Surveillance for antimicrobial resistance and consumption of antimicrobials in South Africa, 2021

health
Department:
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EXECUTIVE SUMMARY

This surveillance report represents the current available information relating to antimicrobial resistance (AMR) and antimicrobial use (AMU) in animals and humans in South Africa over the period from 2016 to 2020. The public private partnership in data sharing has been further expanded to not only include AMR data but also now AMU data in the private sector.

Antimicrobial Resistance in Humans

The AMR surveillance system in humans was built through a collaboration between public and private sector laboratory services and represents a comprehensive view of AMR in blood stream infections (BSIs) for the *Enterococcus faecalis* & *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter spp*. (ESKAPE)[1] pathogens in the country. We have modified the ESKAPE definition to include *E. coli* instead of *Enterobacter* species, and we also added *Enterococcus faecalis* to this definition.

Klebsiella pneumoniae 70% BSIs are nonsusceptible to 3rd generation cephalosporins 40% BSIs are nonsusceptible to 1st generation carbapenems	***Staphylococcus aureus*** 17% BSIs are nonsusceptible to cloxacillin (MRSA)	***Escherichia coli*** 25% BSIs nonsuceptible 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	

Figure 1. Reflection of rates of non-susceptible isolates among blood stream infections in 2020

Klebsiella pneumoniae is the commonest organism isolated 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

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

extended spectrum beta-lactamase (ESBL)-producing *K. pneumoniae*. Currently in South Africa, has increased from 65 to 70% over the past five years, which limits the use of cephalosporins as treatment options. The emergence of carbapenem resistance in *K. pneumoniae* is of concern with one-in-four resistant to carbapenems in 2020.

E. coli had showed increasing resistance to quinolones with one in three isolates resistant to ciprofloxacin, a common empiric treatment for urinary tract infections (UTIs). One in four *E. coli* is an ESBL-producer, resistant to 3rd generation cephalosporins. *P. aeruginosa* isolates regarded as hospital acquired infections (HAIs) are showing resistance of one in five to piperacilln-tazobactam and one in three to carbapenems, which are commonly used as first and second line treatments, respectively. Variations across the provinces for these two organisms highlighted potential differences in empiric treatment regimens between different parts of the country.

Carbapenem resistance in *A. baumannii* is 80%, with consistent findings across the country, as well as increasing levels of resistance over time. One in five isolates show non-susceptibility to tigecycline. This limits treatment options, with respect to the last resort antimicrobial, colistin, which is not registered in the country - requiring a Section 21 approval through the South African Health Products Regulatory Authority (SAHPRA) to procure - being available to treat these resistant infections.

Methicillin resistance in *Staphylococcus aureus* (MRSA) is the only major bacterial resistance mechanism to show a decline over the past five years from 23% to 18%. MRSA rates vary across the provinces. Ampicillin remains the drug of choice for *Enterococcus faecalis*, however ampicillin resistance of *Enterococcus faecium* is greater than 95% but this is not unusual - majority of *E faecium* have always been resistant. with the added growing concern of vancomycin resistance (one of the last resort antimicrobials).

The GERMS-SA[2] surveillance programme showed that resistance to penicillin of 4% for *Streptococcus pneumoniae* occurs mainly in children under five years of age and young adolescents and originates from community settings.

Antimicrobial Use in South Africa

60% are consumed by animals

40% are consumed by humans
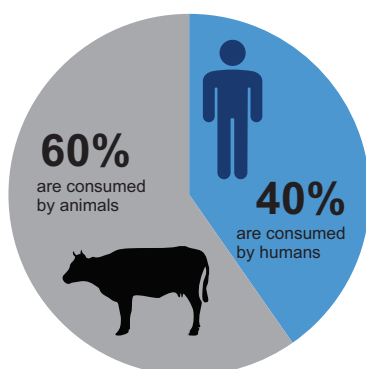
With improvements in the granularity of the South African Revenue Service (SARS) importation data since 2018, we are now able to more accurately split procurement of antibiotics for animal and human health. Procurement for human use made up approximately 40% of total antibiotics imported into the country between 2018 and 2020, whilst the difference, almost 60%, was for animal use. This split in procurement is now more aligned with other international country experiences, with greater procurement for the animal health sector.

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[2] 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/

Antimicrobial Use in Humans

New data sources for AMU have been published in this report, including private sector use data, making comparisons to the previous report difficult.

For the period 2018 to 2020, the public sector procured less than 8% of the total quantity of antibiotics procured for South Africa.

The most used antibiotics in the public sector were extended-spectrum penicillins, accounting for 28% of total antibiotics used in 2020. This was followed by oral trimethoprim-sulfamethoxazole and metronidazole at 13% and 12% respectively. This differs from the previous published report due to a change in the Defined Daily Dose (DDD) calculation used for trimethoprim-sulfamethoxazole.

By contrast, in the private sector extended spectrum pencillins, carbapenems and 3rd generation cephalosporins accounted for 41%, 20%, 13% respectively. Macrolides have more than doubled in proportionate use from 5% to 11% between 2018 and 2020, which may reflect possible increases in use during the COVID-19 pandemic in South Africa from March 2020 and ongoing at the time of writing this report.

The private sector used. more carbapenems as an overall percentage compared to the public sector; but both have high broad-spectrum penicillin usage. Use of antibiotics has the possibility of driving resistance amongst ESKAPE pathogens and should be a target for future monitoring.

Antimicrobial Use in Animals

Reliable data with respect to AMU in animals are generated by the South African Animal Health Association (SAAHA) which represents most pharmaceutical companies providing products for animal health. For the year 2021, the quantities of antibiotics used for companion animals represent 2% of the total use, whereas use for terrestrial and aquatic production animals represent 98%.

With respect to residues of antibiotics in products from food-producing animals, samples were analysed through the National Chemical Residue Monitoring Programme (NCRMP), which includes penicillins, tetracyclines, sulphonamides and macrolides. This programme monitors residues in meat for local and export markets. Antimicrobial residues were detected in only a very low number of samples analysed most likely reflecting. The result of compliance by farmers with withdrawal periods applied prior to slaughter of animals.

Antibiotics and the Environment

This report contains a snapshot of the use and impact of antibiotics in the environment. Surveillance within the water-plant-food interface remains limited in South Africa currently, although research is being done in various aspects e.g., identification and characterisation of multidrug-resistant potential foodborne pathogens from fresh produce and irrigation water. Increased capacity and integration into other structures will need to be investigated to improve the surveillance capacity in this area.

