Surveillance for Antimicrobial Resistance and Consumption of Antibiotics in South Africa 2018-2022

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National Department of Health

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30 YEARS OF FREEDOM
South Africa 1994 - 2024

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

This surveillance report represents the current available information relating to antimicrobial resistance (AMR) and antimicrobial consumption in humans in South Africa from 2018 to 2022.

Antimicrobial Resistance in Humans

The AMR surveillance system in humans was built through the collaboration between the public and private sector laboratory services and represents a comprehensive view of AMR in blood cultures for the ESKAPE[1] pathogens in the country.

Resistance in numbers:

Klebsiella pneumoniae
70% BSIs are nonsusceptible to 3rd generation cephalosporins
40% BSIs are nonsusceptible to 1st generation carbapenems

Staphylococcus aureus
Staphylococcus aureus
17% BSIs are nonsusceptible to cloxacillin (MRSA)

Escherichia coli
25% BSIs nonsusceptible to 3rd generation cephalosporins
33% BSIs are nonsusceptible to ciprofloxacin

Pseudomonas aeruginosa
33% BSIs are nonsusceptible to carbapenems
17% BSIs is nonsusceptible to 3rd and 4th generation cephalosporinds and to piperacillin-tazobactam

Acinetobacter baumannii
80% BSI are resistant to carbapenems

Enterococcus faecium
1.3% BSIs are resistant to vancomycin

Enterococcus faecalis
1.1% BSIs are resistant to vancomycin

***BSI** - Blood Stream Isolate

Klebsiella pneumoniae was the most common isolate derived from blood in both the public and private sectors followed by *Staphylococcus aureus*, *Escherichia coli* and then *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. The prevalence of extended spectrum beta-lactamase (ESBL) producing *K. pneumoniae* has remained on average 70% over the past 5 years, which limits the use of cephalosporins for treatment. The emergence of carbapenem-resistance in *K. pneumoniae* was a growing concern with one third of the isolates showing resistance to carbapenems in 2022.

1 ESKAPE = *Enterococcus faecalis* and *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Escherichia coli*

E. coli showed increasing resistance to quinolones with one in three organisms resistant to ciprofloxacin, which is one of the treatment options for UTI's. It is noted that there was no information on the source of bacteraemia. One in four *E. coli* was an ESBL producer, resistant to 3rd generation cephalosporins.

P. aeruginosa and *A. baumannii* are commonly regarded as healthcare associated organisms. In 2022, approximately 23% of *P. aeruginosa* isolates and 79% of *A. baumannii* isolates were resistant to carbapenems. Variations across the provinces for these two organisms highlighted potential differences in empiric treatment between different parts of the country. Carbapenem resistance occurs in eight out of ten *A. baumannii* isolates. In 2022, 85% of isolates were susceptible to tigecycline. This limits treatment options, with only colistin (which is not registered in the country and requires a license through the South African Health Products Regulatory Authority ((SAHPRA) to procure) being available to treat these resistant infections.

The resistance to cloxacillin for *S. aureus* has declined from 23% to 16% (of which 1 in 6 are methicillin resistant *S. aureus* (MRSA)) over the past 5 years, and resistance varies across the provinces.

Ampicillin remains the treatment of choice for *Enterococcus faecalis*, with the added growing concern of vancomycin resistance (a last resort antibiotic), especially in the Free State and North West provinces.

Antimicrobial Use in Humans

South Africa's antibiotic use in 2018 was 17.9 Defined Daily Doses (DDDs) per 1000/population per day, on par with other BRICS[2] countries and not as high as some other African countries. There has been a 50% annual growth in antibiotic use between 2020 to 2022, driven mainly by the private sector at 64% over this time.

The consumption of antimicrobials by humans in the public sector, sourced from procurement data, shows an increase of 50% over the period 2018-2022 with the main drivers being "Access" antibiotics such as combination spectrum penicillin beta-lactams, lincosamides such as clindamycin and extended spectrum penicillins.

The private sector prescription data, sourced only from private hospitals (excluding primary retail care) shows a different pattern of use with quinolones as the main antibiotic class, followed by combination penicillin beta-lactams and macrolides, such as azithromycin. Both public and private sectors have seen a dramatic increase in quinolone use as well as macrolides specifically over the COVID-19 pandemic period.

Using the World Health Organization's (WHO's) AWaRe[3] categorisation, the public sector ratios of Access, Watch and Reserve antibiotics has shifted with predominantly Watch (52%) followed by Access (48%) and an underreported Reserve antibiotics percentage. Of concern is the rapid increase in Reserve antibiotic use (~40%) as this data did not represent the full extent of the procurement data (i.e. buyouts and Section 21 data is not included for the public sector).

The private sector has a larger proportion of Watch antibiotics (60% of total), followed by Access antibiotics (38%). However, Reserve antibiotic use has decreased by 20% over the period (full data is reflected in the report). This is encouraging, although it comes off a higher base than the public sector, as it may reflect that the focus on antimicrobial stewardship in this sector had an impact.

In general, both sectors showed an increase in use of the antibiotics used to treat Gram-negative drug-resistant infections, in particular carbapenems and colistin.

2 BRICS is the acronym for an association of five major emerging national economies: Brazil, Russia, India, China, and South Africa.

3 An acronym for the World Health Organization's classification of antibiotics for evaluation and monitoring of use into "Access, Watch and Reserve" categories. See WHO's AWaRe Index (https://www.who.int/publications/i/item/2021-aware-classification) for further information.

South Africa's first Global Point Prevalence Study for Healthcare Associated Infections

The Global Point Prevalence Surveillance Study in South Africa, a collaboration between the Infection Prevention and Control (IPC) Technical Working Group (TWG) of the Ministerial Advisory Committee (MAC) on AMR and the University of Antwerp, assessed healthcare associated infections (HAIs) in 52 state hospitals. Conducted via the Global Point Prevalence Survey (GPPS), the study utilised a web-based tool to evaluate HAI rates, antimicrobial prescribing, and usage. The survey included 8,584 patients across public hospitals. The results showed that 27.8% of adults, 46.7% of paediatrics, and 36% of neonates were on antibiotics, with higher usage seen in intensive care units (ICUs).

The overall HAI rate was 7.15%, with variations across age groups and specialties. Surgical site infections contributed 1.45%, device related infections contributed 1.5%, and other HAI (such as blood stream infections, hospital acquired pneumonia, urinary tract infections, and infections of mixed origin), contributed 3.7%.

Adherence to international guidelines for surgical prophylaxis was noted, but longer-than-recommended durations of antibiotic therapy, seen in 81% of cases, raises concern. Key indicators demonstrated 80% adherence to prescribing guidelines. The study revealed progress towards the WHO's AWaRe goal, with 64% of prescriptions using Access, 34% using Watch, and 2% Reserve antibiotics. However, challenges in documenting stop/review dates indicated potential for inappropriate treatment durations.

Conclusion

This report presents South Africa's third report on AMR surveillance. Whilst it has attempted to cover the data that was available, there are significant areas where additional data is needed to inform better policy and decision-making abilities in the future.

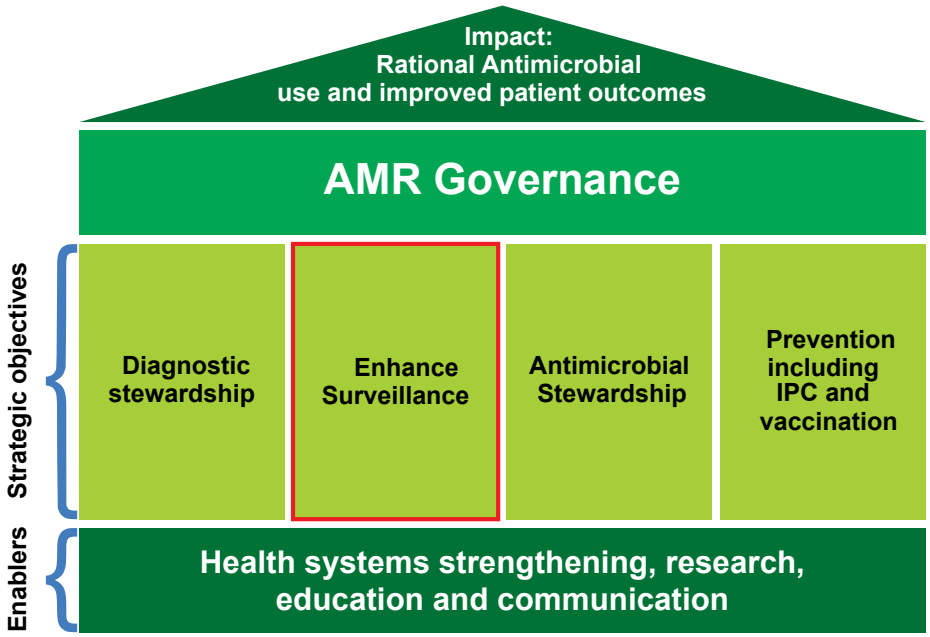
2. Introduction

South Africa pledged its commitment to the World Health Assembly resolution "Combating antimicrobial resistance including antibiotic resistance", adopted in May 2014, to develop a National Action Plan on AMR. By October 2014, the *Antimicrobial Resistance National Strategic Framework, 2014-2024* (AMR Strategic Framework) was developed and launched with the commitment of most of the key stakeholders within the human and animal health, agriculture, as well as science and technology sectors.

The AMR Strategic Framework defines South Africa's approach to manage AMR and limit further increases in resistant microbial infections and improve patient outcomes and livestock production and health. The vision is ***"to ensure the appropriate use of antimicrobials by healthcare and animal health professionals in all health establishments in South Africa to conserve the efficacy of antimicrobials for the optimal management of infections in human and animal health".***

The AMR Strategy Framework consists of five interconnected pillars. Strategic objectives to tackle AMR are presented in **Figure 1** below.

Figure 1: *The South African AMR Strategy Framework with the strategic objectives and key enablers*



This report was developed in fulfilment of one of the main pillars of the AMR Strategic Framework – "Enhance surveillance" with a corresponding objective *"to optimise and report on surveillance of AMR and antimicrobial use in humans and livestock in order to provide reliable data to optimise policy decisions and treatment choice".* The report also seeks to create a consolidated, representative view of AMR and antimicrobial use in South Africa and to monitor trends going forward to evaluate the impact of the AMR Strategy Framework.

A final objective of surveillance is the gathering of data to support research into AMR and other strategic initiatives, policy, and planning decisions within the public health realm, as well as to identify data needs and gaps to support policy decision-making.

Whilst we aim to ensure that the report follows the One Health approach, including human and animal health as it applies to AMR organisms and antimicrobial use, the inclusion of animal and environmental data in this report proved challenging in completeness and were therefore excluded.

3. Abbreviations

AMR	Antimicrobial Resistance
ATC	Anatomical Therapeutic and Chemical
AWaRe	Access, Watch, Reserve
BRICS	Brazil, Russia, India, China, and South Africa
BSI	Blood Stream Isolates
CAI	Community Associated Infection
CLSI	Clinical and Laboratory Standards Institute
DDD	Defined Daily Dose
ESBL	Extended Spectrum Beta-Lactamase
ESKAPE	*Enterococcus faecalis* and *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Escherichia coli*
GPPS	Global Point Prevalence Survey
HAI	Healthcare Associated Infection
IPC	Infection Prevention and Control
ICU	Intensive Care Unit
LMIC	Low- and Middle-Income Country
MAC	Ministerial Advisory Committee
MRSA	Methicillin resistant *S. aureus*
NDoH	National Department of Health
NHLS	National Health Laboratory Service
NICD	National Institute for Communicable Diseases
NICU	Neonatal Intensive Care Unit
SAHPRA	South African Health Products Regulatory Authority
TWG	Technical Working Group
UTI	Urinary Tract Infection
WHO	World Health Organization

4. Antimicrobial Resistance in Humans

This section of the report focuses on AMR data derived from blood culture specimens for all public health facilities (including all levels of care, military, and prisons) and the majority of private-sector hospitals that are serviced by various private laboratory groups (Lancet Laboratories, Ampath, Vermaak and Partners Pathologists, and PathCare). All AMR data for this report can be viewed on the National AMR Dashboard, available through the National Institute for Communicable Diseases (NICD) website, http://www.nicd.ac.za. Further details of the surveillance system and its design can be seen in Annexure A. All statements regarding resistance patterns and trends analysis are based on blood stream isolates (BSIs), which may indicate a selection bias.

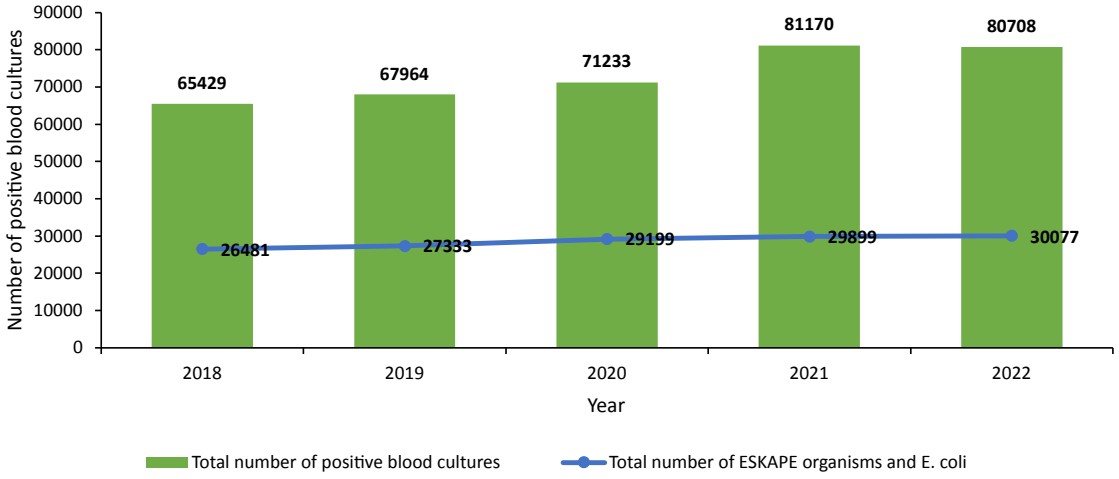
The acronym ESKAPE is used to describe the organisms that currently form part of the surveillance system and characterise an internationally accepted group of AMR-priority pathogens. The ESKAPE acronym[4] stands for the following organisms:

- *Enterococcus faecalis and Enterococcus faecium*
- *Staphylococcus aureus*
- *Klebsiella pneumoniae*
- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Escherichia coli*

4.1 Overall burden of ESKAPE organisms in the public sector

The burden of ESKAPE organisms causing bacteraemia in the entire public sector was calculated for a five-year period (2018-2022) using data from the National Health Laboratory Service (NHLS). The total number of consecutive blood cultures tested increased from 3 610 401 in 2018 to 4 207 656 in 2022. The percentage of ESKAPE organisms identified from all positive blood cultures with antimicrobial susceptibility results decreased during the five-year period, ranging from 41% - 37% (**Figure 2**).

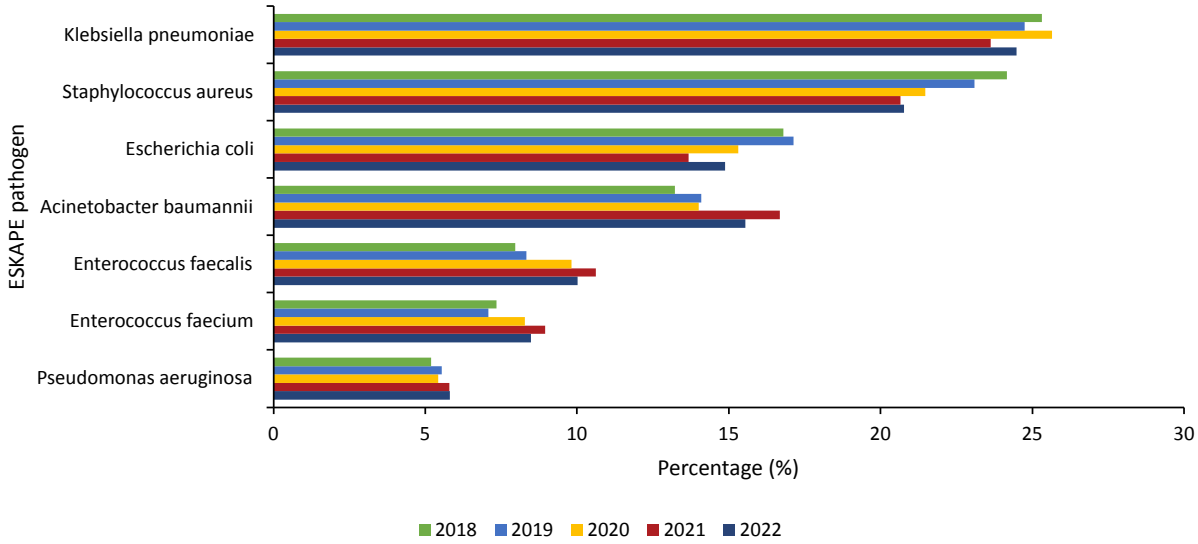
Figure 2: *Burden of ESKAPE pathogens in the public sector, 2018-2022*



4 Helen W. Boucher, George H. Talbot, John S. Bradley, John E. Edwards, Jr, David Gilbert, Louis B. Rice, Michael Scheld, Brad Spellberg, and John Bartlett. Bad Bugs, No Drugs: No ESKAPE! An Update. From the Infectious Diseases Society of America. IDSA Report on Development Pipeline • CID 2009:48 (1 January)

The most common organisms cultured during the five-year period were *K. pneumoniae*, *S. aureus*, followed by *E. coli* and *A. baumannii* (**Figure 3**). During 2020, 2021 and 2022, there was an increase in the number of cases of *A. baumannii*, *E. faecalis* and *E. faecium*.

