susceptibility pattern in 2017 and 2018

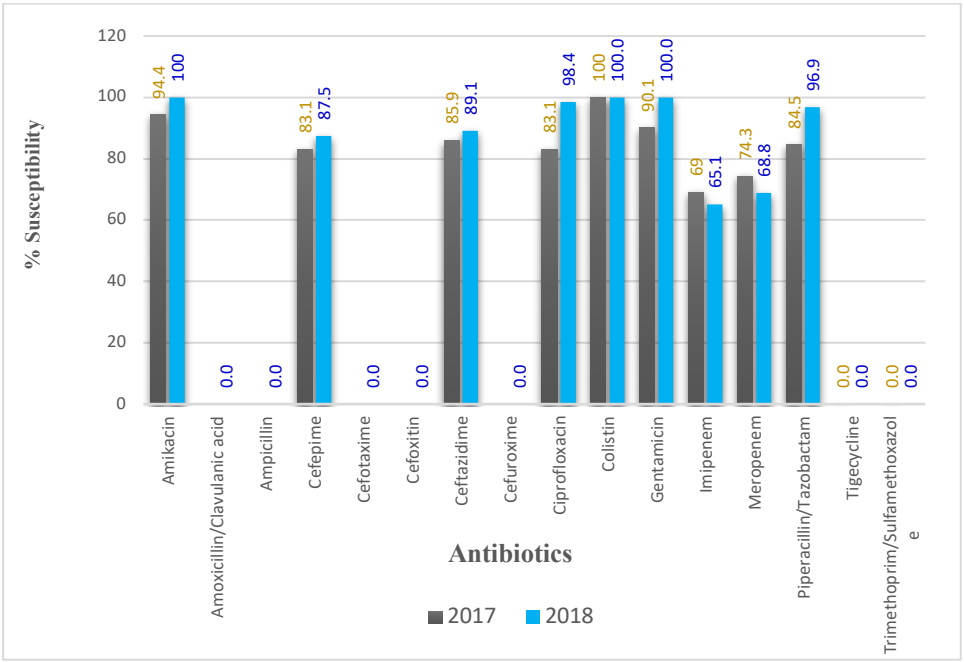

Figure 6: *P. aeruginosa* antibiotic susceptibility pattern in 2017 and 2018

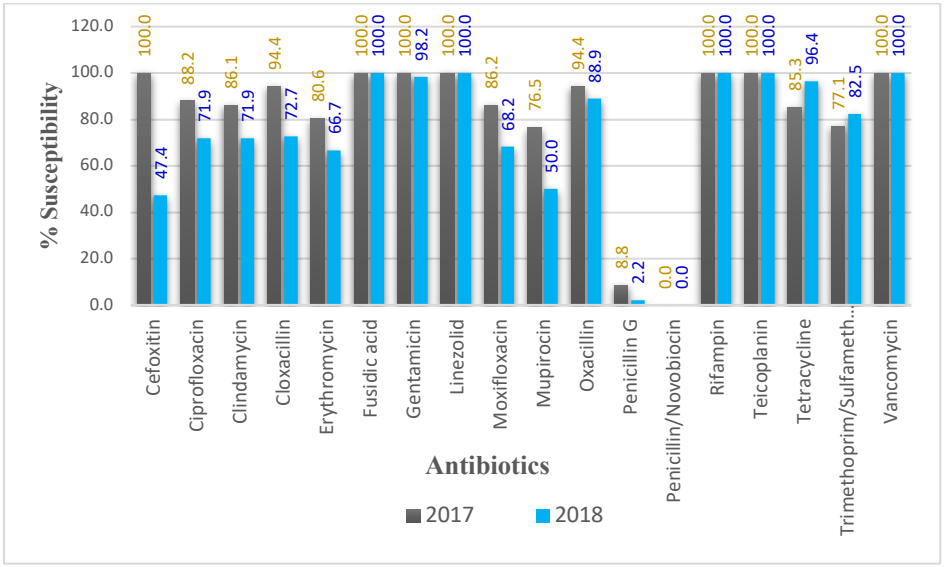

Figure 7: *S. aureus* antibiotic susceptibility pattern in 2017 and 2018

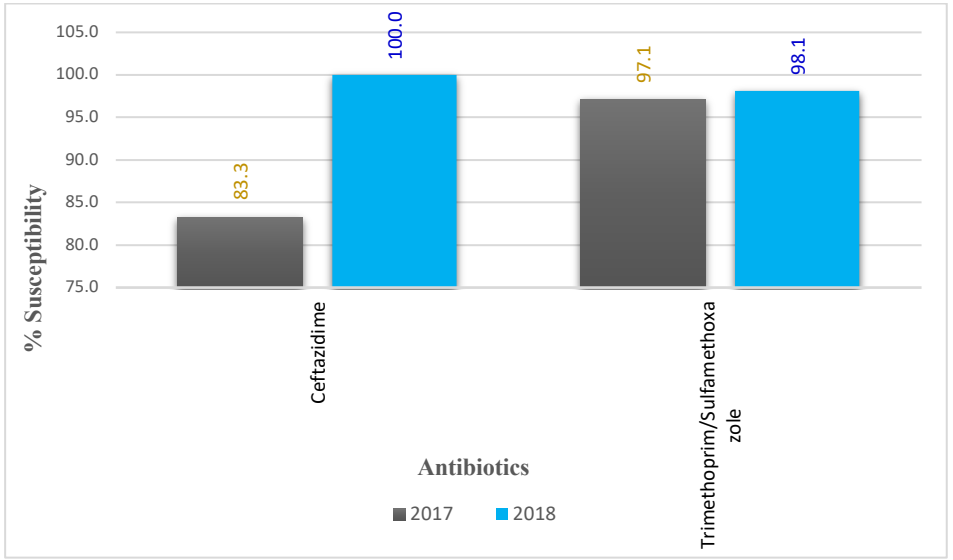