Conclusion

This report represents a considerable advance in the quality of surveillance data available in South Africa, especially for human AMR and AMU surveillance from private and public sectors. There are significant areas where additional data is needed to better inform policy and decision-making abilities in the future.

Quantities of antibiotics used in animal health are reported to the World Organisation for Animal Health (OIE) annually. South Africa currently reports by means of reporting option 2 i.e., the overall amount sold or used in animals by antimicrobial class and separation by type of use and species group. The aim is to advance to reporting option 3 that also includes the routes of administration.

Although national veterinary AMR surveillance data are still not available, this report includes AMR data from point prevalence studies. PPS may be a form of surveillance conducted annually in the poultry and cattle feedlot industries.

Increased capacity in environmental surveillance is required to bring this sector on par with human and animal health. Better integration of environmental, animal and human sector interventions is required for a holistic One Health understanding of AMR in South Africa.

ABBREVIATIONS

AMR	Antimicrobial Resistance
AMU	Antimicrobial Use
API	Active Pharmaceutical Ingredient
ATCC	Anatomical Therapeutic Chemical Classification
AWaRe	Access, Watch and Reserve
BSI	Blood Stream Infection
CLSI	Clinical and Laboratory Standards Institute
DALRRD	Department of Agriculture, Land Reform and Rural Development
DDD	Defined Daily Dose
DTR	Difficult to Treat Resistance
EML	Essential Medicines List
ESBL	Extended Spectrum Beta-Lactamase
ESKAPE	• Official ESKAPE organisms: *Enterococcus faecalis* & *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter spp*. • NICD has modified ESKAPE to include *E. coli* instead of *Enterobacter* species. This modified version is used in this report.
GAP	Global Action Plan
GLASS	GLobal Antimicrobial resistance Surveillance System
HAI	Hospital Acquired Infection
INN	International Non-proprietary Name
LIS	Laboratory Information System
MAC	Ministerial Advisory Committee
MDRO	Multi-Drug Resistant Organisms
MIC	*Minimum Inhibitory Concentration*
MRSA	Methicillin Resistant Staphylococcus aureus
NCRMP	National Chemical Residue Monitoring Programme
NDoH	National Department of Health
NHLS	National Health Laboratory Service
NICD	National Institute for Communicable Diseases
NMC	Notifiable Medical Conditions
OIE	World Organisation for Animal Health
POPIA	Protection of Personal Information Act
SAAHA	South African Animal Health Association
SAHPRA	South African Health Products Regulatory Authority
SARS	South African Revenue Service
SASCM	South African Society for Clinical Microbiology
STG	Standard Treatment Guidelines
UTI	Urinary Tract Infection
WHO	World Health Organisation

2. INTRODUCTION

Surveillance of AMR and AMU is a key pillar of South Africa's *AMR National Strategic Framework, 2018-2024* (AMR Strategic Framework), which defines South Africa's approach to manage AMR, limit further increases in resistant microbial infections, and improve patient outcomes, livestock production, and health.
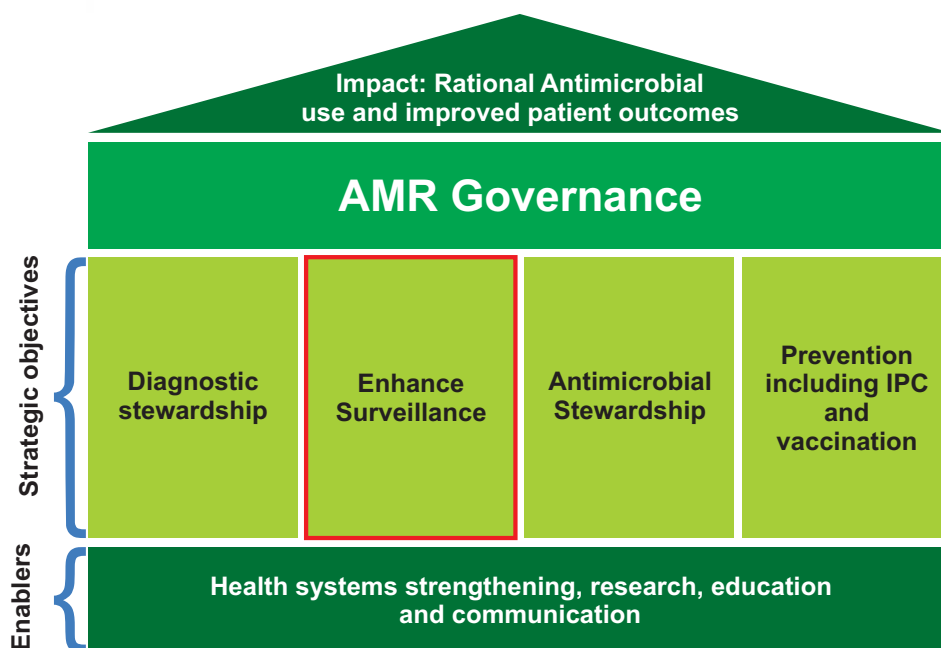

Figure 2. Summary diagram of the South African AMR Strategy

Our mission remains **"to ensure the appropriate use of antibiotics by healthcare and animal health professionals in all health establishments in South Africa to conserve the efficacy of antibiotics for the optimal management of infections in human and animal health".**

This second national surveillance report seeks to create a consolidated, representative view of AMR and AMU in South Africa and to monitor longitudinal trends to evaluate the impact of the AMR Strategy Framework.

In this report, the successful collaboration between public and private institutions and laboratories in South Africa's human health sector enables the sharing of data to enhance our national public health response. Furthermore, such collaborations support South Africa's future objective to develop research into AMR to direct future policy and planning decisions within the human health realm.

This report used human and animal data to estimate a relationship between human and animal health involving resistant bacteria and antimicrobial use. In the next phase, the Ministerial Advisory Committee (MAC) on AMR will be working on incorporating environmental health surveillance, to be able to present a One Health report on AMR and AMU.

Within this report, the term AMR is used to denote bacterial resistance to antibiotics, while AMU denotes Antibiotic or antimicrobial use.