Figure 3: *Percentage breakdown of ESKAPE bacterial organisms in the public sector, 2018-2022*



4.2 AMR at a glance (2018 - 2022 data) – Public and Private Sector

The reporting of AMR in humans was focused on certain key drug/bug combinations from 2018 to 2022, across the public and private health sectors. These data represent the organisms and the antibiotics commonly used to treat them that are the most critical for monitoring and tracking changes in resistance.

4.2.1 *Klebsiella pneumoniae*

K. pneumoniae was one of the most common organisms isolated from blood in both the private and public sectors in South Africa.

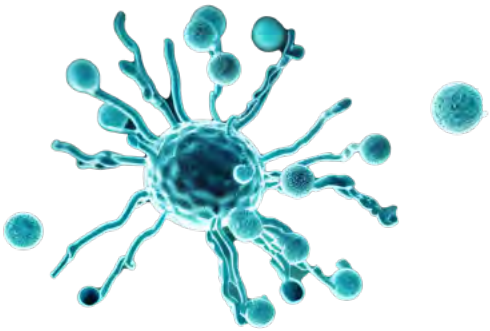
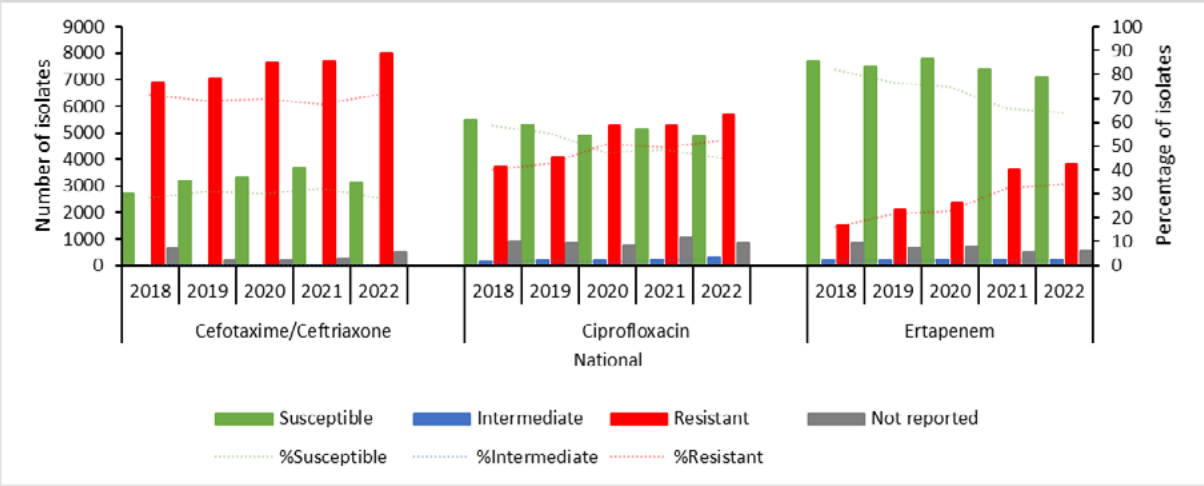
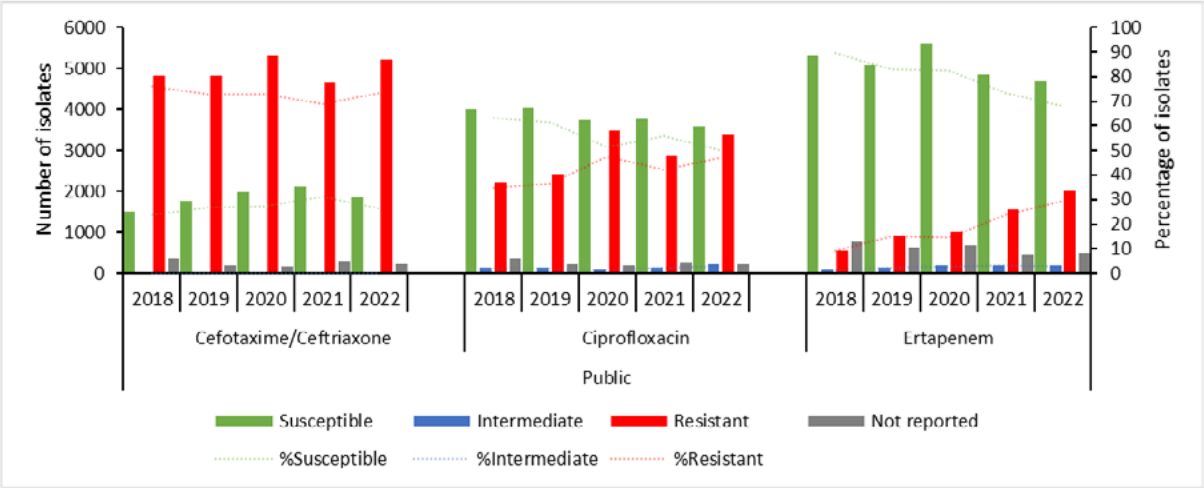
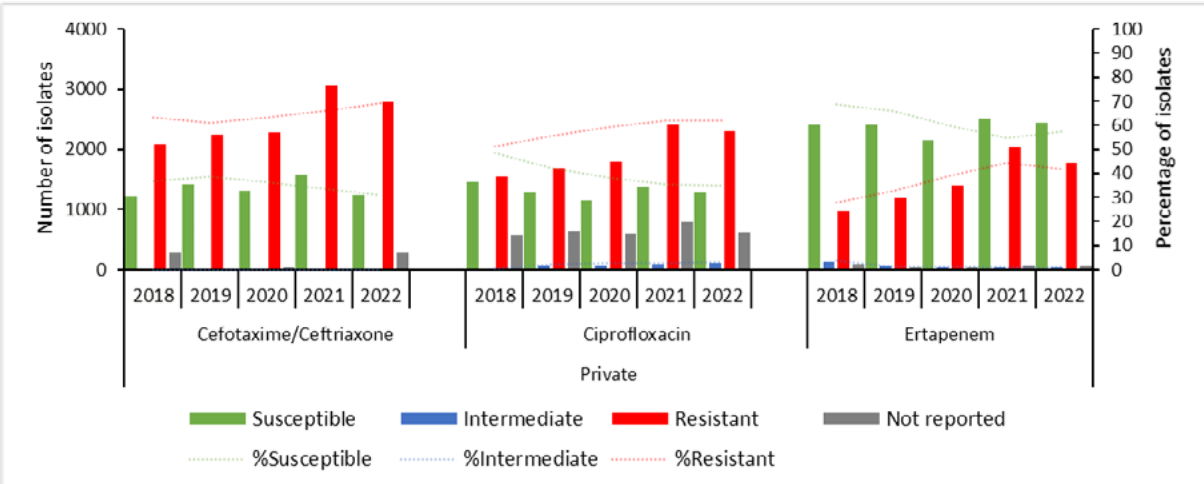


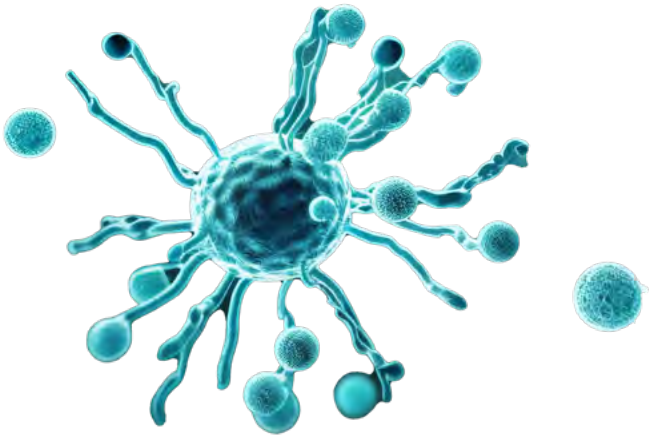
Figure 4: *K. pneumoniae susceptibility to 3rd generation cephalosporins, quinolones and carbapenems, 2018-2022*





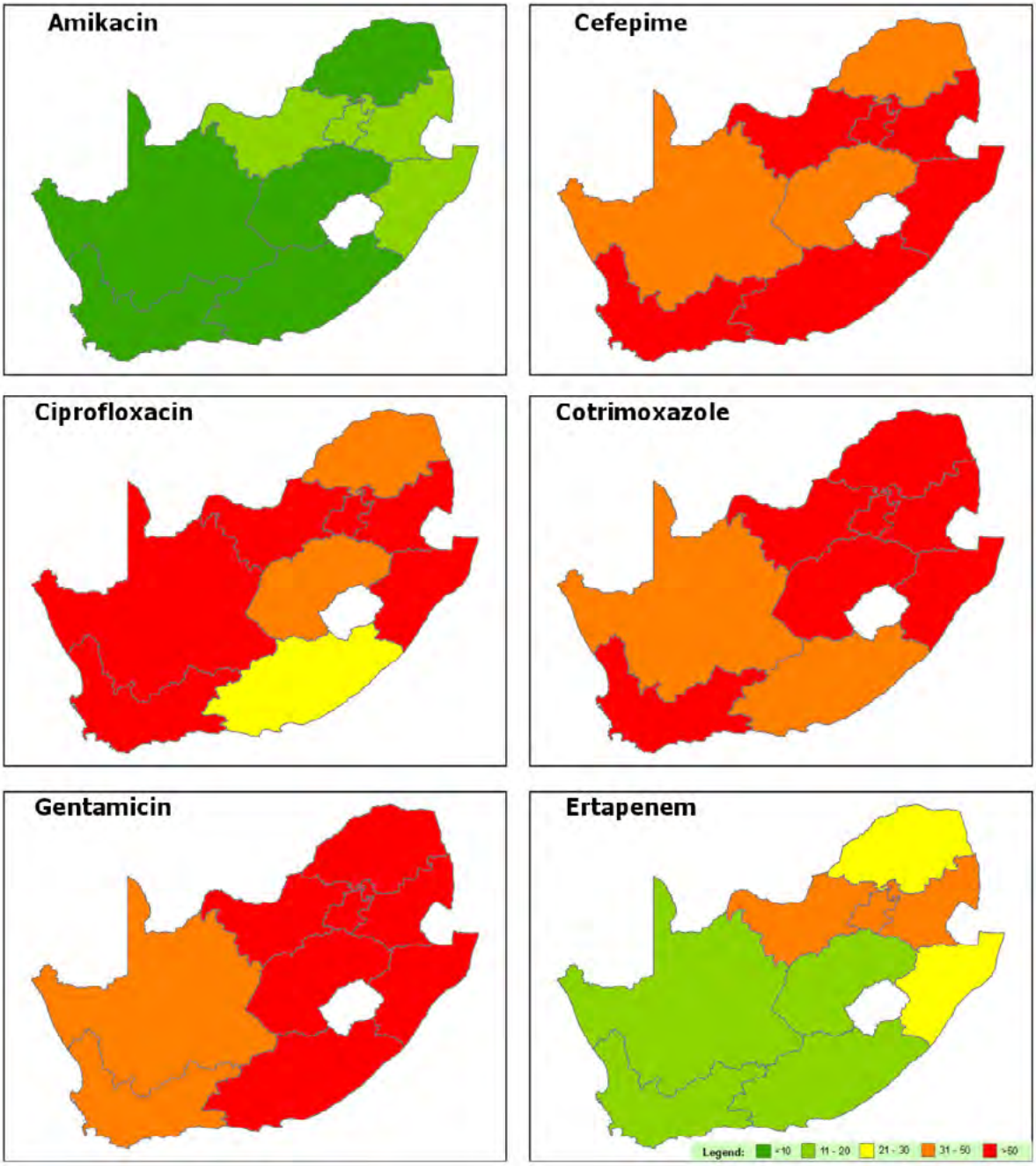


The national prevalence of extended spectrum beta-lactamase (ESBL)[5] producing *K. pneumoniae* remained on average 70% (i.e., resistant to 3rd generation cephalosporins) over the past five years (2018 to 2022) (Figure 4). The presence of an ESBL affects the susceptibility of *K. pneumoniae* to all cephalosporins, and significantly limits the use of this class of antibiotics as a therapeutic option. These ESBL positive isolates often also display associated quinolone resistance (most likely carried on the same plasmid). This often leaves only the carbapenem group of antibiotics as the therapeutic option for treatment of these, the most common blood culture pathogens. During the five-year period, there was a decrease in susceptibility to ciprofloxacin from 58% in 2018 to 45% in 2022 and a corresponding decrease in susceptibility to ertapenem from 82% in 2018 to 64% in 2022. Furthermore, resistance to ertapenem was higher in the private sector ranging from 28% in 2018 to 42% in 2022 compared to the public sector ranging from 9% in 2018 to 29% in 2022 (**Figure 4**). Resistance to 3rd generation cephalosporins remained similar across most provinces in 2022. However, resistance to carbapenems differed across provinces (**Figure 5**).



5 ESBLs are enzymes that confer resistance to most beta-lactam antibiotics, including penicillins and cephalosporins. Infections with ESBL-producing organisms have been associated with poor outcomes.

Figure 5: *Choropleth map for K. pneumoniae by province in South Africa, 2022 (legend shows ranges for % resistant)*

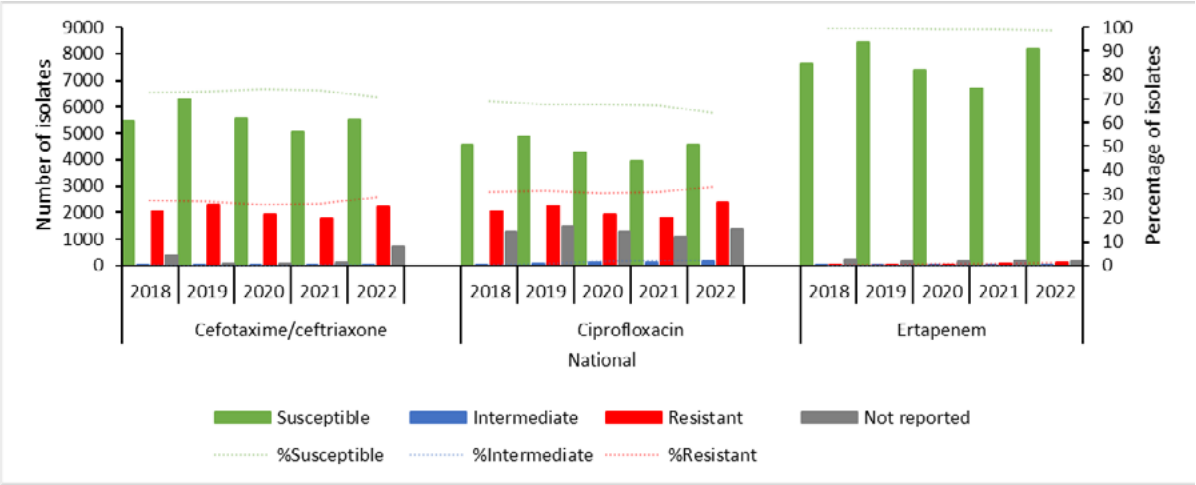


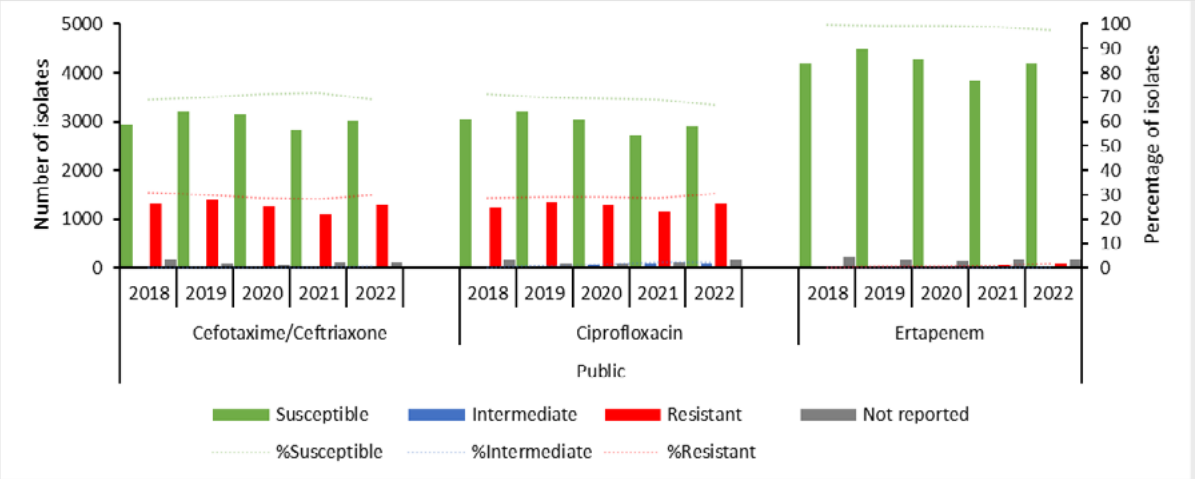
4.2.2 *Escherichia coli*

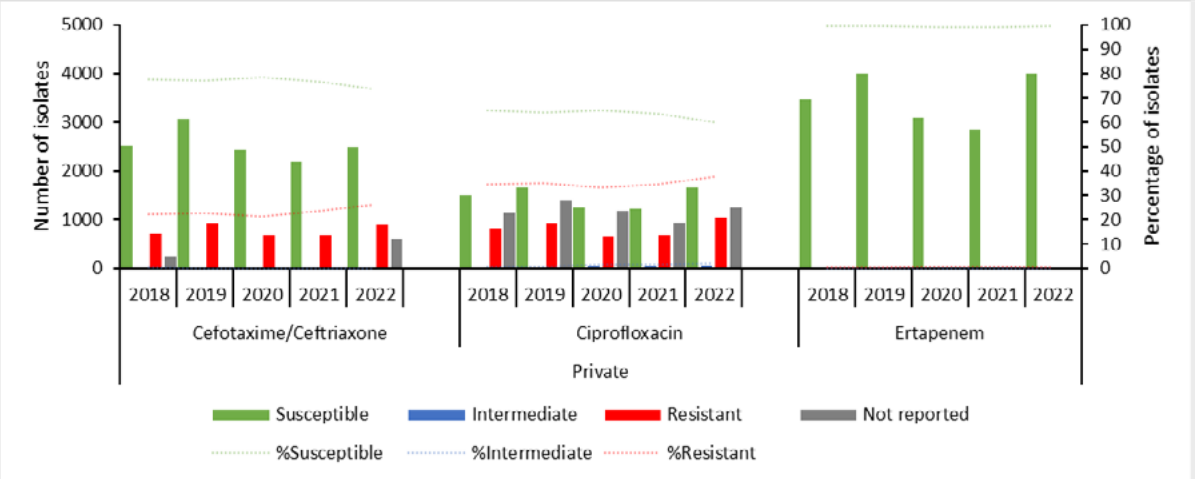
E. coli was the second most common Gram-negative pathogen isolated from blood in South Africa. While the data are unable to differentiate community- from healthcare-associated infections, *E. coli* may reflect community infections associated with urinary tract infections (UTIs). Nationally, resistance to ciprofloxacin (used as a proxy for fluoroquinolones) remained similar from at 31% from 2018 to 2021, increasing slightly to 33% in 2022. In 2022, resistance to ciprofloxacin was higher in the private sector (38%) compared to

the public sector (31%). Of note, susceptibility to 3rd generation cephalosporins was higher in the private sector compared to the public sector **(Figure 6)**. Differences for both fluoroquinolones and 4th generation cephalosporins were shown between geographic areas **(Figure 7)**.