Figure 8: *S. maltophilia* antibiotic susceptibility pattern in 2017 and 2018

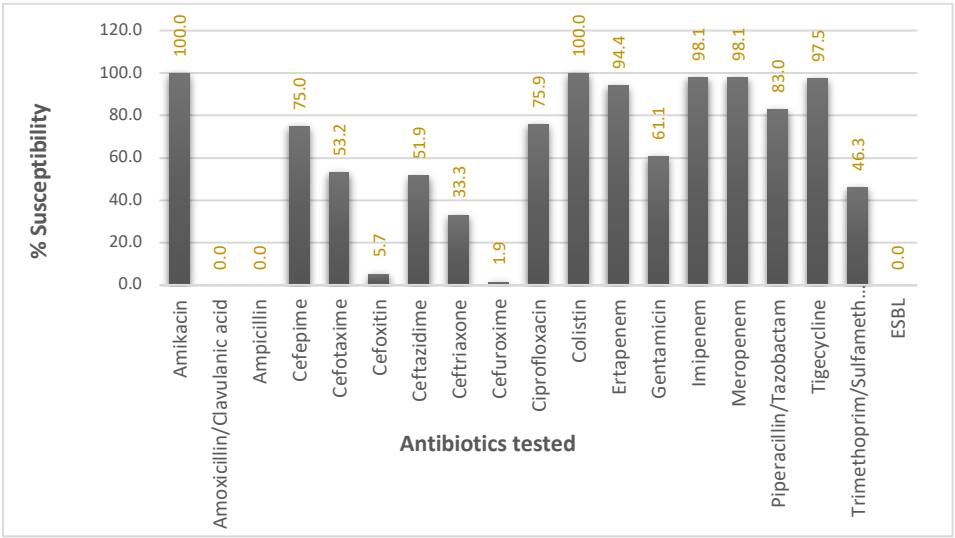

Figure 9: *E. cloacae* antibiotic susceptibility pattern in 2018

Table 2: Antibiotic susceptibility testing patterns for common isolates showing the number of isolates tested