3. ANTIMICROBIAL RESISTANCE IN HUMANS AND ANIMALS

3.1 Antimicrobial resistance in humans

This section of the report focuses on human AMR data derived from blood culture specimens from all public health facilities (including all levels of care, military, and prisons) and most private sector hospitals that are serviced by various private laboratory groups (*i.e.,* Lancet Laboratories, Ampath, Vermaak and Partners Pathologists, and PathCare). It is the output of a long-standing collaboration between public and private sector laboratories facilitated through the South African Society for Clinical Microbiology (SASCM) (Figure 3). All AMR data for this report can be viewed on the National AMR Dashboard, available through the National Institute for Communicable Disease (NICD) website at http://www.nicd.ac.za. Further details of the surveillance system and its design are shown in Annexure A.
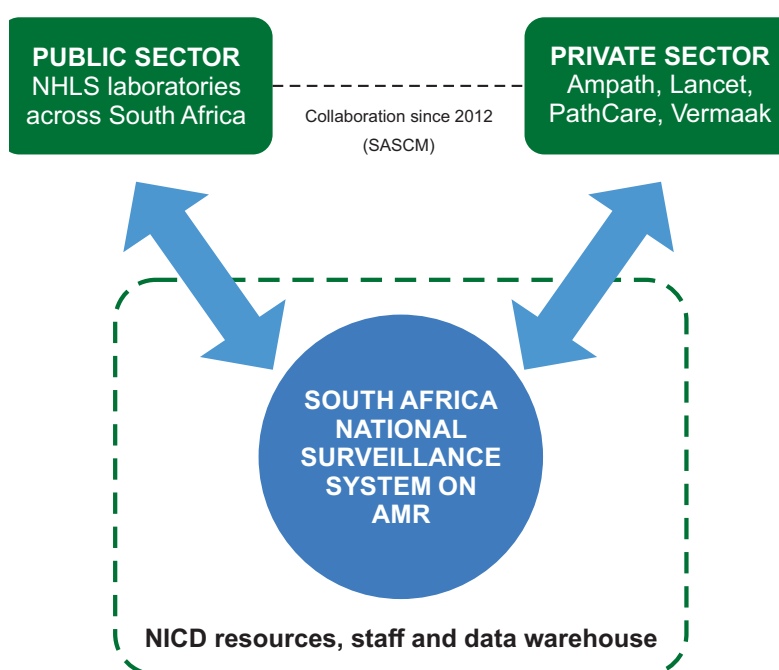

Figure 3. Partnership between public and private sectors

The acronym ESKAPE, used to describe the bacteria that are the most common causes of HAIs, characterise an internationally accepted group of AMR-priority pathogens, and form part of the national surveillance system. The ESKAPE acronym[3] stands for:

- *Enterococcus faecalis and Enterococcus faecium,*
- *Staphylococcus aureus,*
- *Klebsiella pneumoniae,*

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[3] 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)

- *Acinetobacter baumannii,*

- *Pseudomonas aeruginosa,*

- *Enterobacter spp.*

We have modified the ESKAPE group in our surveillance approach to monitor trends in *E.coli* instead of *Enterobacter* species due to the relatively higher contribution of the former in bloodstream infections (BSIs).

Resistance data on *Streptococcus pneumoniae* reported to the World Health Organisation (WHO) GLobal AMR Surveillance System (GLASS) have been included as it represents the leading cause of bacterial pneumonia in South Africa.

3.1.1 Overall burden of ESKAPE bacteria in the public sector

The burden of ESKAPE bacteria causing BSIs in the public sector was calculated for a three-year period (2018 to 2020) using data from the National Health Laboratory Service (NHLS). The total number of consecutive blood cultures tested increased consecutively from 3 610 401 in 2018, to 3 698 756 in 2019, and 3 805 186 in 2020. The percentage of ESKAPE bacteria identified from all positive blood cultures with antimicrobial susceptibility results were constant during the three-year period, ranging from 40% to 41% (Figure 4).
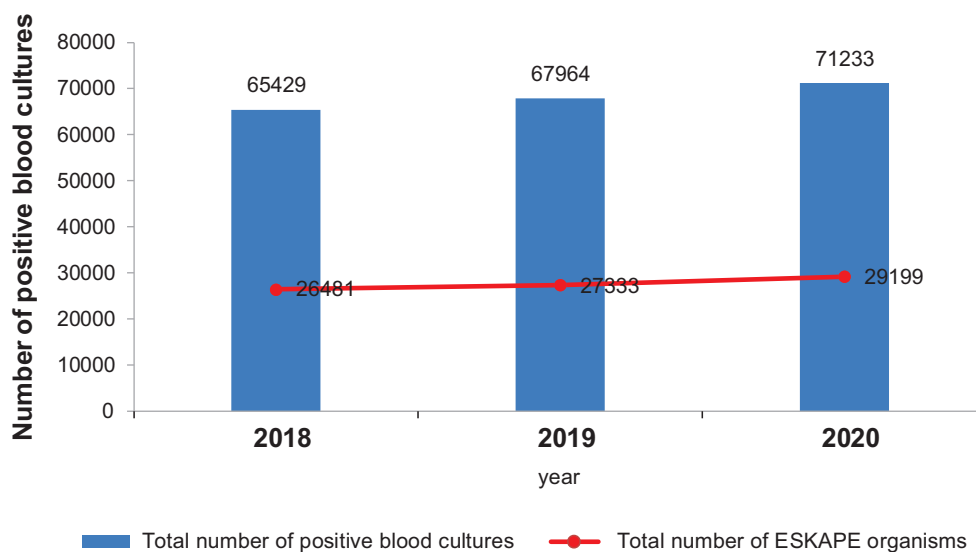

Figure 4. Burden of ESKAPE pathogens in the public sector, 2018 to 2020

The commonest pathogens cultured during the three-year period were *K. pneumoniae* and *S. aureus*, followed by *E. coli* and *A. baumannii* (Figure 5).
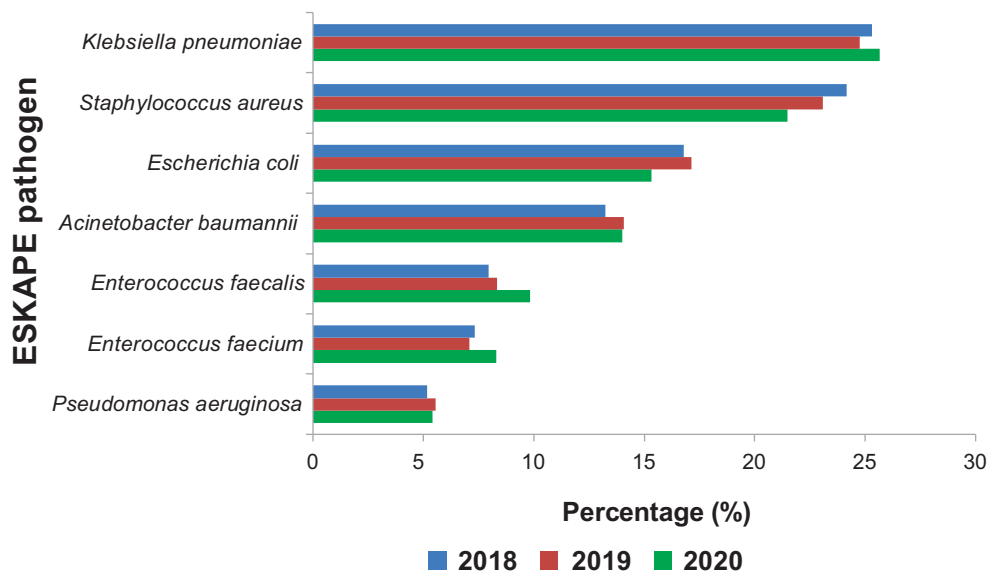
Figure 5. Percentage breakdown of ESKAPE bacterial organisms in the public sector, 2018 to 2020