Figure 6: *E. coli susceptibility to 3rd generation cephalosporins, quinolones and carbapenems, 2018-2022*

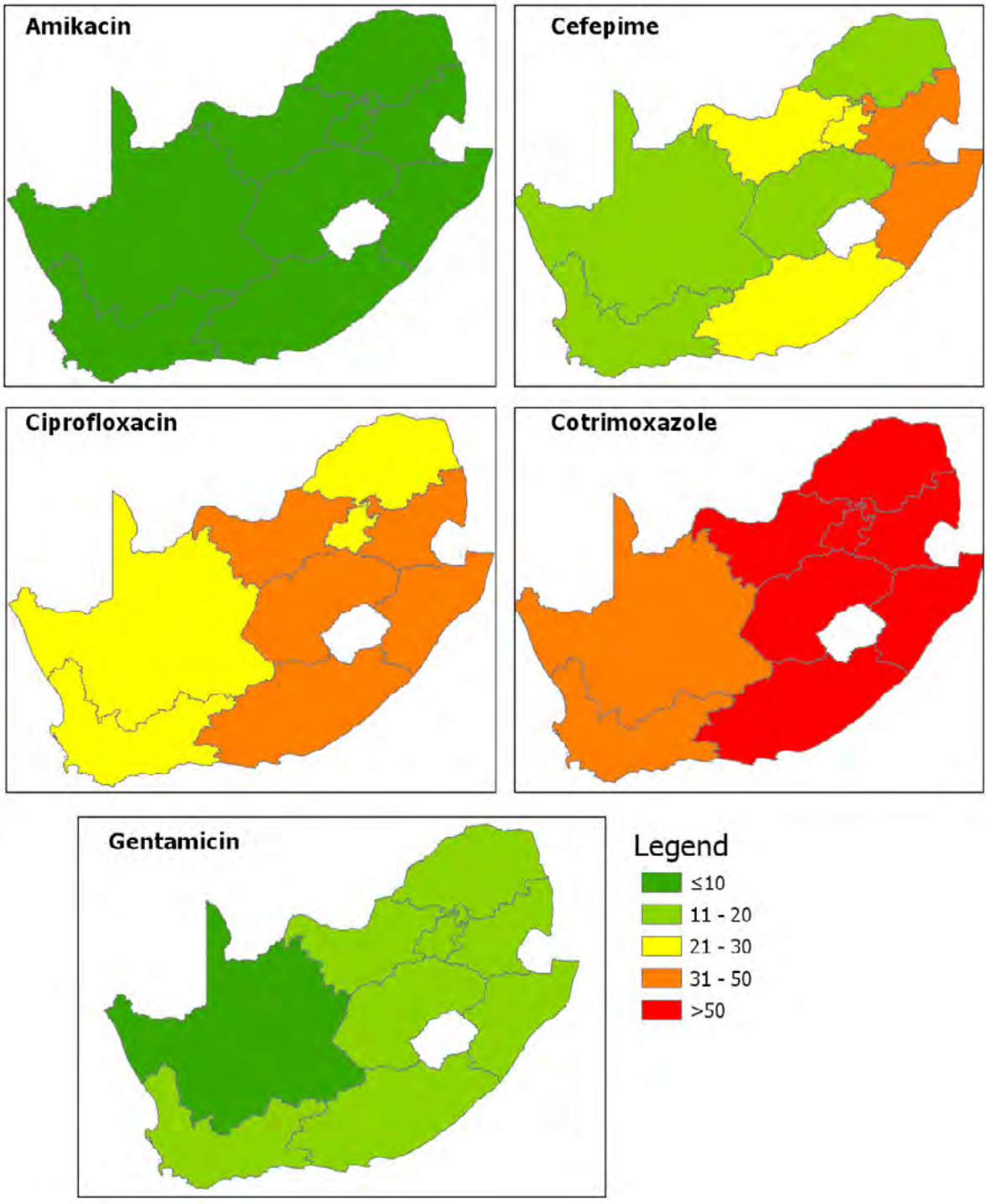






The high prevalence of resistance to fluoroquinolones is of concern, as they are frequently used as one of the antibiotics for treatment of UTIs. However, this high prevalence of resistance may be affected by selection bias, with a larger proportion of healthcare-associated isolates or by specimen collection practices (for example, specimens being taken after a patient has failed therapy, thus increasing the chance of isolating a resistant organism). However, this observed increase in quinolone resistance suggests a need for a prevalence study of community and healthcare acquired UTIs.

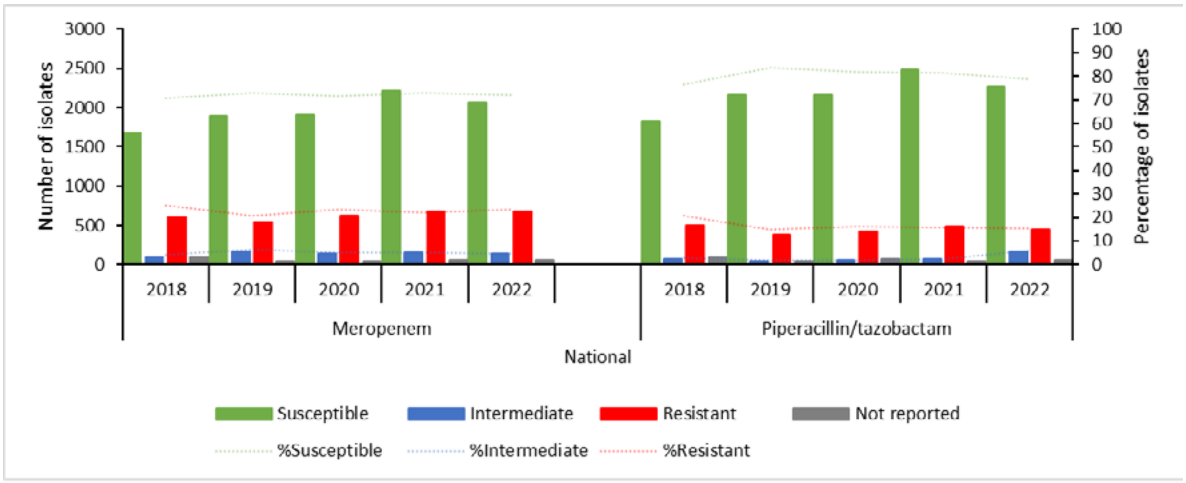
Figure 7: *Choropleth map for E. coli by province in South Africa, 2022 (legend shows ranges for % resistant)*

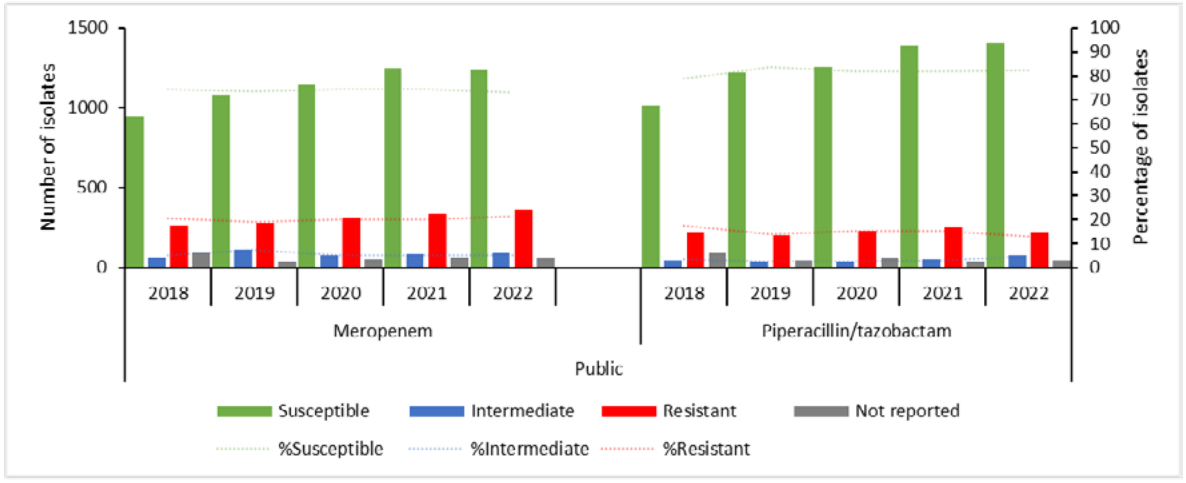


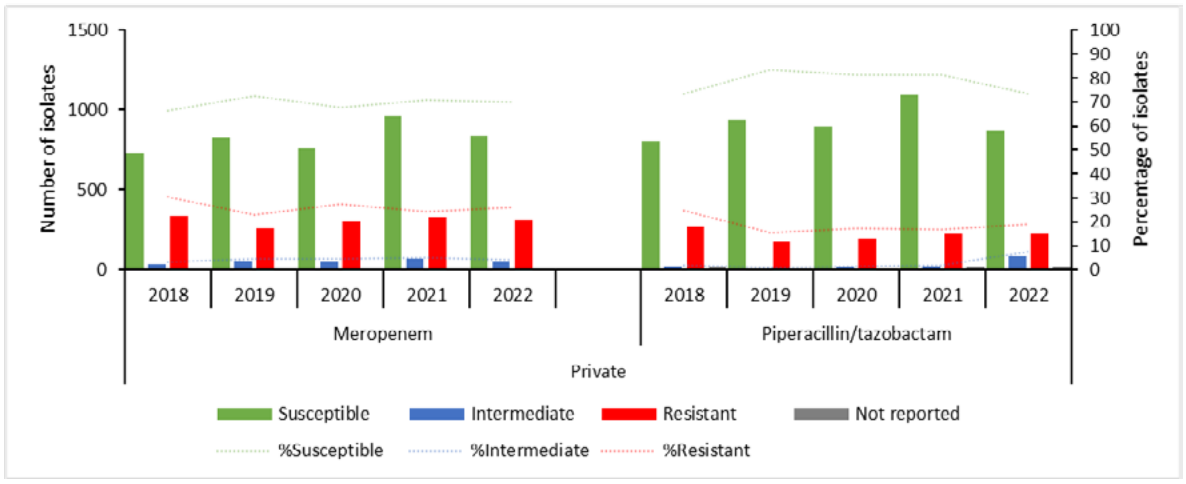
4.2.3 *Pseudomonas aeruginosa* and *Acinetobacter baumannii*

P. aeruginosa and *A. baumannii* are commonly regarded as healthcare-associated pathogens. The 2022 national data showed that 15% of *P. aeruginosa* isolates were resistant to piperacillin/tazobactam, and 23% resistant to meropenem, representing first- and second-line therapeutic options respectively. Importantly, from 2018 there has been a decline in resistance to piperacillin/tazobactam and a corresponding decline in meropenem resistance. This was noted in both the public and private sectors in South Africa **(Figure 8)**.

Figure 8: *Pseudomonas aeruginosa susceptibility to carbapenems and beta-lactams/beta-lactam inhibitors, 2018-2022*

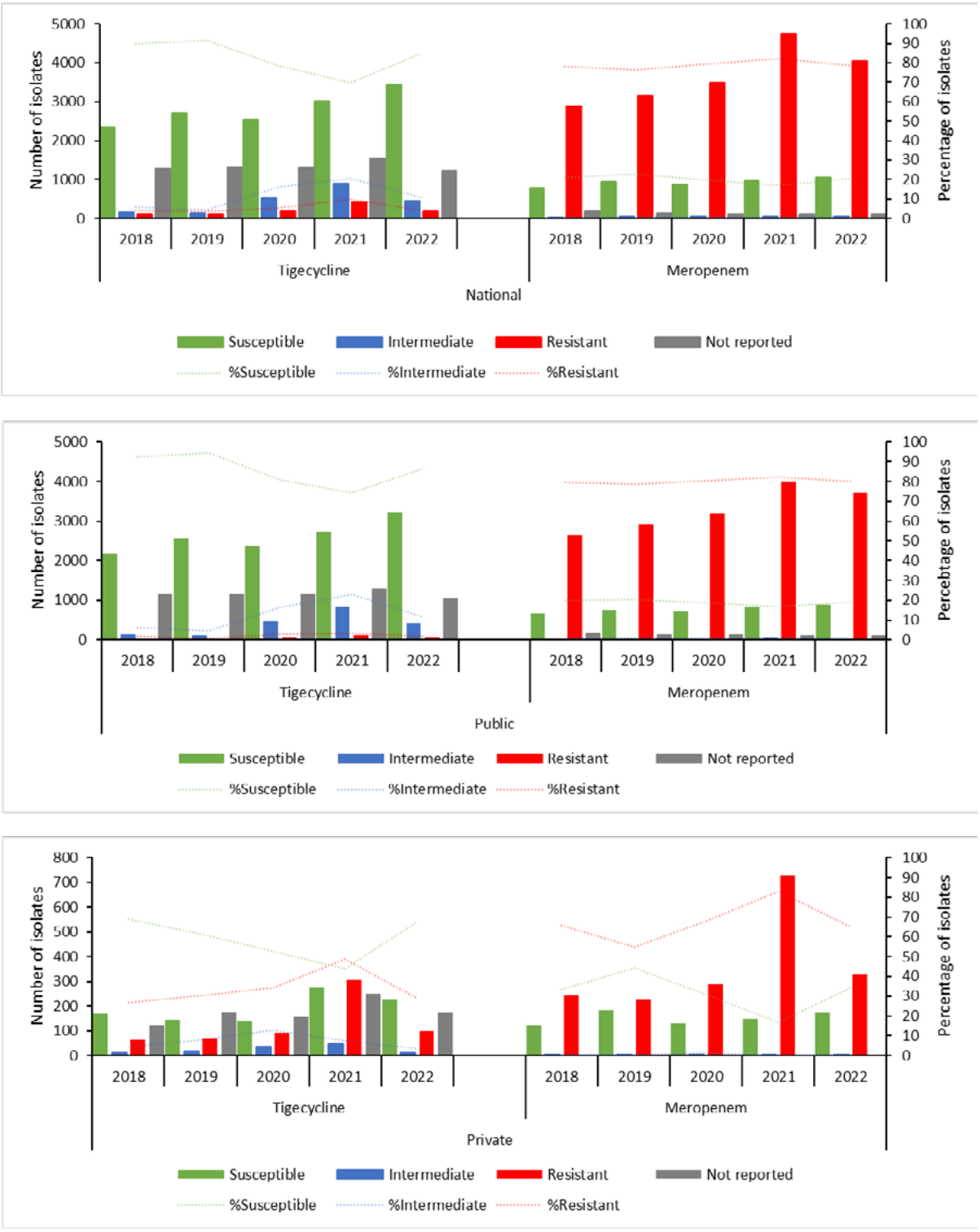






There were also geographic variations in susceptibility to both piperacillin/tazobactam and meropenem against *P. aeruginosa* **(Figure 10)**. These differences may suggest empirical use of these agents, particularly for the Gauteng province as resistance increased from 25% in 2021 to 30% in 2022.

Figure 9: *Acinetobacter baumannii susceptibility to glycylcyclines and carbapenems, 2018-2022*



Carbapenem resistance to *A. baumannii* has been increasing through the years, with resistance observed of 80% of all isolates to meropenem in 2022. However, higher susceptibility was observed in the private sector with 34% compared to the public sector with 19% **(Figure 9)**. This finding was consistent throughout all the provinces **(Figure 11)**. Treatment options for multidrug-resistant *A. baumannii* are very limited, and consist of either colistin, tigecycline or combination treatment. Resistance to tigecycline was recorded at 10% in 2021 with a decline to 4% in 2022. Colistin is associated with nephrotoxicity as well as challenges with access (it is not a registered product in South Africa and can only be procured through approval of a Section 21 application through SAHPRA). There are also concerns around the clinical outcomes in patients treated with tigecycline as a single agent. The NICD's GERMS-SA surveillance, with the objective of providing strategic information regarding trends in pathogens of public health importance, confirmed no *mcr*1-5 plasmid mediated resistance for both *A. baumannii* and *K. pneumoniae*.