	Organisms Year (number of isolates tested)													
	Acinetobacter baumanni		*Enterobacter cloacae*		*Escherichia coli*		*Klebsiella pneumoniae*		*Pseudomonas aeruginosa*		*Stenotrophomonas maltophilia*		*Staphylococcus aureus*	
Antibiotics	2017 *(n=31*	2018 *(n=75*	2017	2018 *(n=55*	2017 *(n=41*	2018	2017 *(n=84*	2018 *(n=89*	2017 *(n=72*	2018 *(n=64*	2017 *(n=36*	2018 *(n=54*	2017 *(n=38*	2018 *(n=57*
Amikacin	29	62		51	41		84	87	71	62				
Amoxicillin / clavulanic acid		2		48	41		84	79		1				
Ampicillin		1		46	41		84	78		1				
Cefepime	29	73		52	41		82	88	65	87.5				
Cefotaxime	21	47		47	41		81	79		1				
Cefoxitin		4		53	41		83	89		1			11	19
Ceftazidime	30	73		54	41		84	89	71	64	6	3		
Ceftriaxone	2			3	1		1	6						
Cefuroxime		2		54	41		84	89		1				
Ciprofloxacin	31	73		54	41		84	88	71	64			34	57
Clindamycin													36	57
Cloxacillin													36	55
Colistin	23	46		54	39		76	78	43	23				
Ertapenem				54	41		81	89						
Erythromycin													36	57
Fusidic acid													17	22
Gentamicin	31	73		54	41		84	88	71	64			36	57
Imipenem	31	73		54	41		84	89	71	63				
Linezolid													31	57
Meropenem	31	74		54	41		84	89	70	64				
Moxifloxacin													29	44
Mupirocin													17	20
Nitrofurantoin		1					1							
Oxacillin													36	45
Penicillin G													34	46
Penicillin / novobiocin													1	5
Piperacillin /	31	73		53	41		84	89	71	64				
Rifampicin													18	21
Teicoplanin													20	21
Tetracycline													34	56
Tigecycline	11	18		40	35		62	72	5	3				
Trimethoprim / Sulfamethoxazo	26	68		54	41		83	89	1	1	35	53	35	57
Vancomycin													30	49

Notes:

a. Each organism has 2017 and 2018 fields to enter susceptibility data, for various antibiotics. The number in the cells represents the number of times the organism isolates was tested for the specific antibiotic.

b. Susceptibility ≥ 90% is highlighted in green, 60%- 89% in orange, ≤ 60% in red

c. Empty cells show that the organism was not tested for that specific antibiotic or the number of isolates was < 30 per reporting period

Table 3: Windhoek Central hospital ICU 2017 and 2018 cumulative antibiogram

Windhoek Central Hospital ICU
2017 and 2018 Antibiograms
Isolates, Jan – Dec

Percent Susceptibility for common isolates causing lower respiratory tract infections

	Organisms (Number of Isolates)													
	Acinetobacter baumannii (31)		*Escherichia coli (41)*		*Klebsiella pneumoniae (84)*		*Pseudomonas aeruginosa (72)*		*Stenotrophomonas maltophilia (36)*		*Staphylococcus aureus (38)*		*Enterobacter cloacae (55)*	
	2017	**2018**	**2017**	**2018**	**2017**	**2018**	**2017**	**2018**	**2017**	**2018**	**2017**	**2018**	**2017**	**2018**
Amikacin	75.9	93.5	100		89.3	100	94.4	100						100
Amoxicillin / clavulanic acid		0	19.5		40.5	51.9		0						0
Ampicillin		0	2.4		0	0		0						0
Cefepime	27.6	28.8	53.7		42.7	83	83.1	87.5						75
Cefotaxime	0	0	53.7		43.2	48.1		0						53.2
Cefoxitin		0	78.0		69.9	94.4		0			100	47.4		5.7
Ceftazidime	13.3	23.3	53.7		41.7	53.9	85.9	89.1	83.3	100				51.9
Ceftriaxone	0		100		0	50								33.3
Cefuroxime		0	51.2		39.3	49.4		0						1.9
Ciprofloxacin	29	30.1	70.7		60.7	65.9	83.1	98.4			88.2	71.9		75.9
Clindamycin											86.1	71.9		
Cloxacillin											94.4	72.7		
Colistin	100	100	100		98.7	100	100	100						100
Ertapenem			97.6		93.8	100								94.4
Erythromycin											80.6	66.7		
Fusidic acid											100	100		
Gentamicin	32.3	47.9	73.2		54.8	55.7	90.1	100			100	98.2		61.1
Imipenem	96.8	91.8	100		94	100	74.3	65.1						98.1
Linezolid											100	100		
Meropenem	96.8	91.9	100		94	100	74.3	68.8						98.1
Moxifloxacin											86.2	68.2		
Mupirocin											76.5	50		
Nitrofurantoin					0									
Oxacillin											94.4	88.9		
Penicillin G											8.8	2.2		
Penicillin / novobiocin											0	0		
Piperacillin / Tazobactam	35.5	32.9	46.3		44.0	77.5	84.5	96.9						83
Rifampicin											100	100		
Teicoplanin											100	100		
Tetracycline											100	96.4		
Tigecycline	90.9	72.2	100		88.7	95.8	0	0						97.5
Trimethoprim / Sulfamethoxaz	38.5	29.4	7.3		24.1	42.7	0	0	97.1	98.1	77.1	82.5		46.3
Vancomycin											100	100		