3.1.2 Antimicrobial resistance at a glance − Public and Private Sector

The reporting of AMR in humans is focused on certain key antibiotic/bacteria combinations, which covers 2016 to 2020 and includes public and private health sectors. These data represent the bacteria and antibiotics commonly used to treat them that are the most critical for monitoring and tracking changes in resistance.

3.1.2.1 *Klebsiella pneumoniae*

K. pneumoniae is one of the commonest bacterial pathogens isolated from blood in both the private and public sectors in South Africa and susceptibility to critical antibiotics has shown a steady reduction over the past five years.

The prevalence of ESBL-producing *K. pneumoniae*[4] (represented here by 3rd generation cephalosporin non-susceptibility) has increased from 65% to 70% between 2016 and 2020 (Figure 6).

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[4]   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.
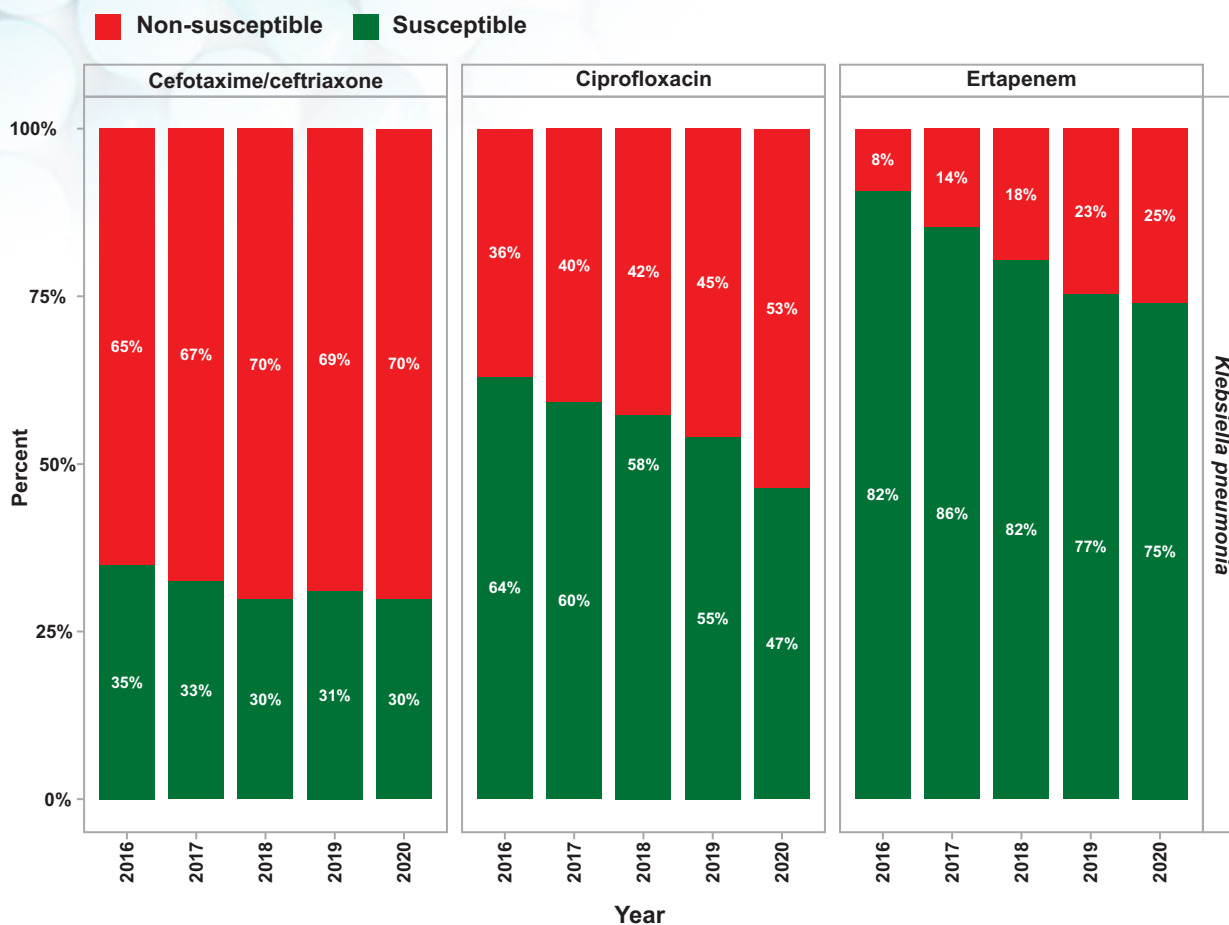
Figure 6. *K. pneumoniae* **% non-susceptible to 3rd generation cephalosporins, quinolones and carbapenems, 2016 to 2020**

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-producing isolates often also display associated quinolone resistance (carried on the same plasmid) and overall, we have seen reducing susceptibility of *K. pneumoniae* to quinolones over the last five years. This often leaves the carbapenem group of antibiotics as the only active therapeutic option for our commonest blood culture pathogen. The emergence of carbapenem resistance in *K. pneumoniae* is of great concern, with 25% of *K. pneumoniae* isolates showing ertapenem resistance in 2020, compared to 8% in 2016, which is a significant increase (Figure 6).