Figure 10: *Choropleth map for Pseudomonas aeruginosa by province in South Africa, 2022 (legend shows ranges for % resistant)*

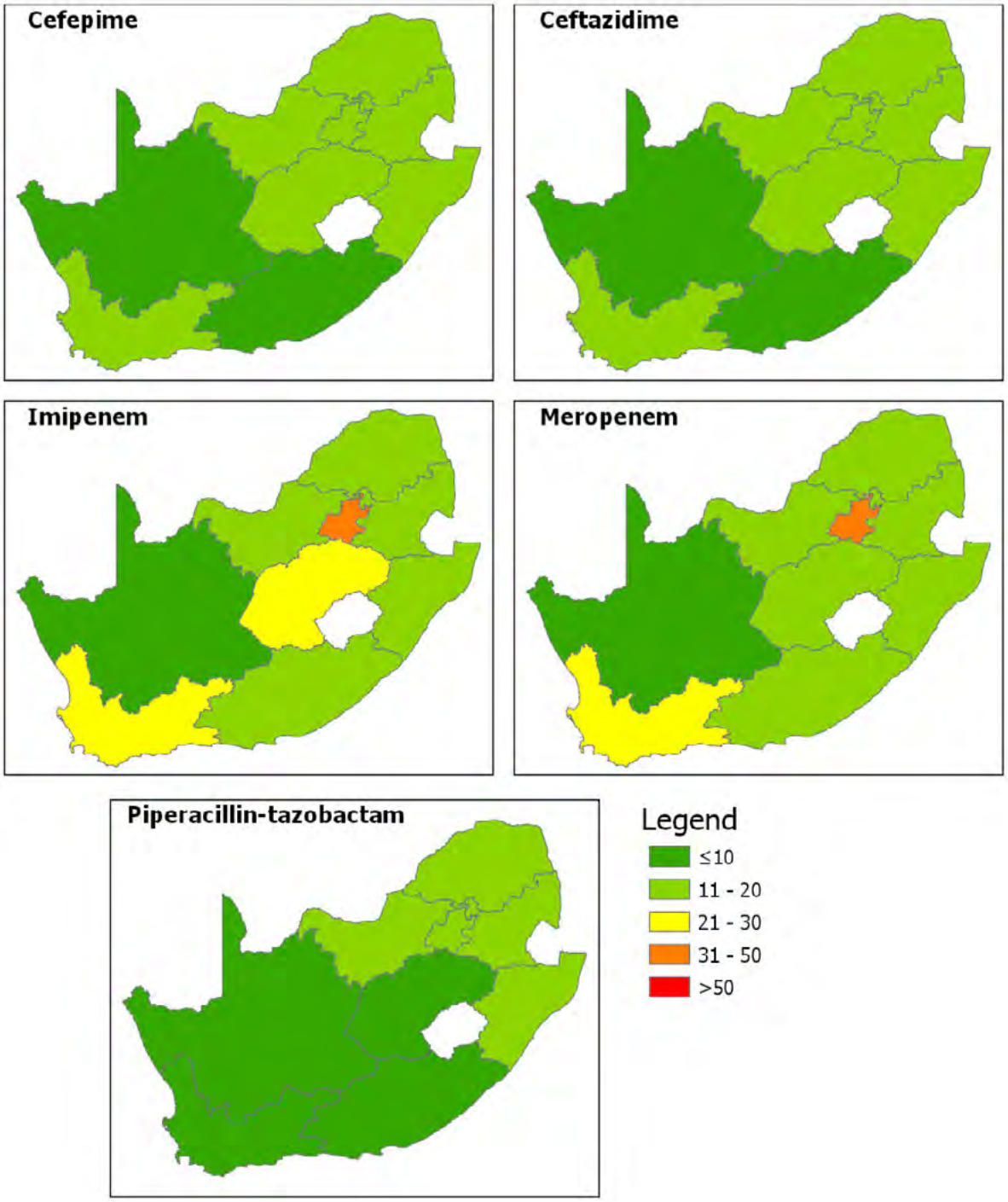
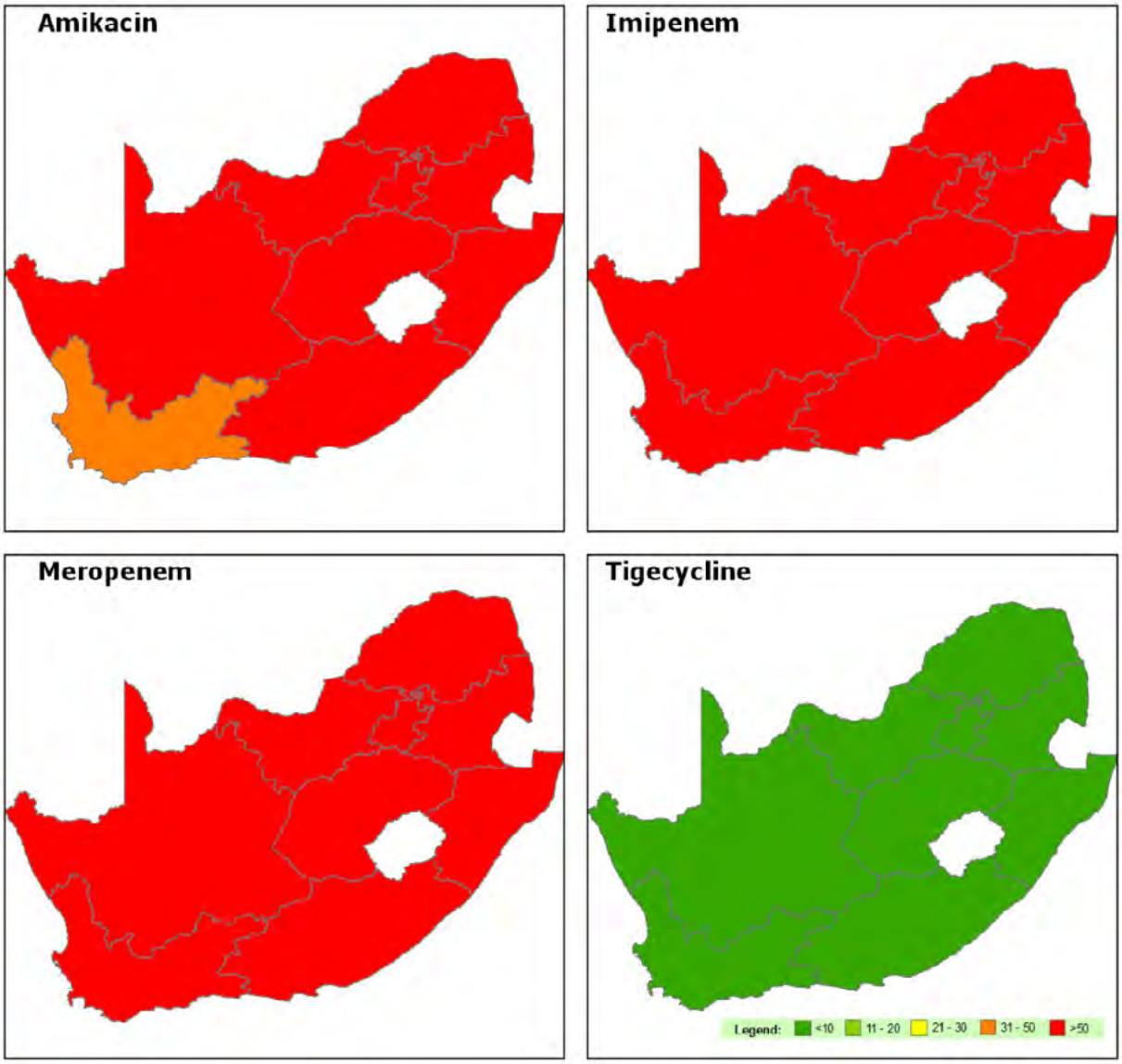


Figure 11: *Choropleth map for Acinetobacter baumannii by province in South Africa, 2022 (legend shows ranges for % resistant)*



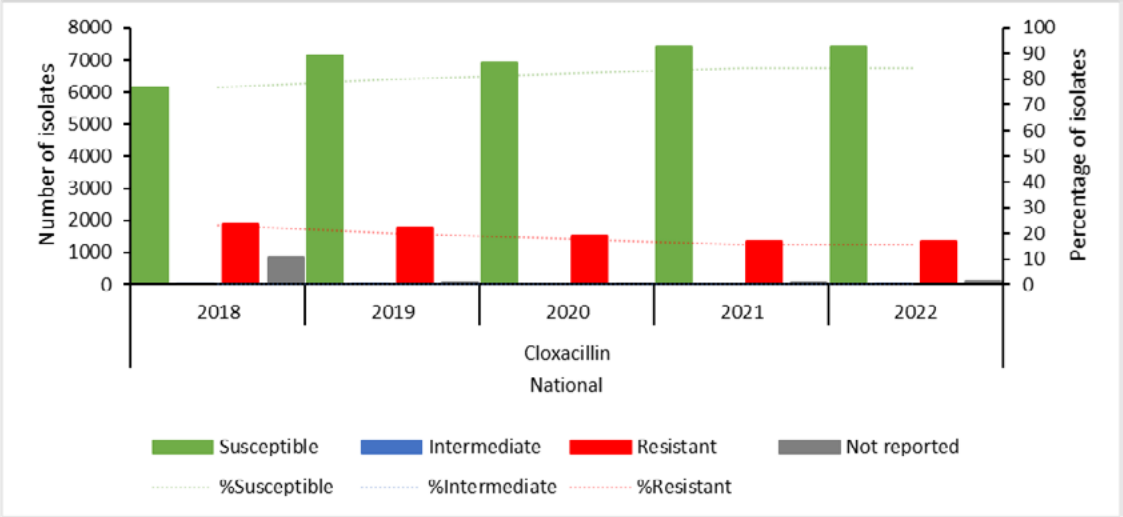
4.2.4 *Staphylococcus aureus*

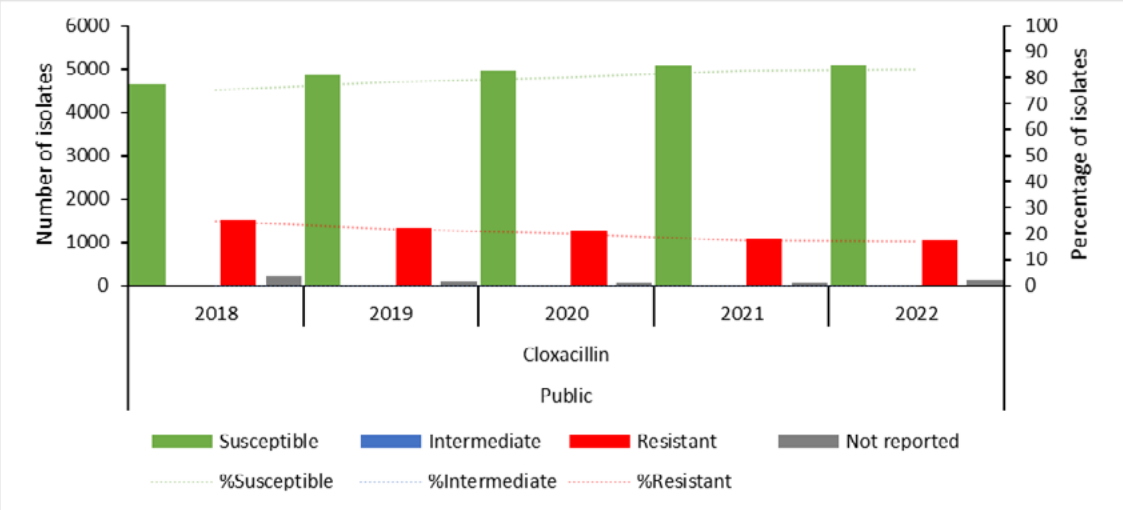
A consistent decline for methicillin-resistant *S. aureus* (MRSA) has been observed, from 23% in 2018 to 16% in 2022 **(Figure 12)**, with resistance varying across the provinces **(Figure 13)**. Active surveillance in selected sites in two provinces has shown that just under 8% of MRSA bacteraemia was community acquired.[6] This is in contrast to the situation in some other countries where >50% of MRSA originate in the community.

6 O. Perovic. A Singh-Moodley, N. P. Govender, R. Kularatne, A. Whitelaw, V. Chibabhai, P. Naicker, N. Mbelle, R. Lekalakala, V. Quan, C. Samuel, E. Van Schalkwyk; for GERMS-SA. A small proportion of community-associated methicillin-resistant Staphylococcus aureus bacteraemia, compared to healthcare-associated cases, in two South African provinces, Eur J Clin Microbiol Infect Dis. DOI 10.1007/s10096-017- 3096-3; August 2017

The mainstay of treatment for MRSA remains vancomycin, and vancomycin resistance, while it has been noted in other countries, has not yet been reported in South Africa.

Figure 12: *Staphylococcus aureus susceptibility to methicillin, 2018-2022*





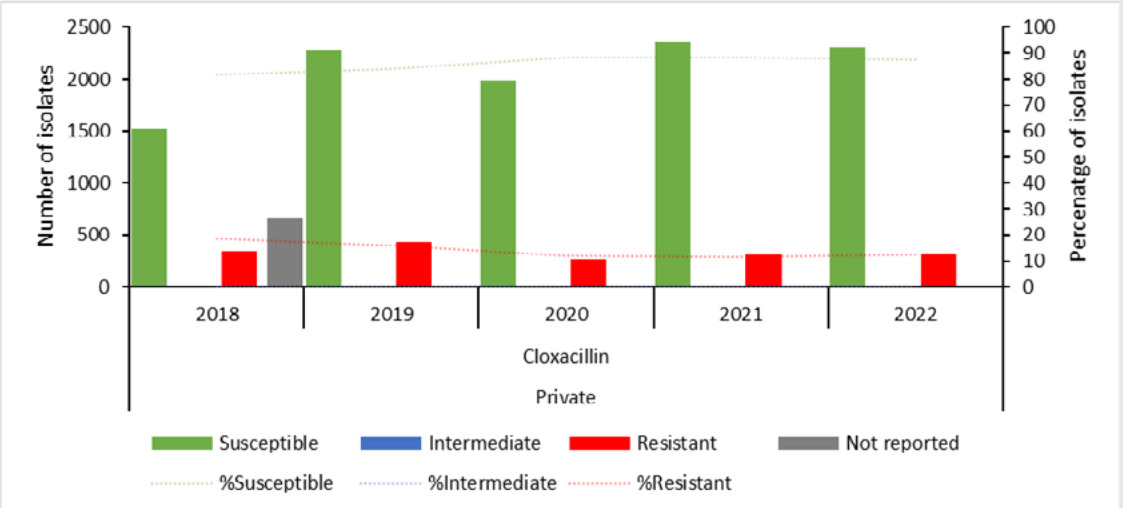
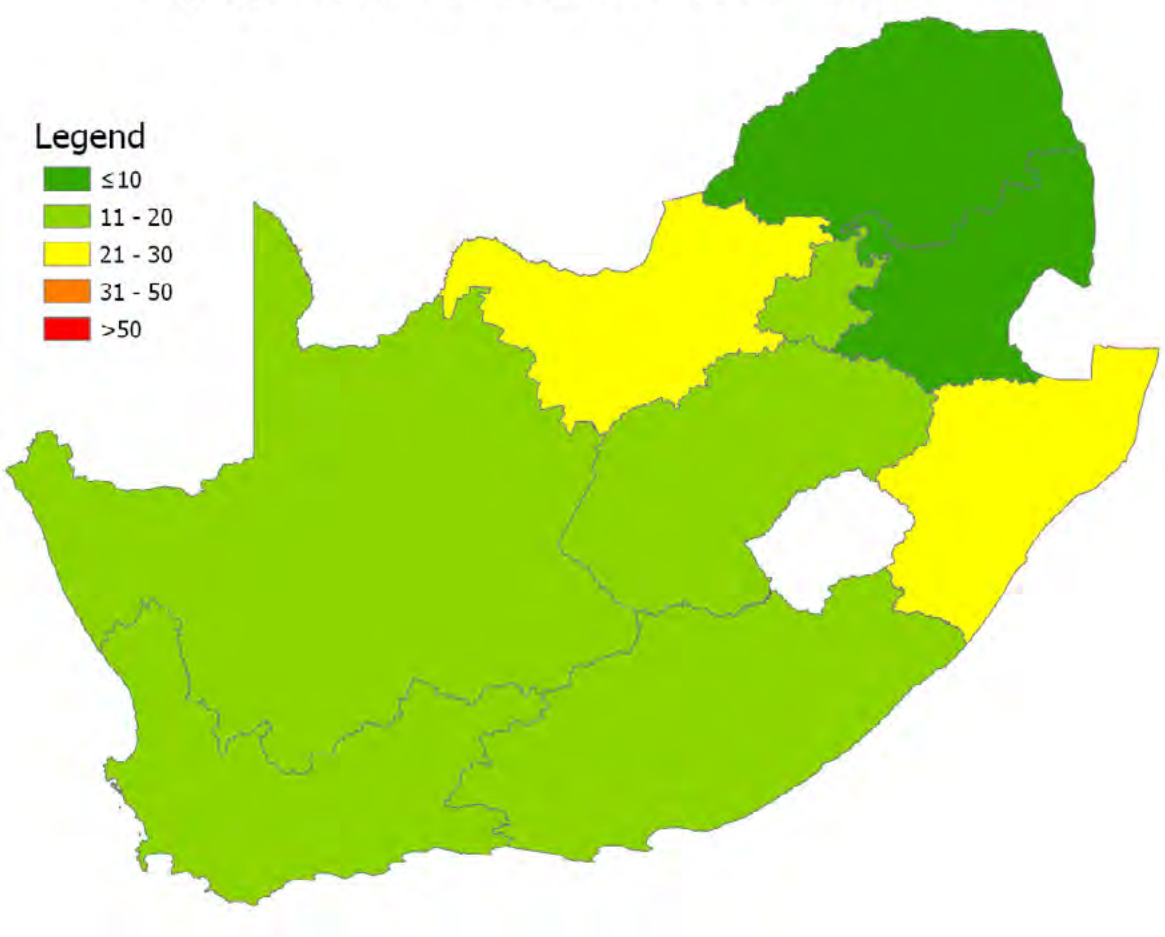


Figure 13: *Choropleth map for Staphylococcus aureus by province in South Africa, 2022 (legend shows ranges for % resistant)*



4.2.5 *Enterococcus faecalis* and *Enterococcus faecium*

E. faecalis was commonly susceptible to ampicillin (which remains the treatment of choice), with resistance at 7% in 2022 **(Figure 14)**. In contrast, ampicillin resistance in *E. faecium* was seen in more than 95% of isolates in line with global distribution **(Figure 15)**. In 2022, the Free State and North West provinces showed higher resistance to ampicillin compared to other provinces **(Figure 16)**.