Notes:

a. Each organism isolates were tested for various antibiotics. The number in the cells represents the percentage susceptibility of each organism isolates to the corresponding antibiotic.

b. Susceptibility ≥ 90% is highlighted in green, 60%- 89% in orange, ≤ 60% in red

c. Empty columns show that the organism was not tested for that specific antibiotic or the number of isolates is < 30 per reporting period

Table 4: Annual susceptibility changes from 2017 to 2018 cumulative antibiograms

Organism	Antibiotics	% susceptibility 2017	% susceptibility 2018	Difference in % susceptibility	P-value
Acinetobacter baumannii	Amikacin	75.9	93.5	17.6	0.015**!**
	Cefepime	27.6	28.8	1.2	0.905
	Ceftazidime	13.3	23.3	10	0.255
	Ciprofloxacin	29	30.1	1.1	0.868
	Gentamicin	32.3	47.9	15.6	0.140
	Imipenem	96.8	91.8	-5	0.353
	Meropenem	96.8	91.9	-4.9	0.360
	Piperacillin/ Tazobactam	35.5	32.9	-2.6	0.797
	Trimethoprim/ sulfamethoxazole	38.5	29.4	-9.1	0.400
Klebsiella pneumoniae	Amikacin	89.3	100	10.7	0.002**!**
	Amoxicillin/ Clavulanic acid	40.5	51.9	11.4	0.144
	Cefepime	42.7	83	40.3	<0.001**!**
	Cefotaxime	43.2	48.1	4.9	0.535
	Cefoxitin	69.9	94.4	24.5	<0.001**!**
	Ceftazidime	41.7	53.9	12.2	0.107
	Cefuroxime	39.3	49.4	10.1	0.179
	Ciprofloxacin	60.7	65.9	5.2	0.480
	Colistin	98.7	100	1.3	0.309
	Gentamicin	54.8	55.7	0.9	0.903
	Piperacillin/ Tazobactam	44	77.5	33.5	<0.001**!**
	Trimethoprim/ sulfamethoxazole	24.1	42.7	18.6	0.010

Organism	Antibiotics	% susceptibility 2017	% susceptibility 2018	Difference in % susceptibility	P-value
Pseudomonas aeruginosa	Amikacin	94.4	100	5.6	0.058
	Cefepime	83.1	87.5	4.4	0.478
	Ceftazidime	85.9	89.1	3.2	0.582
	Ciprofloxacin	83.1	98.4	15.3	0.003!
	Gentamicin	90.1	100	9.9	0.010!
	Imipenem	74.3	65.1	-9.2	0.628
	Meropenem	74.3	68.8	-5.5	0.478
	Piperacillin/ Tazobactam	84.5	96.9	12.5	0.015!
Staphylococcus aureus	Cefoxitin	100	47.4	-52.6	0.003*
	Ciprofloxacin	88.2	71.9	-16.3	0.069
	Clindamycin	86.1	71.9	-14.2	0.111
	Cloxacillin	94.4	72.7	-21.7	0.009*
	Erythromycin	80.6	66.7	-13.9	0.146
	Moxifloxacin	86.2	68.2	-18	0.080
	Mupirocin	76.5	50	-26.5	0.098
	Oxacillin	94.4	88.9	-5.5	0.377
	Tetracycline	100	96.4	-3.6	0.056
	Trimethoprim/ sulfamethoxazole	77.1	82.5	5.4	0.533
Stenotrophomonas maltophilia	Trimethoprim/ sulfamethoxazole	97.1	98.1	1	0.765

Meaning of symbols: != Statistically significant increase in numbers of susceptible isolates; * = Statistically significant decrease in the number of susceptible isolates

DISCUSSION

To the best of our knowledge, this is the first study to describe the susceptibility pattern of pathogens commonly associated with LRTIs in ICUs in Namibia. Also, it is the first study to formulate cumulative antibiograms of the said pathogens. Further, this is the first study to analyse the changes in susceptibility of pathogens causing LRTIs. This study identified the common pathogens causing LRTIs in the ICUs of referral hospitals in Namibia, and their susceptibilities have been assessed. The study has shown increases in susceptibility of *A. baumannii, K. pneumoniae,* and *P. aeruginosa* to commonly tested antibiotics, and decreases in the susceptibility of *S. aureus* to penicillinase-resistant penicillins and cephalosporins. Finally, the study has generated antibiograms that would be ideal to guide empiric therapy for the period studied.