Resistance to cephalosporins is similar across most provinces in 2020 (Figure 7).
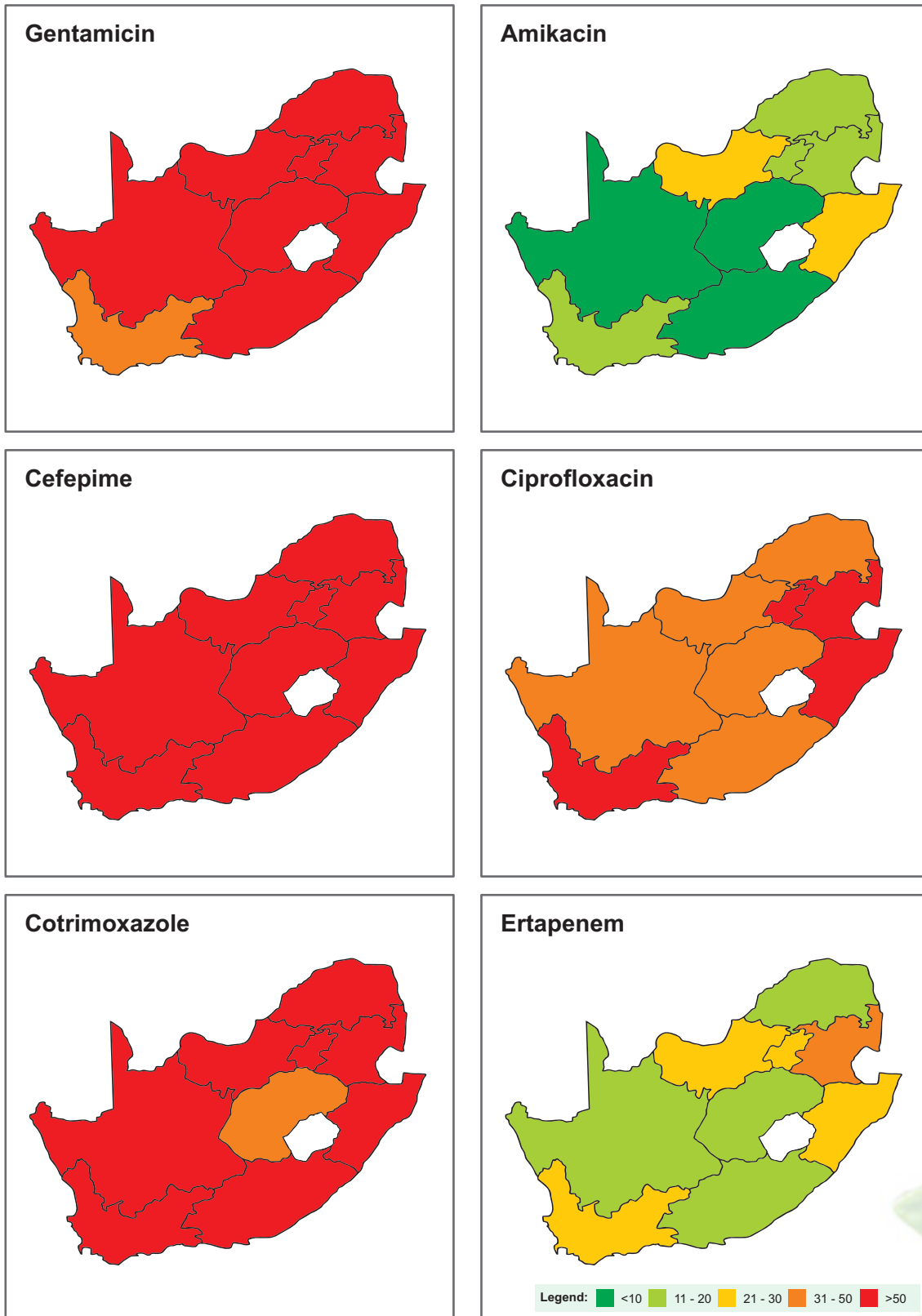
Klebsiella pneumoniae

Gentamicin

Amikacin

Cefepime

Ciprofloxacin

Cotrimoxazole

Ertapenem

Legend: <10 11 - 20 21 - 30 31 - 50 >50

Figure 7. Map for _K. pneumoniae_ by province in South Africa, 2020 (legend shows % non-susceptible ranges)

3.1.2.2 *Escherichia coli*

E. coli is the second most common Gram-negative bacterial BSI reflects in South Africa. While the data are unable to differentiate community- from HAIs, *E. coli* often reflect community infections associated with UTIs. Isolates show an increase in quinolone non-susceptibility (such as ciprofloxacin resistance) from 28% in 2016 to 32% in 2020 (Figure 8), with geographic differences (Figure 9).
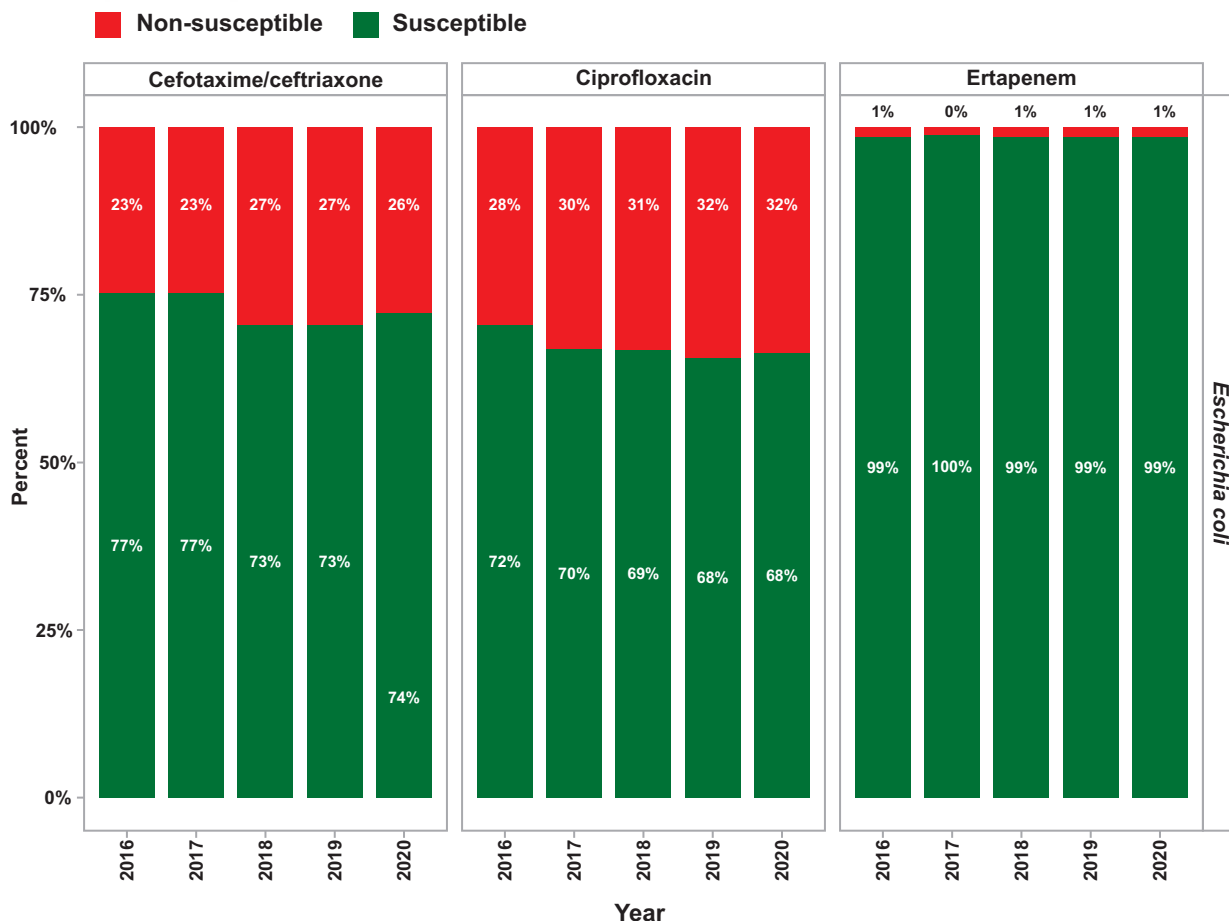