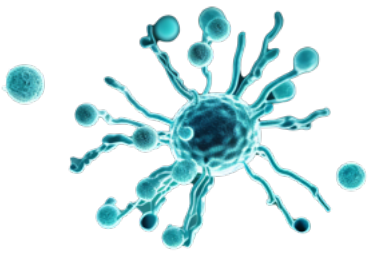
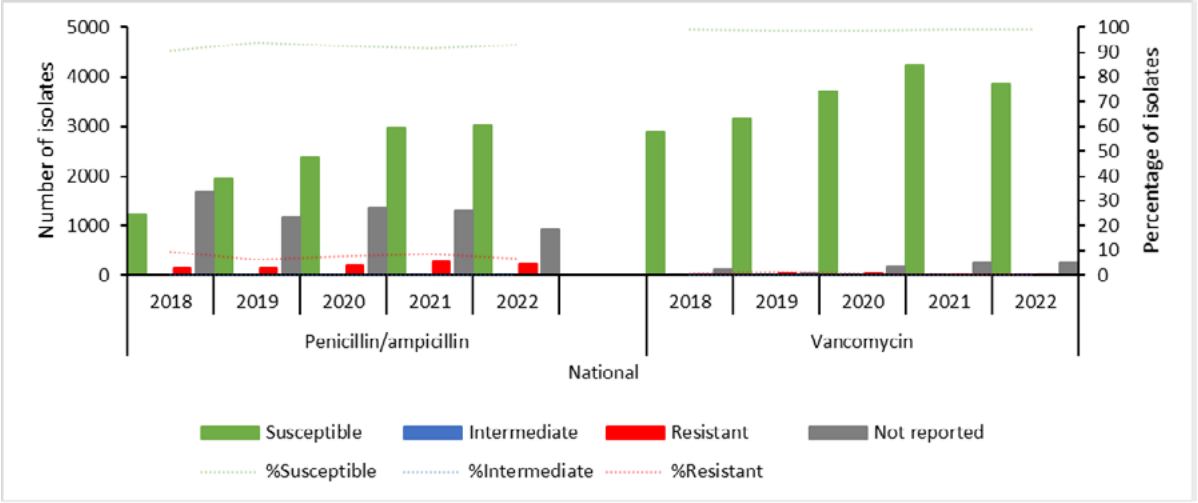
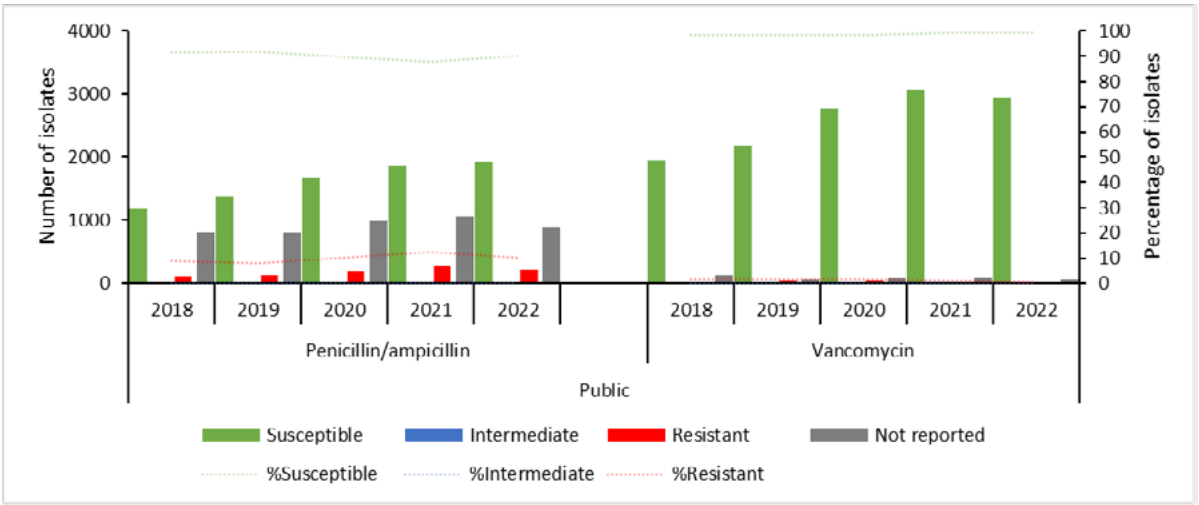


Figure 14: *Enterococcus faecalis susceptibility to ampicillin and vancomycin, 2018-2022*





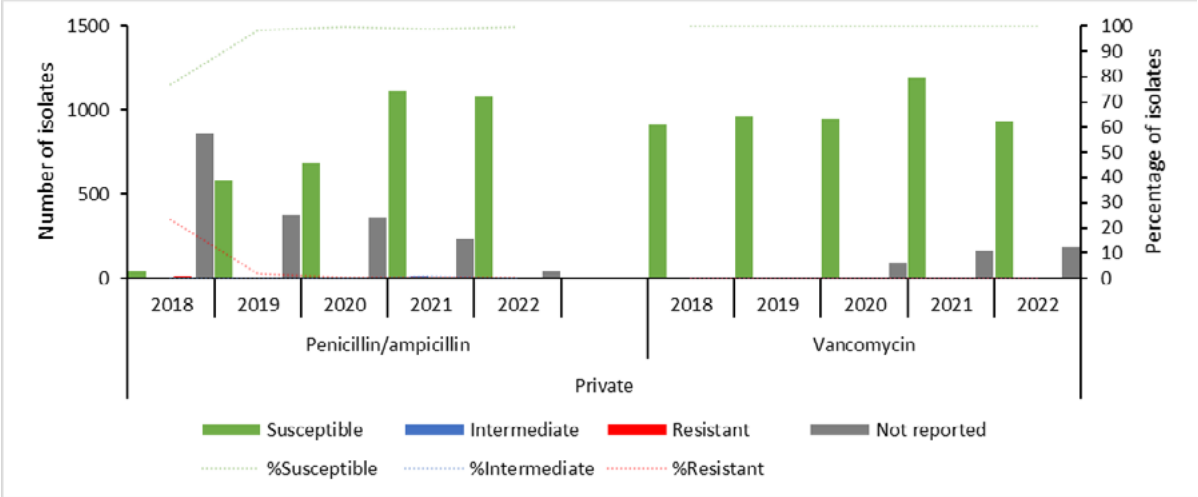
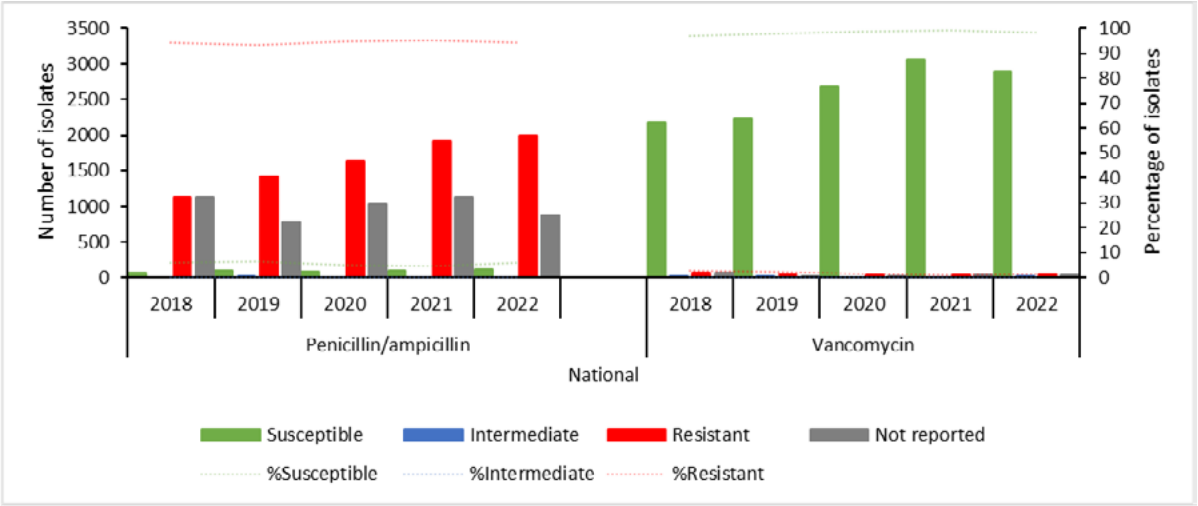
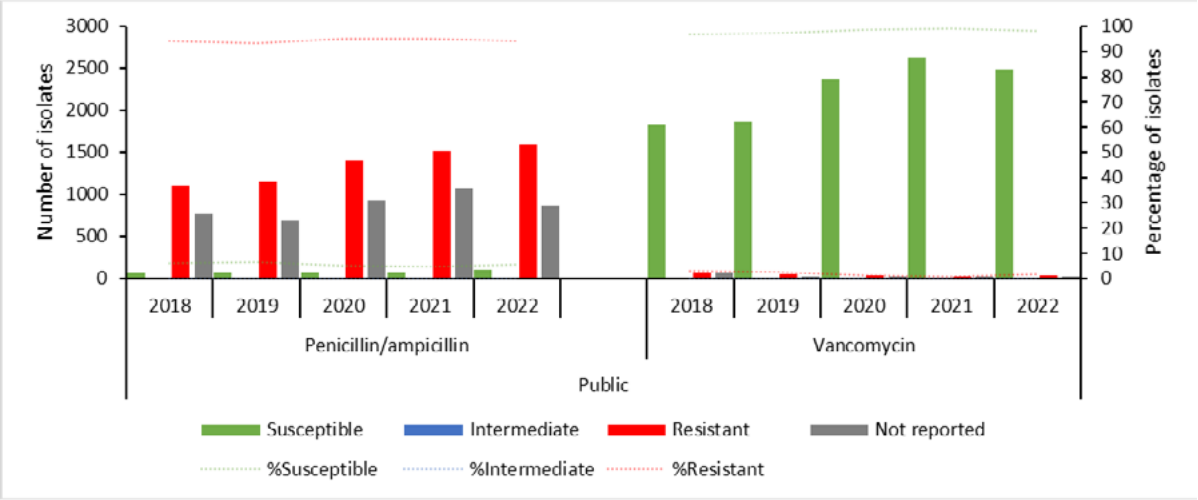
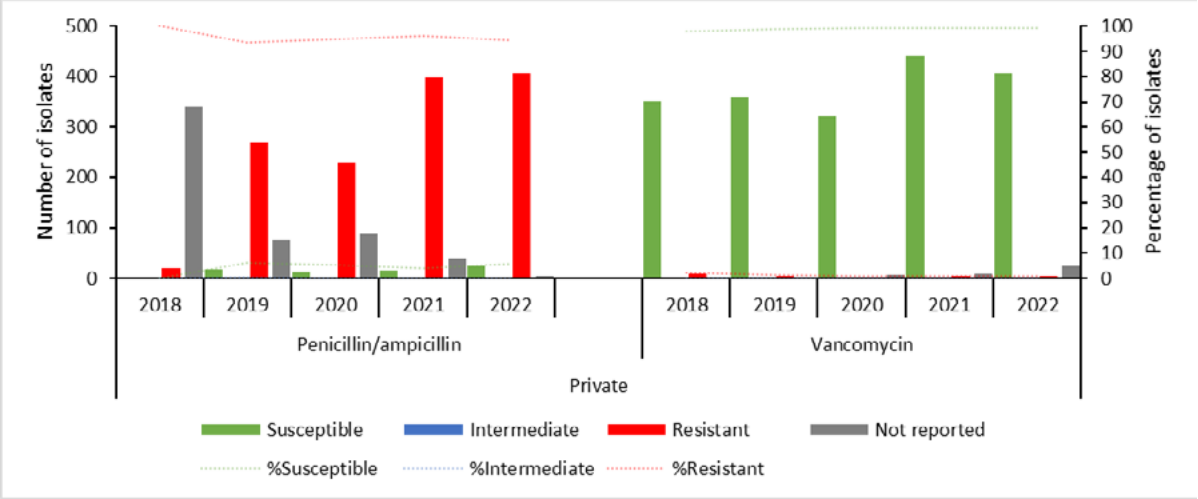


Figure 15: *Enterococcus faecium susceptibility to ampicillin and vancomycin, 2018-2022*







Of concern is the resistance to vancomycin in enterococci. This is a therapeutic challenge as there are limited alternatives to vancomycin, especially in the public sector. Vancomycin resistance of 5% in *E. faecalis* was recorded in 2016 and is now present in 1% of blood culture isolates. While vancomycin resistance remains uncommon in *E. faecalis*, it may become an emerging problem in *E. faecium* **(Figure 15)**, although resistance has dropped nationally over the last 5 years with an average of 2%. No geographic variations were noted in 2022 **(Figure 17)**.

Figure 16: *Choropleth map for E. faecalis by province in South Africa, 2022 (legend shows ranges for % resistant)*