In this study, we observed between and within hospital differences in the isolate types and isolate frequencies. For instance, *Enterobacter sp.* and *E. coli* were the most frequently identified organisms associated with LRTIs in Oshakati Intermediate Hospital's ICU in 2017, while for Windhoek Central Hospital they were *K. pneumoniae* and *P. aeruginosa*. Within hospital differences included frequency and isolate differences. For example, from 2017 to 2018, the most frequent isolate in Oshakati Intermediate Hospital's ICU changed from *Enterobacter sp* to *P. aeruginosa*. It is worthy of note that *P. aeruginosa* was not amongst the isolates in 2017, and *E. coli* was not amongst the isolates in 2018. While *Enterobacter sp* were identified in both years, the frequency dropped from 22.2% in 2017 to 12.5% in 2018. For Windhoek Central Hospital, in 2017, the most frequent isolates were *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, and *E. coli*. In 2018, *E. coli* was replaced by *A. baumanii*, while the others remained on the list of isolates. There were relatively small changes

in the frequencies of the organisms that were identified in both years. Six of the seven organisms that have been associated with LRTI in the ICUs in Namibia – namely: *P. aeruginosa, K. pneumoniae, E.coli, A. baumanii, Enterobacter sp,* and *S. aureus* – have been associated with LRTI in other countries (18) (19) (20) (21). Nonetheless, there were differences in frequencies. For example: in Romania, the most common organisms were *A. baumannii* (64%), *Klebsiella sp.* (35%) and *S. aureus* (29%) (16); in Egypt, they were *K. pneumonia* (33.5%), *Staphylococcus spp*. (23.2%) and *E. coli* (19.3%) (17); while in Uganda, they were *K. pneumonia* (22.03%), *A. baumanii* (18.6%) and *P. aeruginosa* (8.5%) (21). The differences in frequency may be associated with differences in the number of samples, which may be subject to study designs.

Regarding susceptibility, the different isolates from Windhoek Central hospital ICU in 2017 and 2018 were similar. *K. pneumoniae* isolates were highly susceptible to amikacin, colistin and carbapenems in both 2017 and 2018, showing a lack of emergence of resistance. This is comparable with a study conducted in Uganda, where *K. pneumonia* was highly susceptible to amikacin and imipenem (21). In another study, *K. pneumoniae* isolates were less than 50% susceptible to all the antibiotics tested except colistin (17). In contrast to the findings of this study, a study that was conducted in the United States of America found that *K. pneumoniae* isolates were resistant to carbapenems. Statistically significant increases in susceptibility to amikacin, second and fourth generation cephalosporins and piperacillin-tazobactam were noted for *K. pneumoniae* but this change could not be explained. The importance of local susceptibilities cannot beemphasised more.

The 2018 Windhoek central Hospital ICU cumulative antibiogram showed that *A. baumannii* isolates were more than 70% susceptible to tigecycline, carbapenems,

amikacin and colistin. In this study, there was a statistically significant increase in the susceptibility of *A. baumannii* to amikacin from 75.9% to 93.3% from 2017 to 2018 (p=0.015); however, no explanation is currently available for this change. Nonetheless, the change may be associated with a double increase in the number of *A. baumannii* isolates. *E. coli* isolates were highly susceptible to amikacin, carbapenems and tigecyclines, which is like the findings of a study in Egypt (17). Susceptibility of *E. coli* to ciprofloxacin in Switzerland was 92.1% which is higher than the susceptibility of *E. coli* this study, 70.7%. Its susceptibility in 2018 was not assessed because the number of isolates were less than 30. *P. aeruginosa* isolates from Windhoek central were more than 70% susceptible to all antibiotics tested in 2017 and more than 60% susceptible to all other antibiotics tested in 2018, this is different from the findings in Romania, where *P. aeruginosa* ICU isolates were poorly susceptible (< 30%) to antibiotics tested. A study conducted in Uganda found that *P. aeruginosa* isolates were less susceptible to amikacin (21), which is not consistent with the findings of this study, emphasising the importance of local studies.