Figure 8. *E. coli* % non-susceptible to 3rd generation cephalosporins, quinolones and cephalosporins, 2016 to 2020
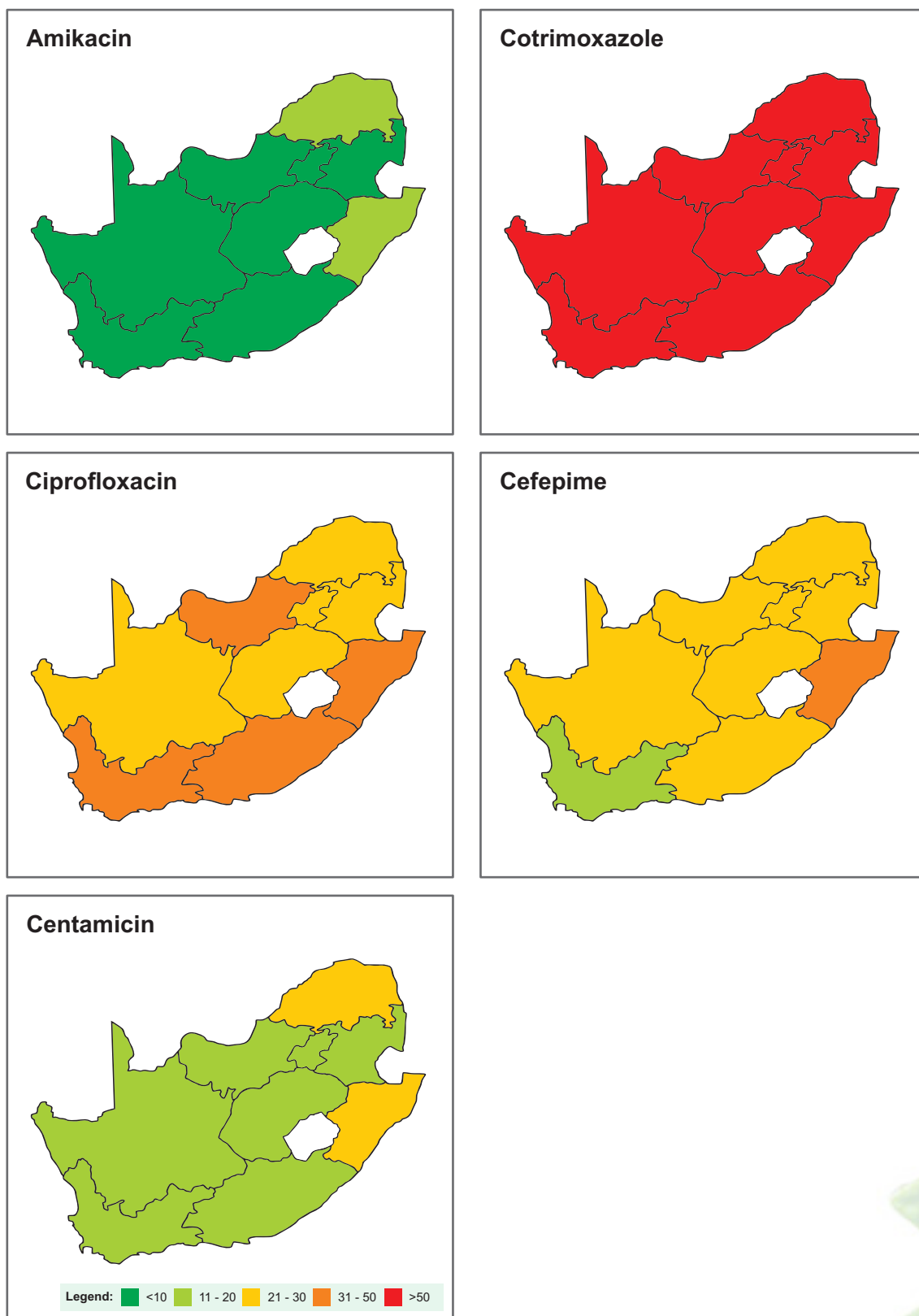
Escherichia coli

Figure 9. Choropleth map for *E. coli* by province in South Africa, 2020 (legend shows % non-susceptible ranges)

This high prevalence of resistance is of concern, as quinolones are frequently used as empiric treatment of UTIs. However, the 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 pathogen). However, this observed increase in quinolone resistance suggests a need for a prevalence study of community acquired UTIs.