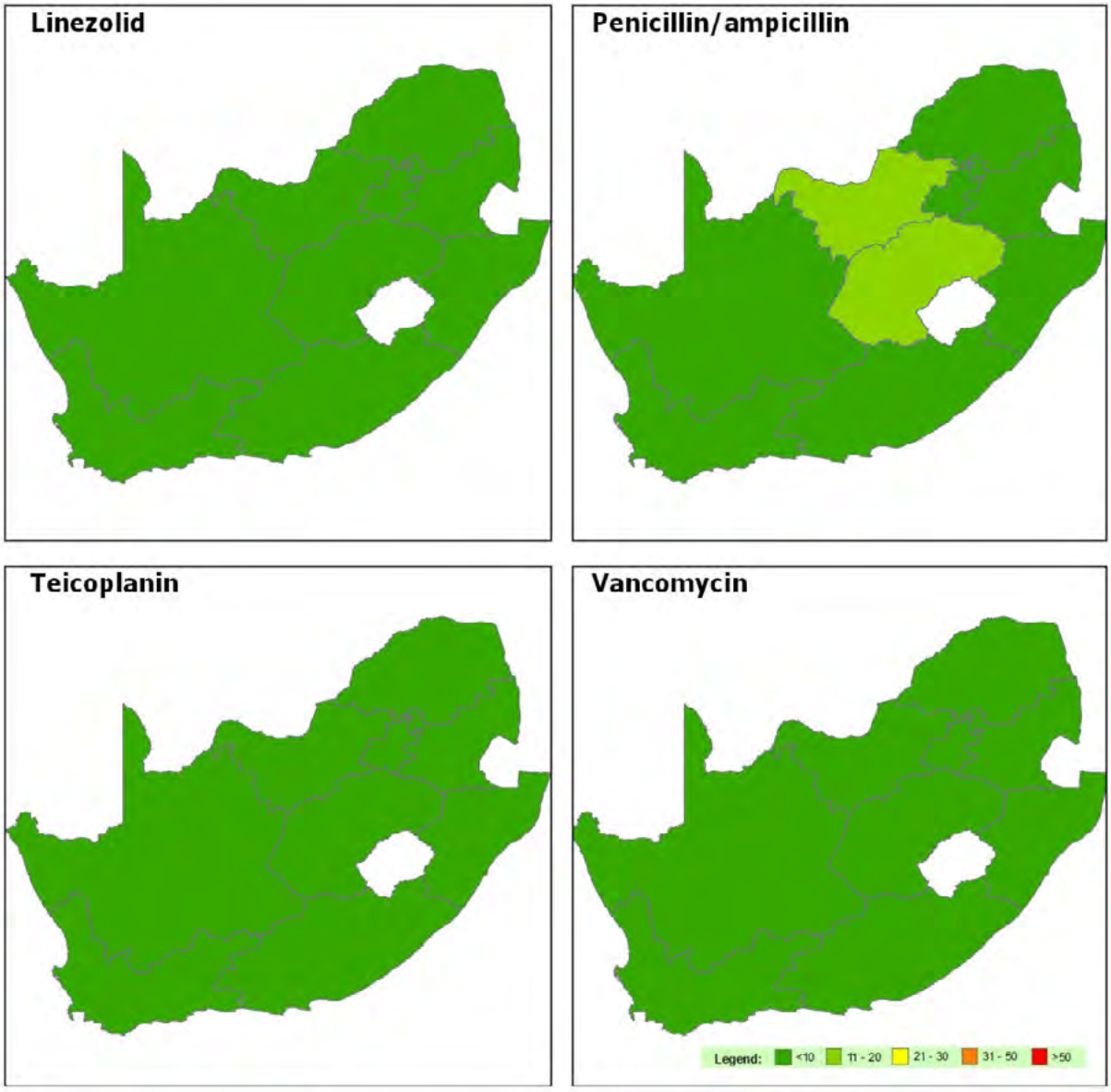
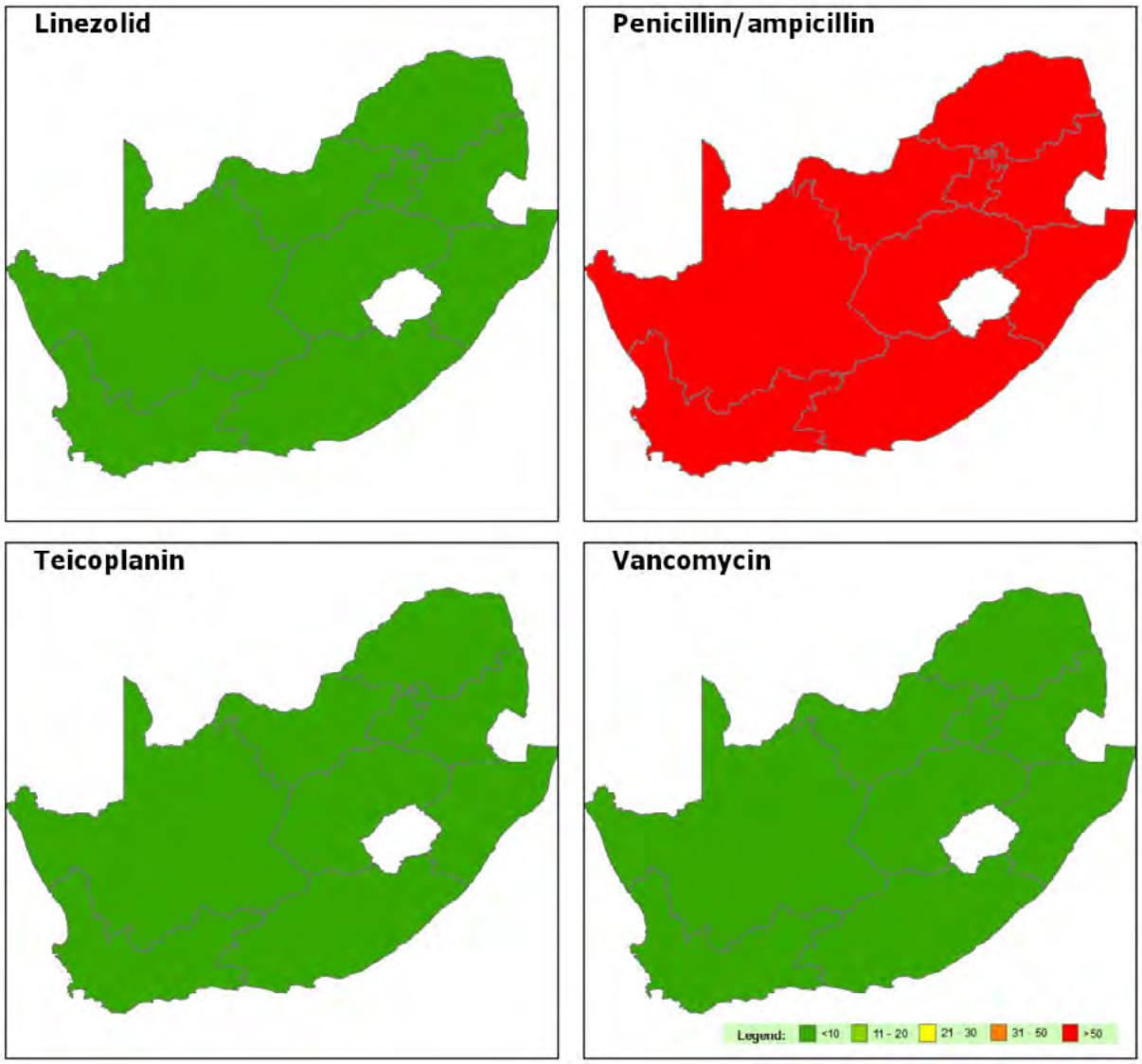


Figure 17: *Choropleth map for E. faecium by province in South Africa, 2022 (legend shows ranges for % resistant)*



4.2.6 AMR in Community Acquired Uncomplicated Urinary Tract Infections

A pilot study was conducted to determine the AMR and epidemiology in adult women with culture-confirmed community-acquired uncomplicated UTIs at a primary healthcare facility in Gauteng Province over the period April 2022 to June 2023.

Midstream urine specimens were taken from enrolled non-pregnant female patients aged more than 18 years old with signs and symptoms suggestive of a UTI. Laboratory testing was performed at the NICD, and antimicrobial susceptibility testing was interpreted using the Clinical and Laboratory Standards Institute (CLSI) guidelines. A total of 4 675 female patients were screened and 406 (9%) were enrolled. Out of this, 31% (n=125) had culture-confirmed UTI with an incidence risk of 26 /1 000 female patients. The median age was 30 years (interquartile range [IQR], 27-37) and 4% (n=17) were HIV-infected. Among 130 uropathogens cultured, *Escherichia coli* (58%) and Group B *Streptococcus* (15%) were predominant pathogens. Among Gram-negatives organisms (n=91), susceptibility to tested antibiotics was ≥80%, except to ampicillin-sulbactam (41%, 95% confidence interval [CI] 31-51), trimethoprim-sulfamethoxazole (47%, 95% CI 36-57), and tetracycline (59%, 95% CI 48-69). Susceptibility to gentamicin among Gram-positives (n=39) was 63% (95% CI 36-84).

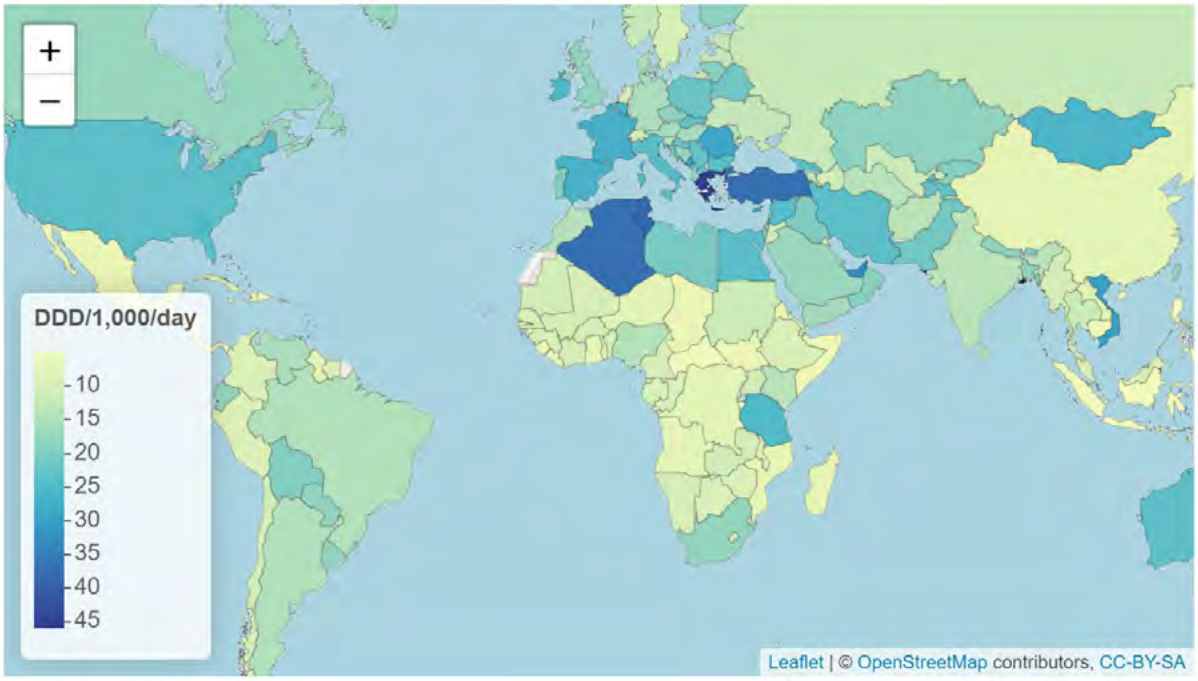
In conclusion, there was low AMR found in community acquired UTI's, supporting current treatment guidelines for uncomplicated catheter associated UTIs. Gram-positive bacteria with reduced susceptibility to gentamicin and Gram-negative resistant to the first line antibiotics underscored the need for ongoing community-based surveillance.

5. Consumption of antimicrobials in the human sector

5.1 Human consumption in South Africa compared to global levels

According to the 2018 information on Antimicrobial Consumption as published by the GRAM study[7], South Africa's antimicrobial use was estimated at 17.9 DDDs per 1000/population per day[8]. This consumption estimate was not as high as other African Countries namely Algeria (36.8), Tunisia (38), Egypt (24) and Tanzania (25). It was similar to other BRICS[9] countries, however, it was still lower than most of the high-income countries.

Figure 18: *Global antibiotic consumption and usage in humans, 2000 to 2018: a spatial modelling study. Lancet Planetary Health 2021.*



If you use these modelled estimates on antibiotic consumption and antibiotic usage, please cite this publication as a reference:
Browne AJ, Chipeta MG, Haines-Woodhouse G, et al. Global antibiotic consumption and usage in humans, 2000 to 2018: a spatial modelling study. Lancet Planetary Health 2021

MORU Tropical Health Network · Big Data Institute, University of Oxford · GRAM · Oxford Centre for Global Health Research · IHME

South Africa's antibiotic usage in children as a proportion of children under 5 years old receiving an antibiotic for a lower respiratory tract infection was around 47.5%. This proportion, as reported by caregivers, was lower than northern African and Asian low- and middle-income countries (LMICs) and higher than other LMICs in Africa where there are potentially greater barriers to accessing primary healthcare services for children. The optimal level for this indicator was not clear from the GRAM Study.

7 Browne AJ, Chipeta MG, Haines-Woodhouse G, et al. Global antibiotic consumption and usage in humans, 2000 to 2018: a spatial modelling study. Lancet Planetary Health 2021

8 Population data sourced from Stats SA and medical Scheme membership data.

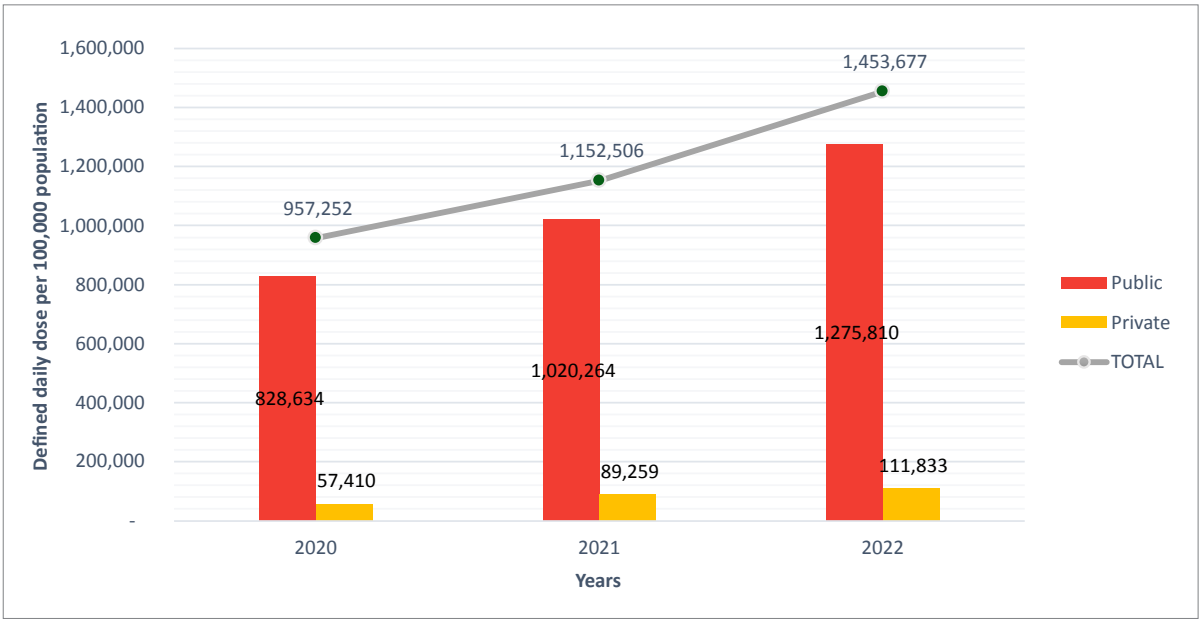
9 BRICS is the acronym for an association of five major emerging national economies: Brazil, Russia, India, China, and South Africa.

Combining public and private sector antimicrobial use based on the available data, there was a 50% increase over the 3-year period with the public sector total use making up 87% of the country's use on a per 100,000 population level **(Figure 19)**.

Limitations of the dataset for the public sector include the fact that the data only reflected procurement values against medicines procured on tender and therefore excludes buyouts from provincial procurement units (whether on tender or not), and all Section 21 data.

Limitations of the dataset for private include that it represented prescribing data for private hospitals only and excluded all consumption in the retail and primary healthcare areas. It also only reflected two thirds of the entire private sector hospitals as not all hospital groups chose to share their data. Constraints and lack of clear understanding of how to calculate DDDs for combination antibiotics, solution-based formulations, and those with different oral and parenteral formulations might result in errors in this dataset as verification of this step was not part of the data gathering process. This process will be refined with future reports.

Figure 19: *Total antibiotic consumption and procurement results for South Africa by sector in DDD/100,000 population.*



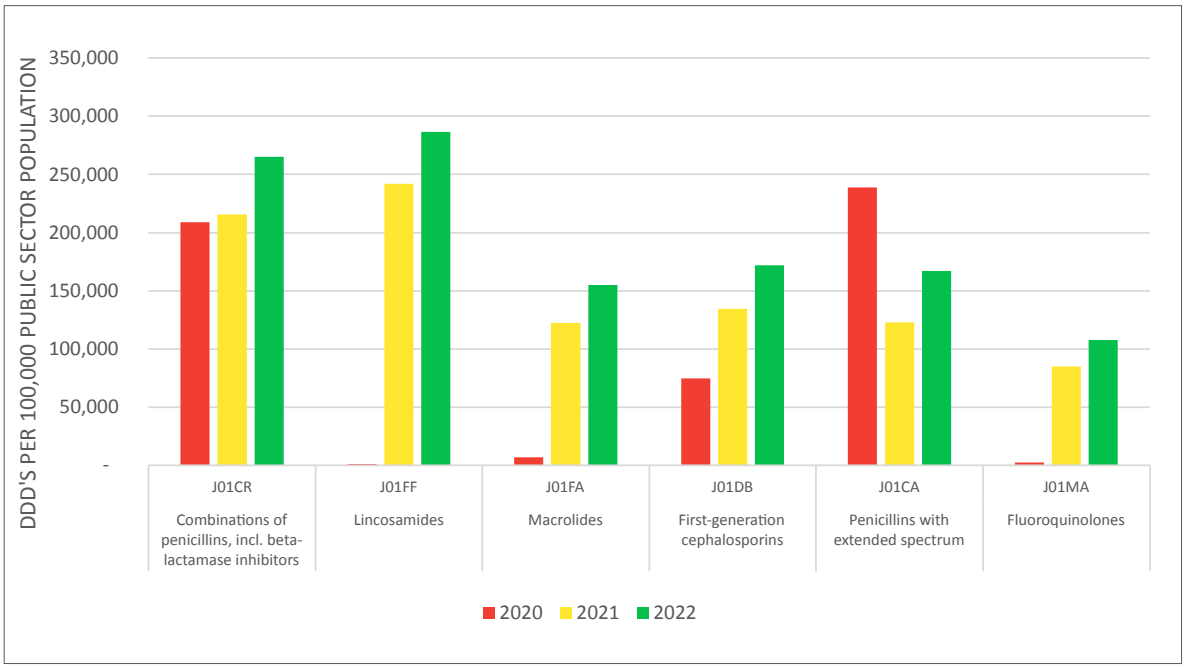
5.2 Human consumption in South Africa's public healthcare sector

NDoH demand planning data is used as a proxy for medicine consumption. This data is generated from quantities of medicines issued to and received by health establishments, based on extracts from existing electronic stock management systems used at health establishments in each province. This data is primarily collected for demand planning purposes and undergoes several stringent and approved processes to ensure accuracy. This data is then expressed as DDDs per 100,000 uninsured inhabitants.[10] DDDs were taken from the WHO definitions (available from www.whocc.no/atc_ddd_index/). This dataset represented both the primary healthcare as well as hospital procurement up to tertiary level care for all provinces in the country.

10 Guidelines on Implementation of the Antimicrobial Strategy in South Africa: One Health Approach and Governance. National Department of Health, June 2017

The public sector procurement saw a 50.81% annual growth rate over the 5-year period (**Figure 19**). The top 6 antibiotic classes procured were combination penicillin with beta-lactams, lincosamides, macrolides, 1st generation cephalosporins, penicillins with extended spectrum, and fluroquinolones also showed an increase over time.