There was a statistically significant decrease in the susceptibility of *S. aureus* to cefoxitin from 100% to 47.4%. Moreover, there was also a decrease in the susceptibility of *S. aureus* to penicillinase-resistant antibiotics. According to the Centres of Disease Control and Prevention (CDC), Methicillin-resistant Staphylococcus aureus (MRSA) may also be resistant to fluoroquinolones, erythromycin and clindamycin in addition to cephalosporins and carbapenems(37). The decrease in susceptibility rates to all these antibiotics was observed except for carbapenems because they were not tested. This indicated the egression of MRSA, which is of great concern to the healthcare system.

This study has limitations. The study used laboratory-based data; therefore, whether the infection is community-acquired or hospital-acquired cannot be established. The results of this study cannot be generalised, meaning they cannot be applied to other hospital ICUs or wards. The cumulative antibiograms formulated in this study should be interpreted with caution, as the findings of this study revealed the irregularity in NIP antibiotics testing practices. In some organisms, < 30 isolates were tested per antibiotics.

In conclusion. Meropenem in combination with gentamicin are the recommended empiric therapy for patients with LRTIs in Windhoek Central hospital ICU. Meropenem will cover gram-negative pathogens and gentamicin will cover *P. aeruginosa* and *S. aureus*. Aminoglycosides and β-lactams are known to have synergistic effects when used in combination(38).

Recommendations

There is a need to build local capacity with the intention of initiating active surveillance of antibiotic susceptibility in Namibia. This will promote the appropriate prescribing of antibiotics empirically, reducing the emergence of antimicrobial resistance across the country.

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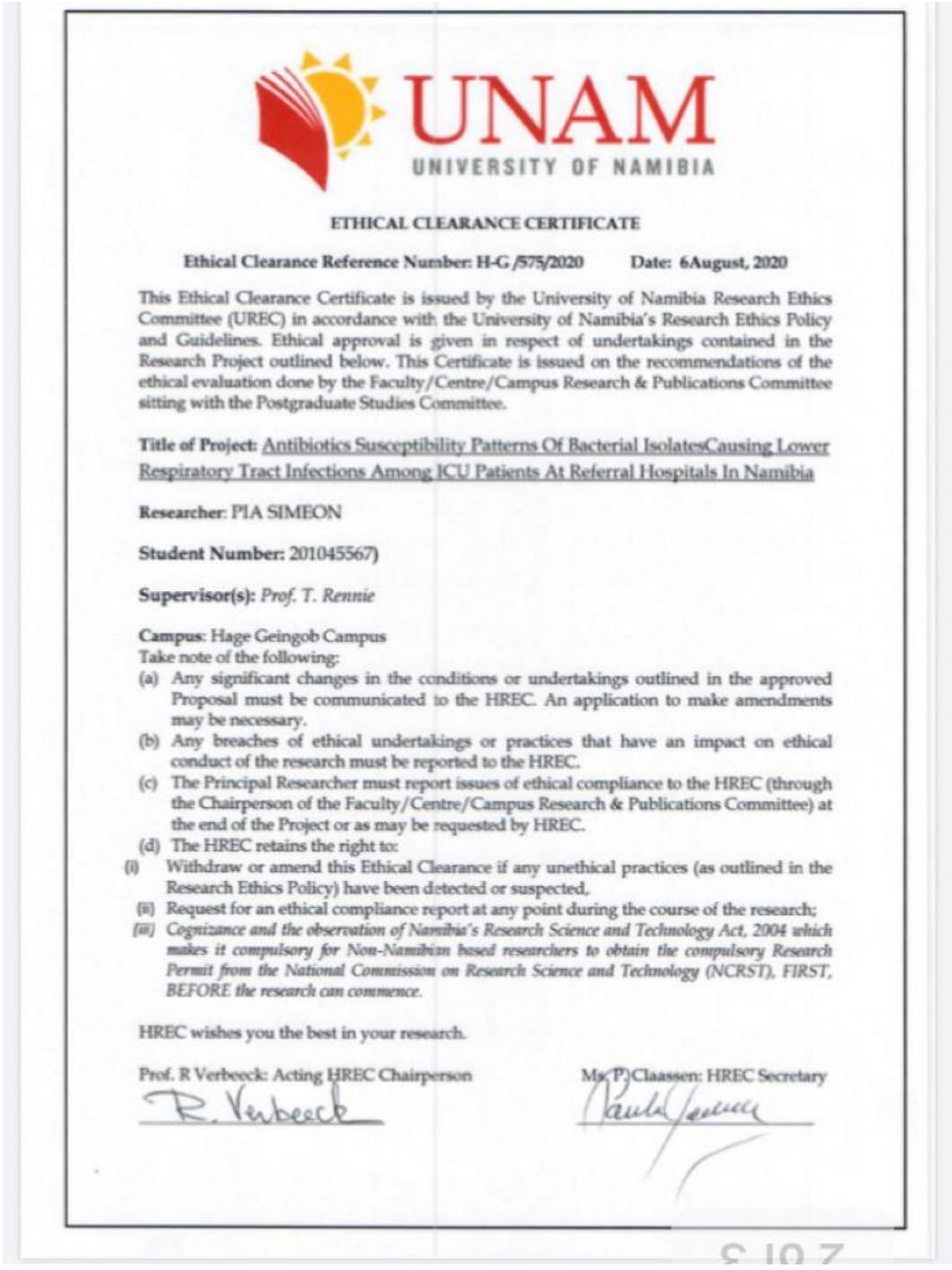
APPENDICES