3.1.2.3 *Pseudomonas aeruginosa* and *Acinetobacter baumannii*

P. aeruginosa and *A. baumannii* are commonly regarded as healthcare-associated pathogens. The 2020 data shows that one-fifth of *Pseudomonas* isolates are resistant to piperacilln-tazobactam, and a quarter are resistant to carbapenems. Importantly, there has been a decline in resistance to piperacilln-tazobactam and no changes for carbapenems from 2016 – 2020 (Figure 10). Explanation for reduced resistance might be due to the implementation of antimicrobial stewardship (AMS) and reduced use of agents for empirical treatment. At this point in time, it is difficult to correlate this with antibiotic use data, as the public healthcare sector has easier access to the carbapenems, and the private healthcare sector that uses these medicines extensively is not completely represented in this report.
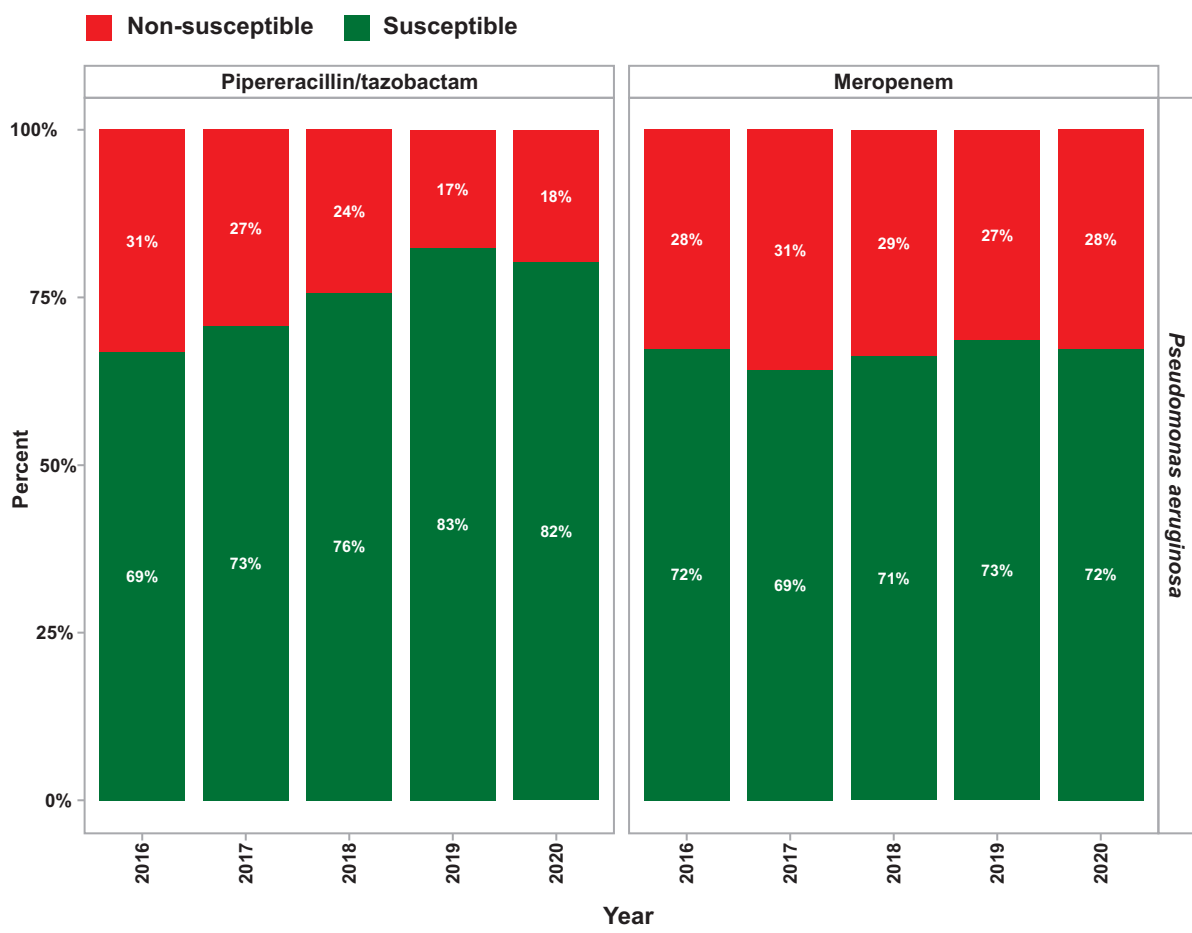

Figure 10. *Pseudomonas aeruginosa* % non-susceptible to piperacilln-tazobactam and carbapenems, 2016 to 2020
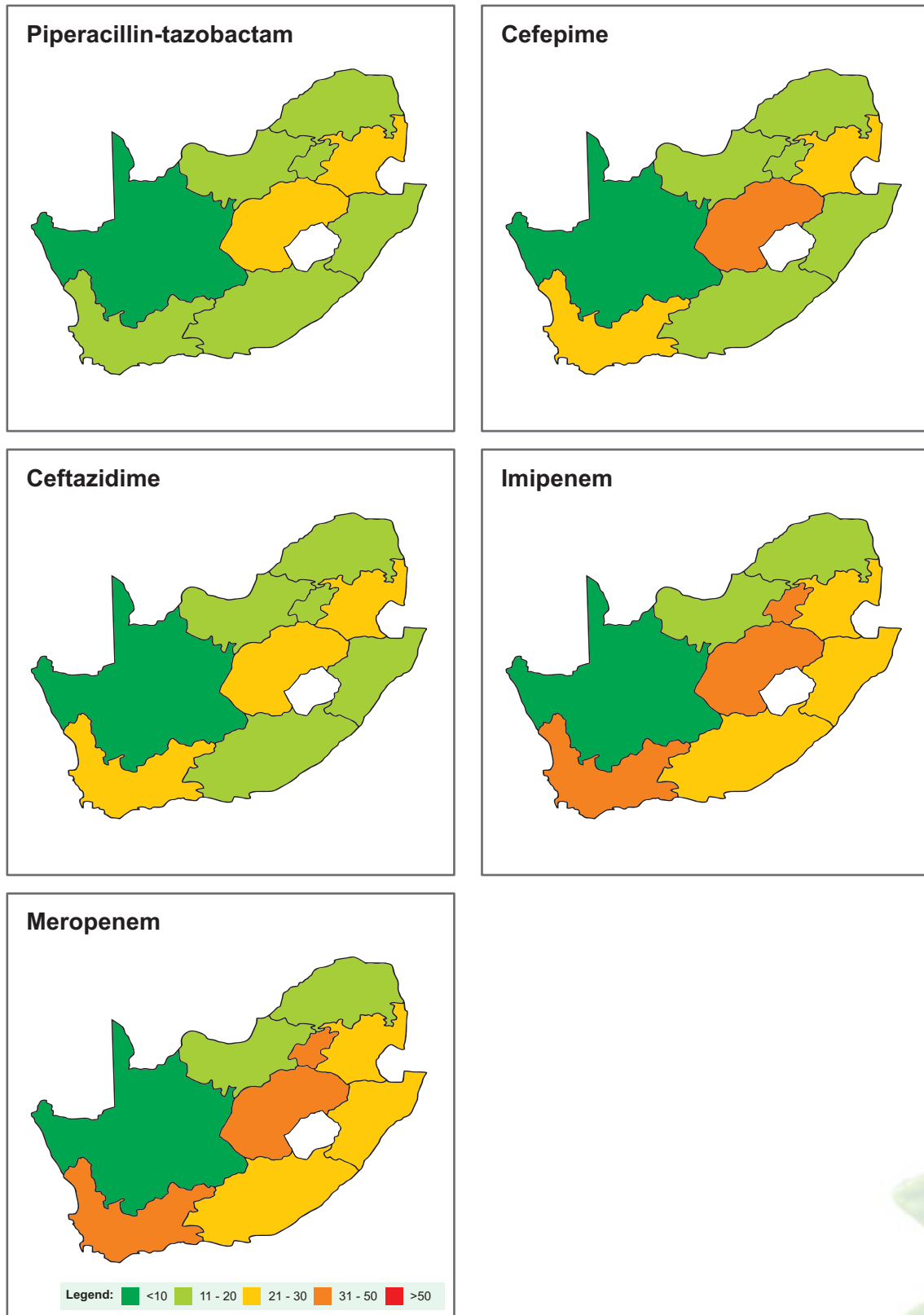
Pseudomanas aeruginosa