Figure 20: *Public sector procurement by ATC class – top antibiotics. (DDDs/100,000 population)*



The procurement of broad-spectrum penicillins increased by 32% since 2018 whilst 3rd generation cephalosporins increased by 23%. There was a dramatic increase in the procurement of lincosamides and macrolides, driven in part by the doubling of volumes over the COVID-19 pandemic years of 2020-2022 (**Figure 20**).

There was a decrease of 6% in the use of antibiotics to treat drug-resistant infections such as vancomycin for MRSA. However, there was an increased use of 43% of antibiotics to treat ESBL (carbapenems and cefepime) infections (**Figure 21**).

It was not possible to measure the increased used in colistin or the newer Reserve antibiotics (for example ceftazidime-avibactam) to treat carbapenem resistant infections as that data is part of the Section 21 or buyouts data from hospitals and not easily collated nationally.

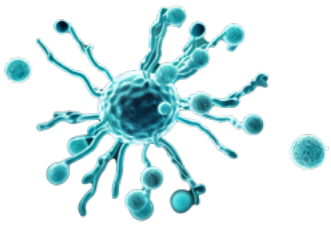
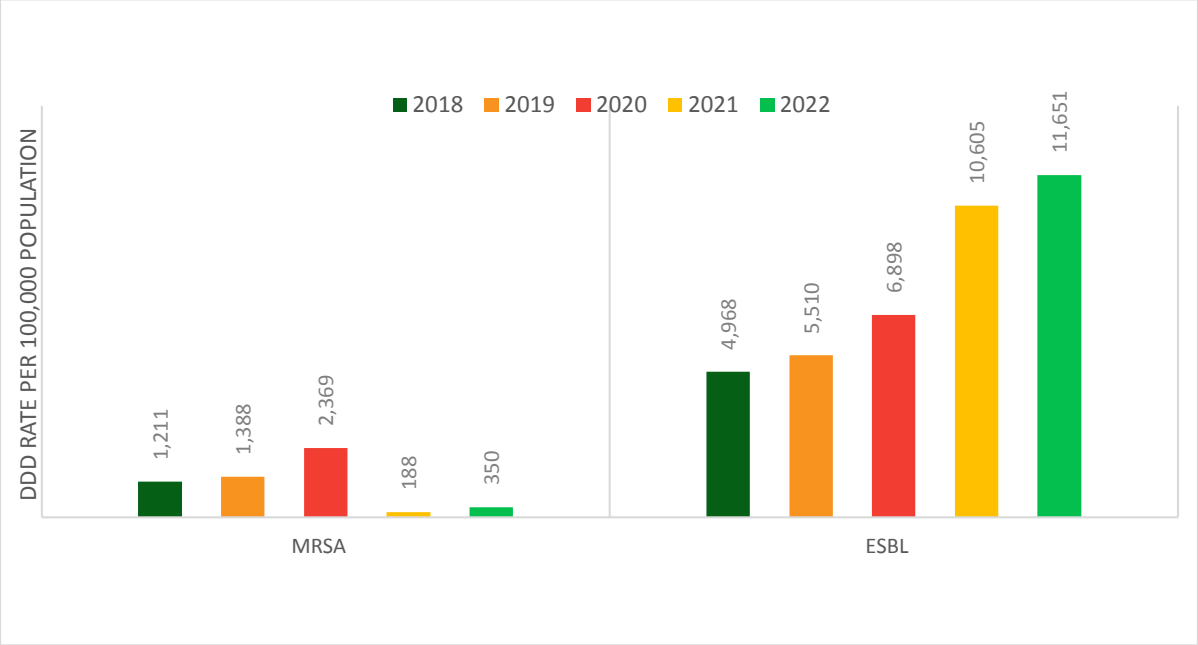


Figure 21: *Public sector trend in DDDs for antibiotics to treat drug- resistant infections (DDDs/100,000 uninsured population)*



5.3 Human consumption in South Africa's private healthcare sector

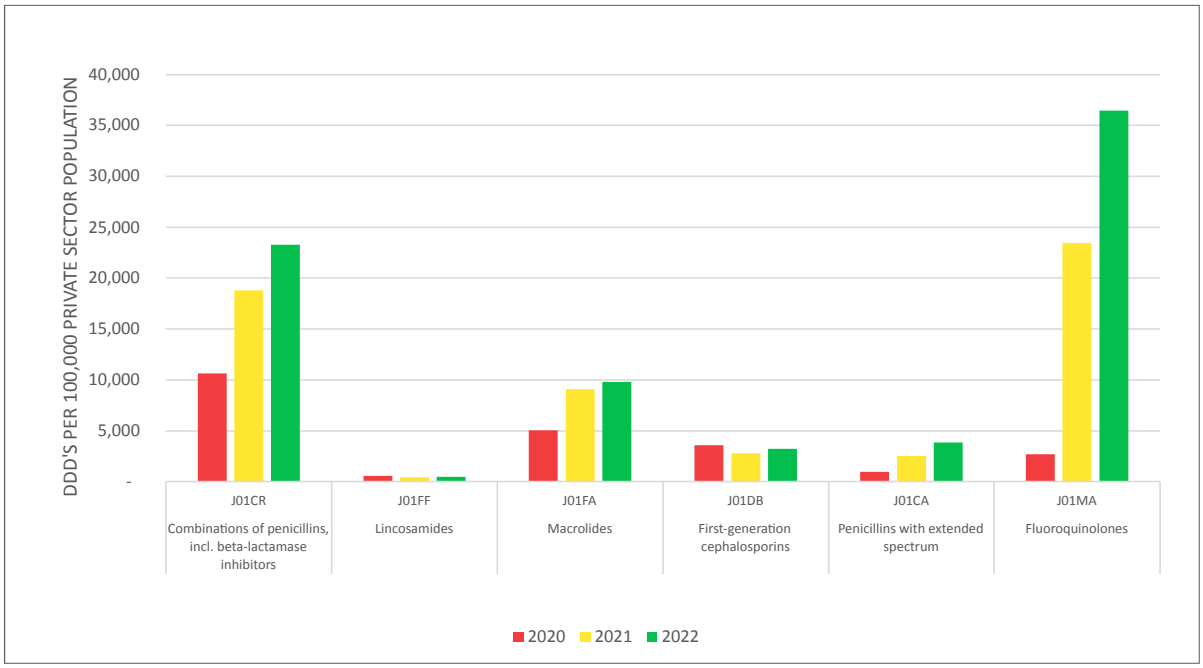
The private sector dataset represented 3 of the 4 large private hospital groups who are members of the Hospital Association of South Africa[11] and included prescription data for in-patients in hospitals. It therefore represents a more hospital-centric dataset than that of the public sector. In future, retail and primary care data is intended to be included in the report.

The private sector showed an increase of 64% over the 3-year period from 2020-2022 (**Figure 19**).

Fluroquinolones were the top prescribed antibiotics followed by combination penicillin beta-lactams, macrolides, and 1st generation cephalosporins. The impact of COVID-19 pandemic on these antibiotics was also dramatic, with macrolide use increasing by 63%, whilst fluoroquinolone use increased 13-fold (**Figure 22**).

11 Hospital groups submitting data included Life, Lenmed and Mediclinic.

Figure 22: *Private sector procurement by ATC class – top antibiotics. (DDDs/100,000 insured population)*



Private sector consumption data showed an increasing use of medication to treat Gram-negative ESBL resistant infections such as carbapenems and cefepime. An increase of carbapenem use alone was 23%. Antibiotics used to treat MRSA infections reduced over time by 23%, as also seen in the public sector.

As the private sector included consumption data for the newer antibiotics used to treat carbapenem-resistant infections, over the three-year period between 2020 to 2022, there was a usage increase of 73%.

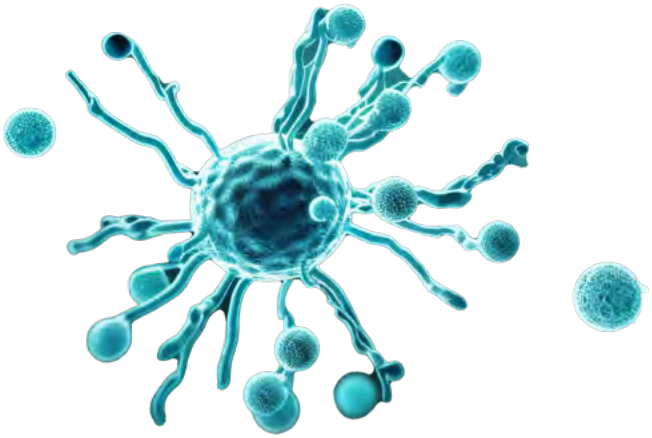
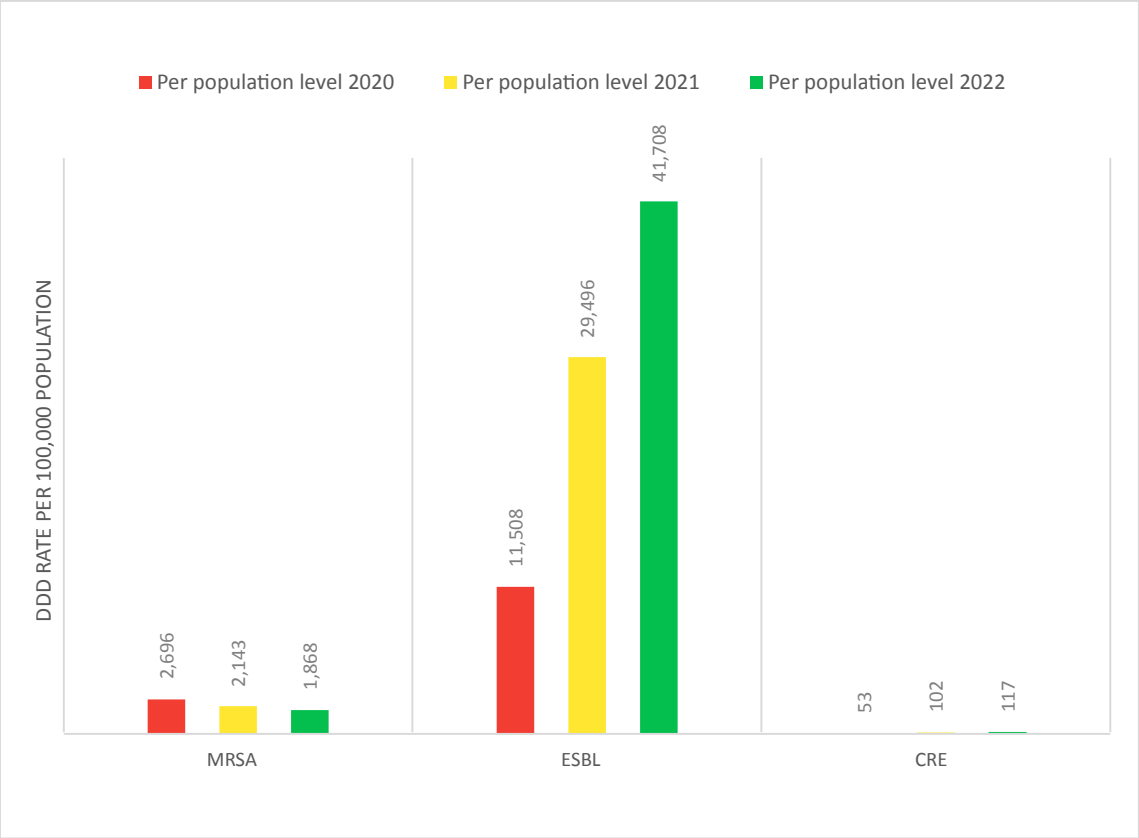


Figure 23: *Private sector trend for antibiotics to treat drug-resistant infections (DDDs/100,000 population)*



5.4 Access, Watch and Reserve (AWaRe) Index

Using the lens of the Access, Watch and Reserve (AWaRe)[12] index on the available data, there was a dramatic change in the public sector's proportion of Access and Watch antibiotic use.

Access antibiotics, which in the past made up the core of treatment at 79%, dropped to 48% of total use with a concomitant increase in Watch antibiotic use to 52% of the total basket of antibiotics. Reserve antibiotics made up less than 0.03%, however the data was limited on their use.

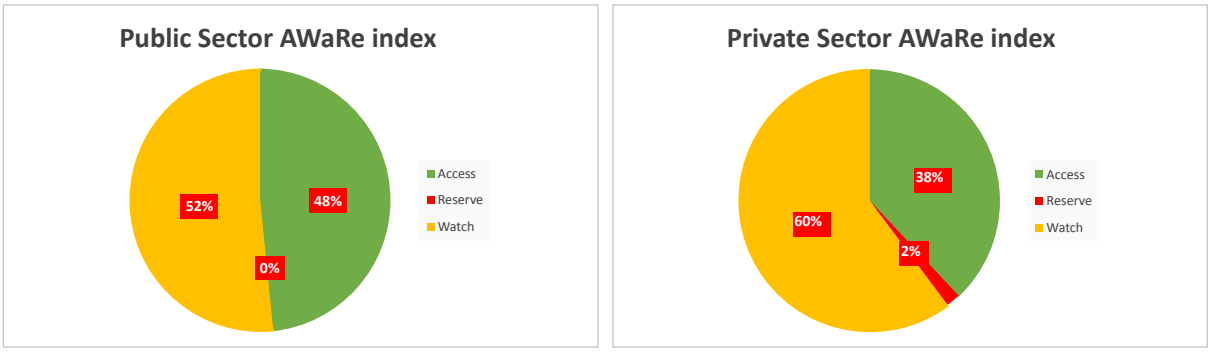
The data showed that the private sector used fewer Access antibiotics (38%) compared to Watch antibiotics (60%). However, data from services covered by this sector are only hospital-based and are therefore biased. Only 2% Reserve antibiotics were used in this sector.

12 An acronym for the World Health Organization's classification of antibiotics for evaluation and monitoring of use into "Access, Watch and Reserve" categories. See WHO's AWaRe Index (https://www.who.int/publications/i/item/2021-aware-classification) for further information.

Table 1: *Antibiotics categorised into Access, Watch and Reserve groups*

ACCESS	WATCH	RESERVE
•Amoxicillin •Amoxicillin and clavulanic acid •Ampicillin •Benzathine benzylpenicillin •Benzylpenicillin •Cefalexin, cefazolin •Chloramphenicol •Clindamycin •Cloxacillin •Doxycycline •Gentamicin, amikacin •Metronidazole •Nitrofurantoin •Phenoxymethylpenicillin •Procaine benzylpenicillin •Spectinomycin •Sulfamethoxazole and trimethoprim	•Anti-psuedomonal penicillins with beta-lactamase inhibitor (e.g. piperacillin and tazobactam) •Carbapenems and penems (e.g. imipenem and cilastatin, meropenem) •Third generation cephalosporins with or without beta-lactamase inhibitor (e.g. cefixime, cefotaxime, ceftazidime, ceftriaxone) •Glycopeptides (e.g. teicoplanin, vancomycin) •Macrolides (e.g. azithromycin, clarithromycin, erythromycin) •Quinolones and fluoroquinolones (e.g. ciprofloxacin, levofloxacin, moxifloxacin)	•Aztreonam •Fourth generation cephalosporins (e.g. cefepime) •Fifth generation cephalosporins (e.g. ceftaroline) •Daptomycin •Fosfomycin (intravenous) •Oxazolidinones (e.g. linezolid) •Polymixins (e.g. colistin) •Tigecycline

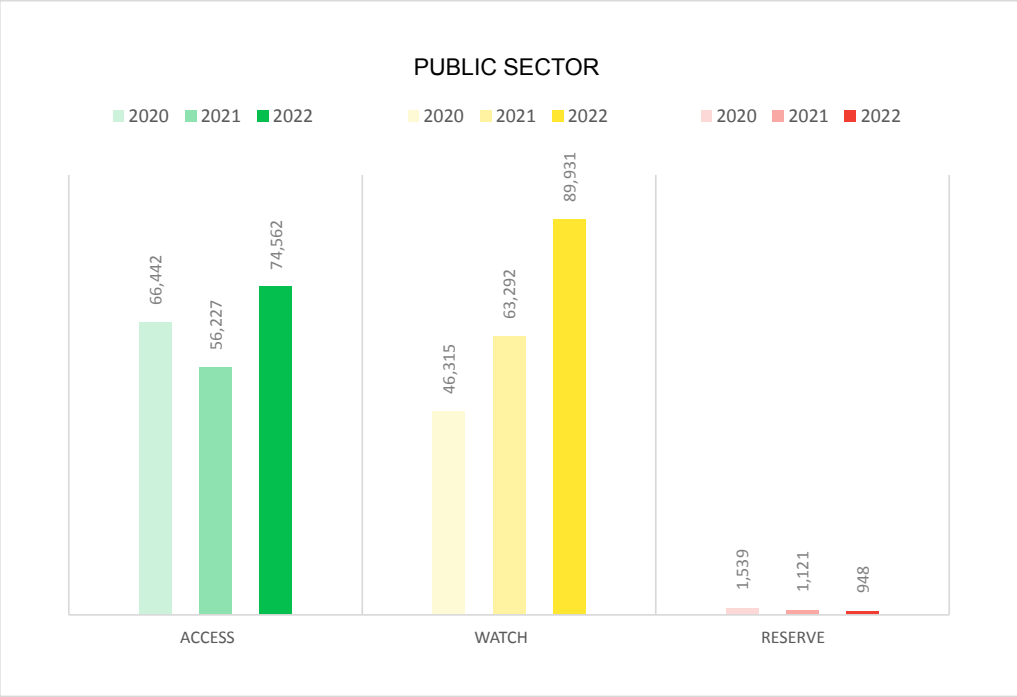
Figure 24: *AWaRe index by sector (2018 - 2022 combined)*



It is interesting to note the larger annual increases in procurement for public sector for Access (58%), Watch (53%) and Reserve (40%) antibiotics. This increased use could reflect increasing resistance, especially for ESBL Gram-negative infections (**Figure 25**).