Ethical clearance certificate



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ETHICAL CLEARANCE CERTIFICATE

Ethical Clearance Reference Number: H-G /575/2020 **Date: 6August, 2020**

This Ethical Clearance Certificate is issued by the University of Namibia Research Ethics Committee (UREC) in accordance with the University of Namibia's Research Ethics Policy and Guidelines. Ethical approval is given in respect of undertakings contained in the Research Project outlined below. This Certificate is issued on the recommendations of the ethical evaluation done by the Faculty/Centre/Campus Research & Publications Committee sitting with the Postgraduate Studies Committee.

Title of Project: Antibiotics Susceptibility Patterns Of Bacterial IsolatesCausing Lower Respiratory Tract Infections Among ICU Patients At Referral Hospitals In Namibia

Researcher: PIA SIMEON

Student Number: 201045567)

Supervisor(s): *Prof. T. Rennie*

Campus: Hage Geingob Campus
Take note of the following:

(a) Any significant changes in the conditions or undertakings outlined in the approved Proposal must be communicated to the HREC. An application to make amendments may be necessary.
(b) Any breaches of ethical undertakings or practices that have an impact on ethical conduct of the research must be reported to the HREC.
(c) The Principal Researcher must report issues of ethical compliance to the HREC (through the Chairperson of the Faculty/Centre/Campus Research & Publications Committee) at the end of the Project or as may be requested by HREC.
(d) The HREC retains the right to:

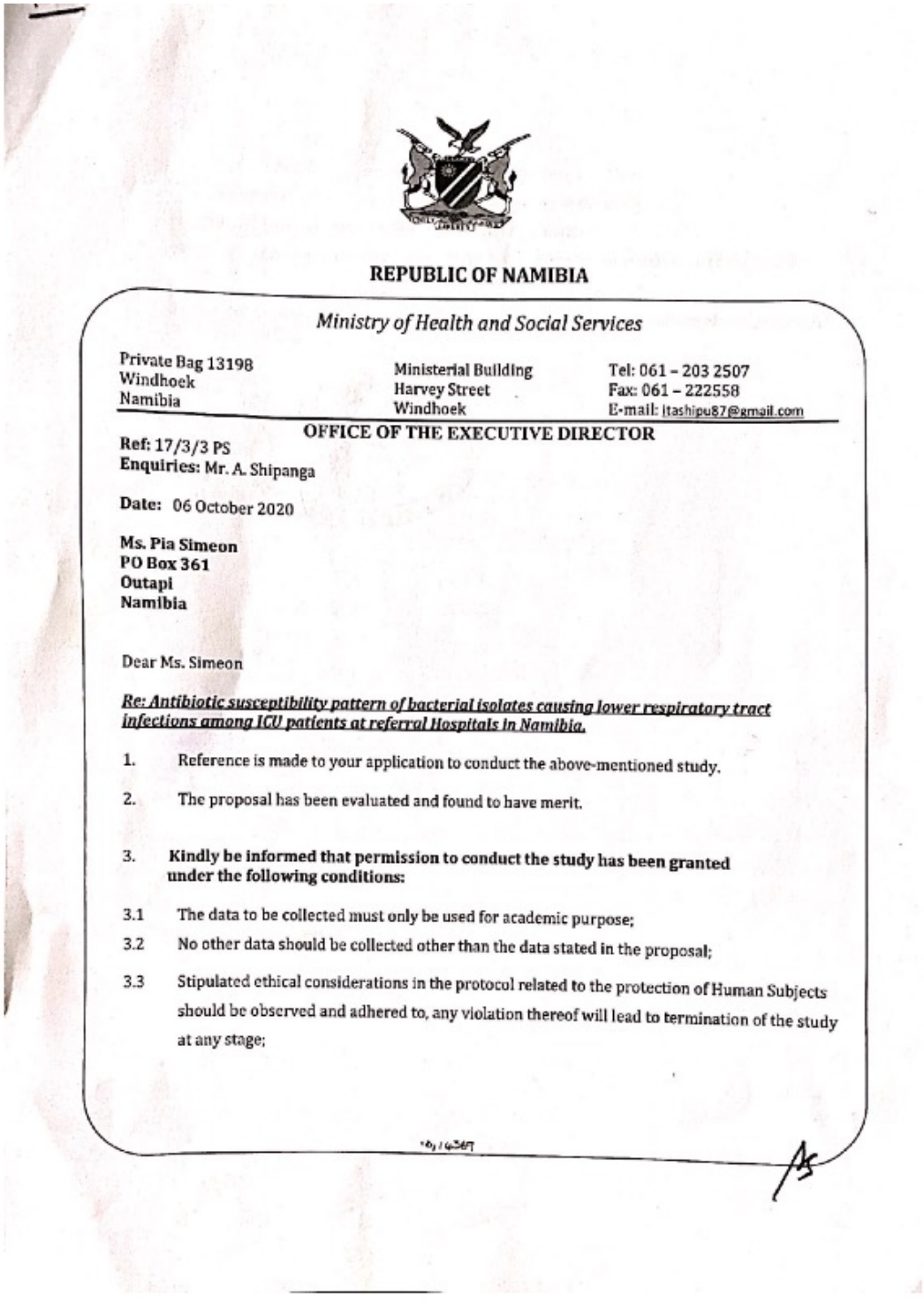
(i) Withdraw or amend this Ethical Clearance if any unethical practices (as outlined in the Research Ethics Policy) have been detected or suspected,
(ii) Request for an ethical compliance report at any point during the course of the research;
(iii) *Cognizance and the observation of Namibia's Research Science and Technology Act, 2004 which makes it compulsory for Non-Namibian based researchers to obtain the compulsory Research Permit from the National Commission on Research Science and Technology (NCRST), FIRST, BEFORE the research can commence.*

HREC wishes you the best in your research.

Prof. R Verbeeck: Acting HREC Chairperson

Ms. P. Claassen: HREC Secretary

Research permission letter



REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

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OFFICE OF THE EXECUTIVE DIRECTOR

Ref: 17/3/3 PS
Enquiries: Mr. A. Shipanga

Date: 06 October 2020

Ms. Pia Simeon
PO Box 361
Outapi
Namibia

Dear Ms. Simeon

Re: Antibiotic susceptibility pattern of bacterial isolates causing lower respiratory tract infections among ICU patients at referral Hospitals in Namibia.

1. Reference is made to your application to conduct the above-mentioned study.

2. The proposal has been evaluated and found to have merit.

3. **Kindly be informed that permission to conduct the study has been granted under the following conditions:**

3.1 The data to be collected must only be used for academic purpose;

3.2 No other data should be collected other than the data stated in the proposal;

3.3 Stipulated ethical considerations in the protocol related to the protection of Human Subjects should be observed and adhered to, any violation thereof will lead to termination of the study at any stage;

3.4 A quarterly report to be submitted to the Ministry's Research Unit;

3.5 Preliminary findings to be submitted upon completion of the study;

3.6 Final report to be submitted upon completion of the study;

3.7 Separate permission should be sought from the Ministry for the publication of the findings.

4. All the cost implications that will result from this study will be the responsibility of the applicant and not of the MoHSS.

Yours sincerely,

EXECUTIVE DIRECTOR
MINISTRY OF HEALTH AND SOCIAL SERVICES

BEN NGOMBE
EXECUTIVE DIRECTOR