The private sector, on the other hand, showed an annual increase in Access use (65%), with a much larger increase in Watch use (92%) and a 20% decrease in Reserve antibiotic use. This is encouraging and hopefully indicates that antimicrobial stewardship activities are taking place and improving appropriate use, thereby shifting use from Reserve to Watch categories (**Figure 25**).

Figure 25: *Trend in use of Access, Watch and Reserve antibiotics, by sector*



6. First Global Point Prevalence Survey (GPPS) Study in South Africa.

To date, there has been no national surveillance of HAIs in South Africa. The IPC TWG of the MAC-AMR collaborated with the University of Antwerp, Belgium for South African state hospitals to participate in the Global Point Prevalence Survey (GPPS) to assess the rate of HAIs, antimicrobial prescribing, and usage. The GPPS is a simple, freely available web-based tool (available online at https://www.global-pps.com/) which can be applied to healthcare facilities. It has an optional HAI module which South Africa used, that gave insight into IPC application and antimicrobial usage related to HAIs.

Permission to conduct the survey was obtained from the National and Provincial Departments of Health.

A pilot study of 6 hospitals in 2022 served as a steep learning curve for the participating hospitals and proved useful when the first GPPS was conducted from May to August 2023. This initiative was led by Prof Shaheen Mehtar and Dr Heather Finlayson with support from South African Provinces and the IPC TWG.

Of the participating hospitals, data from 52 sites was validated and was presented here, these were mainly public hospitals across all 8 provinces and included primary, secondary and tertiary hospitals.

Of the 8 584 patients documented, 2 696 were on antimicrobials on the day of data collection. Overall, 27.8% adults, 46.7% paediatrics and 36% neonates were on at least one antibiotic. As expected, antibiotics were more commonly prescribed in the ICU of all three age groups (60.7%, 79.3%, 45.9% respectively).

The proportional use of antibiotics by age and speciality is shown in Table 3. There was a preponderance of beta-lactam antibiotic groups in all prescriptions. Extended spectrum penicillin (with or without beta-lactamase inhibitors) as well as 3rd generation cephalosporins were the most common groups used for community associated infections (CAIs), whereas carbapenems, penicillin with beta-lactamase inhibitors, aminoglycosides and glycopeptides were the leading antibiotics used in HAIs. Polymyxins (colistin) were predominantly used in neonatal intensive care units (NICUs) for HAIs.

Table 2: *The proportional use of antibiotics by adult, paediatric and neonatal units. The last two columns reflect the antibiotics used for CAI and HAI. Note the use of polymyxin in NICU and HAI.*

ATC4	Antibiotics Subgroup	overall	AMW	ASW	AICU	PMW	PICU
J01CA	Penicillin with extended spectrum	15	11,2	6,2	6,3	28,2	17,7
J01CE	Beta−lactamase sensitive penicillin	1,6	1	0,3		1,6	5,2
J01CF	Beta−lactamase resistant penicillin	3	2,7	6,9	0,9	2,2	
J01CR	Penicillin incl. beta−lactam. inh.	**21,9**	**25,5**	**38,5**	**22,9**	14,7	3,1
J01DB	First−generation cephalosporins	4,8	5,3	9,2	4,9	1,6	
J01DD	Third generation cephalosporins	**13,6**	**17,9**	7,2	11,7	**19**	10,4
J01DE	*Fourth−generation cephalosporins*	0,5			3,6		
J01DH	Carbapenems	6,7	1,7	4,9	**18,4**	3,5	15,6
J01EE	Comb. Sulfonamides/trimethoprim	3,9	5,8	2	4,5	1,6	6,2
J01FA	Macrolides	4,1	7,3		2,7	4,3	4,2
J01FF	Lincosamides	0,7		1,5			
J01GB	Other aminoglycosides	9,8	3,8	4,1	4,5	**18,2**	**14,6**
J01MA	Fluoroquinolones	2,6	2,5	4,1		1,6	**9.3**
J01XA	Glycopeptide antibacterials	2,6		2	4,9	1,4	8,3
J01XD	Imidazole derivatives	5,5	**10,1**	7,9	4		4,2
J01XX	Other antibacterials		0,2	0,2			
JO1XB	*polymyxins*						

AMW= Adult medical ward; ASW = Adult surgical ward; AICU = adult intensive care unit;
PMed = paediatric medicine; PICU = paediatric intensive care unit; NICU = neonatal intensive care unit.
CAI = community associated infection; HAI = healthcare associated infection.

Surgical antibiotic prophylaxis comprised mainly of beta-lactamase inhibitors (33.7%) and first generation cephalosporins (32%). Medical antibiotic prophylaxis was distributed across the common antibiotic groups.

Almost 87.5% of patients received empiric therapy; 12.5% were on targeted therapy of which neonates received targeted therapy 20% of the time unlike the paediatric and adult patients (10.5% and 2.8% respectively).

The overall HAI rate for the country was 7.15%. Surgical-site infections contributed 1.45%, device-related infections contributed 1.5%, and other HAIs, (such as blood stream infections, hospital acquired pneumonia, UTIs, and infections of mixed origin) contributed 3.7%. HAIs were more common in the neonatal and paediatric settings (12.5%) compared to an adult HAI rate of 5.5%, mainly associated with mixed and blood stream infections. HAIs were higher in ICU's, the adult ICU HAI rate was 23.9%, with mixed origin and blood stream infections contributing the most infections. In the adult surgical wards, the HAI rates were 5.6% where surgical site infections made up 2.7%.

During the survey, 8 584 patients were admitted. Of these, 41% had a peripheral line, 4.8% had a central venous line, 14.6% had an indwelling urinary catheter, 5.3% had tubes and drains, 3.3% had an invasive endotracheal tube, and 2.2% had non-invasive respiratory support.

Of the total, 2 527 patients had previously been admitted to hospital in the last 3 months and 656 (26.2%) had received previous antibiotic therapy. Four percent had a prior ICU admission whilst 18% had been admitted in a general medical ward. A third of patients on antibiotics had had surgery during their current admission.

Antibiotics were most prescribed for pneumonia and surgical site infection which together made up 39% of all antibiotics prescribed. The other indications were for central nervous system infection, intra-abdominal sepsis, lower UTI, bone and joint infections, tuberculosis, gastrointestinal infections, obstetrics and bacteraemia.

For the most part, international guidelines regarding the type of antibiotic were adhered to for surgical prophylaxis with first generation cephalosporins being the most commonly used. There was also some use of penicillin with beta-lactamase inhibitors and imidazoles. Occasionally, other cephalosporins were also used.

However, the duration of surgical prophylaxis was longer than the guidelines recommended. Of the 254 surgical patients evaluated, a single dose of antibiotic was administered in only 19% of cases (12% received one day and 68% received more than one day of therapy).

Quality indicators measured included the reasons for the prescription documented in the notes (85%), and where the prescriptions were guideline compliant (80%). Stop/review dates were only found in 36 % of the clinical notes for medical wards. Similar findings were noted for surgery and intensive care. This may lead to inappropriately long treatment durations driving excessive antimicrobial use.

The key prescribing patterns documented were: 80% of antibiotics were administered intravenously; 26.5% of patients were on more than one antibiotic for a diagnosis; and 30.5% were receiving more than one antibiotic on the day of data collection.

The WHO AWaRe goal is that 60% of all antibiotics used at country level should be from the Access group. In South Africa, of the 3 632 prescriptions, 64% used Access, 34% used Watch, and 2% were prescribed Reserve antibiotics. Reserve antibiotics were used more frequently in the ICU (6%) compared to medical and surgical wards (1%). For surgical prophylaxis and pneumonia, Access antibiotics were still the most predominantly prescribed (92% and 57% respectively). Watch antibiotics were prescribed in 42% of patients with pneumonia, followed by 1% of Reserve antibiotics. Surgical prophylaxis prescriptions only had 8% of Watch antibiotics and no Reserve (**Figure 26**).

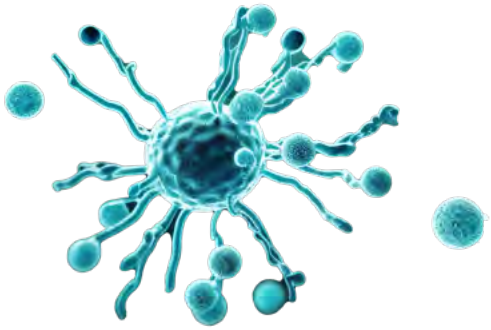
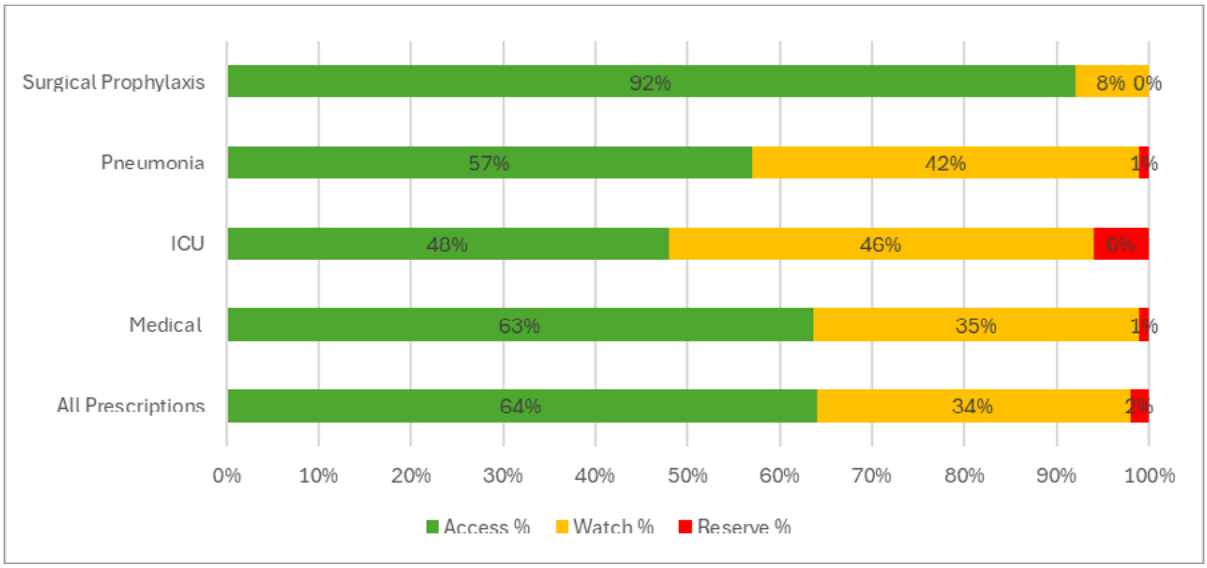


Figure 26: *AWaRe antibiotics prescribed across the country with specific reference to the commonest most common use by Ward type and for Pneumonia*



7. ACKNOWLEDGEMENTS

This report was compiled by the members of the Surveillance and IPC TWGs of the MAC on AMR in collaboration with the NICD, private sector laboratories and the Hospital Association of South Africa. We would also like to acknowledge the South African Medical Research Council for their role in deriving the outcomes for this report.

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8. Annexure A - Background to the existing surveillance system

8.1 Design of AMR Surveillance System

Surveillance for AMR is a key public health priority in South Africa. The NICD is the responsible entity, which coordinates, collates, and analyses AMR surveillance data. Since 2016, this has become a unified process between the public (NHLS) and private sector laboratories where previously these reports were released individually by the South African Society for Clinical Microbiology (SASCM).

There are two tiers of surveillance:

- Laboratory based AMR surveillance (LARS) which collects laboratory and clinical data from a selection of sentinel sites consisting primarily of academic and large referral laboratories in the public sector.
- Electronic surveillance (ES) which uses data from the NHLS Laboratory Information System as well as from major private laboratories, reported in the form of resistance heat maps.

In addition, data was included from sentinel sites from public sector hospitals as listed:

Charlotte Maxeke Johannesburg Academic Hospital, Chris Hani Baragwanath Hospital, Dr George Mukhari Hospital, Frere Hospital, Grey's Hospital, Groote Schuur Hospital, Helen Joseph Hospital, Inkosi Albert Luthuli Central Hospital, King Edward VIII Hospital, Livingstone Hospital, Mahatma Gandhi Hospital, Nelson Mandela Academic Hospital/Mthatha Tertiary RK Khan Hospital, Steve Biko Academic Hospital, Tygerberg Hospital, and Universitas Hospital.

For the analysis of ESKAPE pathogens, results of antimicrobial susceptibility testing (AST) were interpreted in accordance with the CLSI 2016 guidelines and were categorised as susceptible (S) and non-susceptible [which includes intermediate (I) and resistant (R)]. All laboratories have an External Quality Assurance program for quality checks and all private laboratories and the majority of NHLS laboratories are SANAS (South African National Accreditation Society) accredited.

Data were omitted for those hospitals that tested less than 30 ESKAPE pathogens for a particular antimicrobial agent.

8.2 Case definitions used

Patients with blood stream infections who cultured ESKAPE organisms were included. Once the data was uploaded into the central data warehouse a linking algorithm was used to create unique patient identifiers, which enabled the de-duplication of results within a 21-day patient episode (the start of the 21 days being defined as the first occurrence of resistance to a given antibiotic for a given pathogen for that unique patient). This same case definition was implemented for public and private laboratory groups.

The results of this report should be interpreted with caution. Several factors might have introduced bias, resulting in either an overestimation or underestimation of AST reporting.

8.3 Limitations to the data source

Some key limitations to the data include:

- Lack of standardisation in the collection of specimens at health facilities. This includes insufficient information provided by healthcare professionals requesting tests, of the indication for blood culture. This in turn means that the organisms isolated cannot be linked to a primary source of infection (e.g. respiratory tract, urinary tract, central nervous system, etc.) and cannot be differentiated as either hospital or community acquired.
- Limited access to microbiology laboratory services in some health facilities (either due to logistic constraints or financial constraints), resulting in limited blood cultures being requested.

- The syndromic approaches to certain diseases whereby health professionals treat empirically without ordering diagnostics tests as first line. If specimens are collected, they may only be collected if empiric treatment fails, and may result in an over-representation of resistant pathogens.
- Differences in testing methodologies and data capture between laboratories in the public sector and between the public and private sector.
- Data may have been incomplete due to missing cases not captured on the LIS or non-standardised coding of ESKAPE pathogens and antimicrobial agents at diagnostic laboratories.
- For some sentinel hospitals, not all ESKAPE pathogens may have been represented. This may be due to ESKAPE pathogens not being isolated at a particular sentinel hospital in 2016.

8.4 World Health Organisation Global Antibiotic Surveillance System (WHO GLASS)

South Africa, through the NICD as the national coordinating centre, also participates in the WHO global surveillance system on AMR, called the WHO Global Antibiotic Surveillance System (GLASS). WHO GLASS is reliant upon countries to conduct their own national surveillance and then report it to a central database which allows international collaboration and sharing of progress on AMR situation.

One of the aims of GLASS is to promote national surveillance systems with harmonised global standards. Data sets required by GLASS are requested with a more comprehensive approach to surveillance standards.

To fulfil GLASS requirements, tier 1 laboratory-based surveillance is used for AMR data from GERMS[13], and reported for two organisms: *Staphylococcus aureus* and *Streptococcus pneumonia* for a 5-year period from blood specimens. *S. aureus* surveillance was performed at 5 sentinel sites in two provinces and *S. pneumonia* surveillance is conducted nationally. Both organisms were part of an enhanced surveillance program whereby additional information was obtained about the patients including demographic, clinical, laboratory, origin of the specimen (hospital and community), source of bacteraemia, clinical signs and symptoms and outcome data.

The additional information is important for better planning of treatment approaches in different patient groups and determining the origination of MRSA. The additional information for *S. pneumonia* was important to allow the follow up of the immunisation program implementation phases, including the determination of the impact of the pneumococcal conjugate vaccine. These data reflect resistance of *S. pneumoniae* amongst blood isolates and not from throat, nose or ear specimens where antibiotic treatment is not recommended.

8.5 Human Antimicrobial Use Data Sources

There are three existing sources of antimicrobial use data in South Africa. Each of the data sources currently available have some minor gaps in the completeness of information to allow a comprehensive view of antimicrobial use to be formulated:

- South African Revenue Services (SARS) import data, which contains the volume of antimicrobials (in kgs) and rand value imported into the country (as either the final product or as the Active Pharmaceutical Ingredient). This data now distinguishes between antimicrobials for use in humans or animals as the tariff coding system was updated in 2017 to reflect this difference. They also exclude any antimicrobials produced in South Africa and those procured in terms of Section 21 of the Medicines and Related Substance Act 101 of 1965.
- The RSA Pharma database reflects procurement data from the public sector. It consists of deliveries data to facilities from the relevant suppliers against contracts awarded by the NDoH since 2015. This data reflects provincial usage patterns but does not distinguish between hospital and community levels and excludes the non-contract purchases (buy-outs) and Section 21 purchases made by provinces and institutions.

13 GERMS-SA is a nationwide network of clinical microbiology laboratories (in the public and private sector) which participate in an active laboratory-based surveillance programme for pathogens of public health importance. Available at http://www.nicd.ac.za/index.php/germs-sa/

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