Figure 11. Choropleth map for *Pseudomonas aeruginosa* by province in South Africa, 2020 (legend shows % non-susceptible ranges)

There are also regional variations in susceptibility of *P. aeruginosa* to both piperacillin-tazobactam and carbapenems (Figure 11), particularly lower rates of resistance to piperacillin-tazobactam in the Northern Cape, Eastern Cape, Western Cape, North West and Gauteng Province; the Western Cape, Gauteng and the Free State have higher carbapenem resistance. This may reflect regional differences in the empirical use of these antimicrobials. This underpins the importance of regional antimicrobial susceptibility testing data for empirical treatment choices.
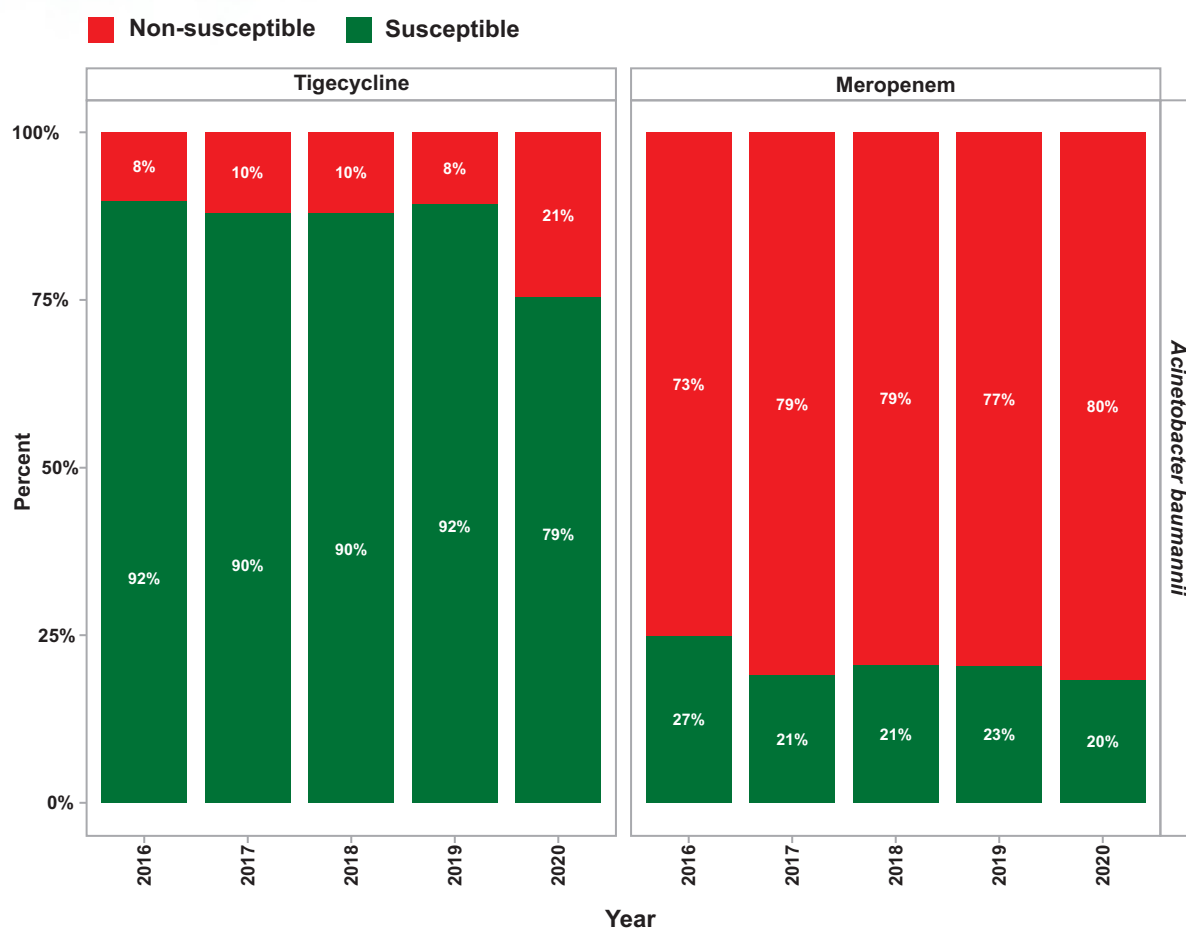

Figure 12. *Acinetobacter baumannii* **% non-susceptible to aminoglycosides and meropenem, 2016 to 2020**

A. baumannii resistance to *carbapenems* has been increasing through the years, with resistance observed in 80% of all isolates in 2020 (Figure 12). This finding is consistent throughout the provinces (Figure 13). Treatment options for Difficult to Treat-Resistant *A. baumannii* i.e., those resistant to first line antibiotics (beta-lactams and quinolones) are very limited, and comprise of colistin, tigecycline or combination treatment. Tigecycline resistance in *A. baumannii* was 21% in 2020. 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 for certain indications such as BSIs. Colistin resistance confirmed by the plasmid borne *mcr-1* gene plasmid has been reported in *Klebsiella spp* and *E. coli*[5] in the previous publication.

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[5]   M Newton-Foot, Y Snyman, M R B Maloba, A Whitelaw; Plasmid-mediated mcr-1 colistin resistance in Escherichia coli and Klebsiella spp. clinical isolates from the Western Cape region of South Africa. Antimicrobial Resistance and Infection control. 3 August 2017
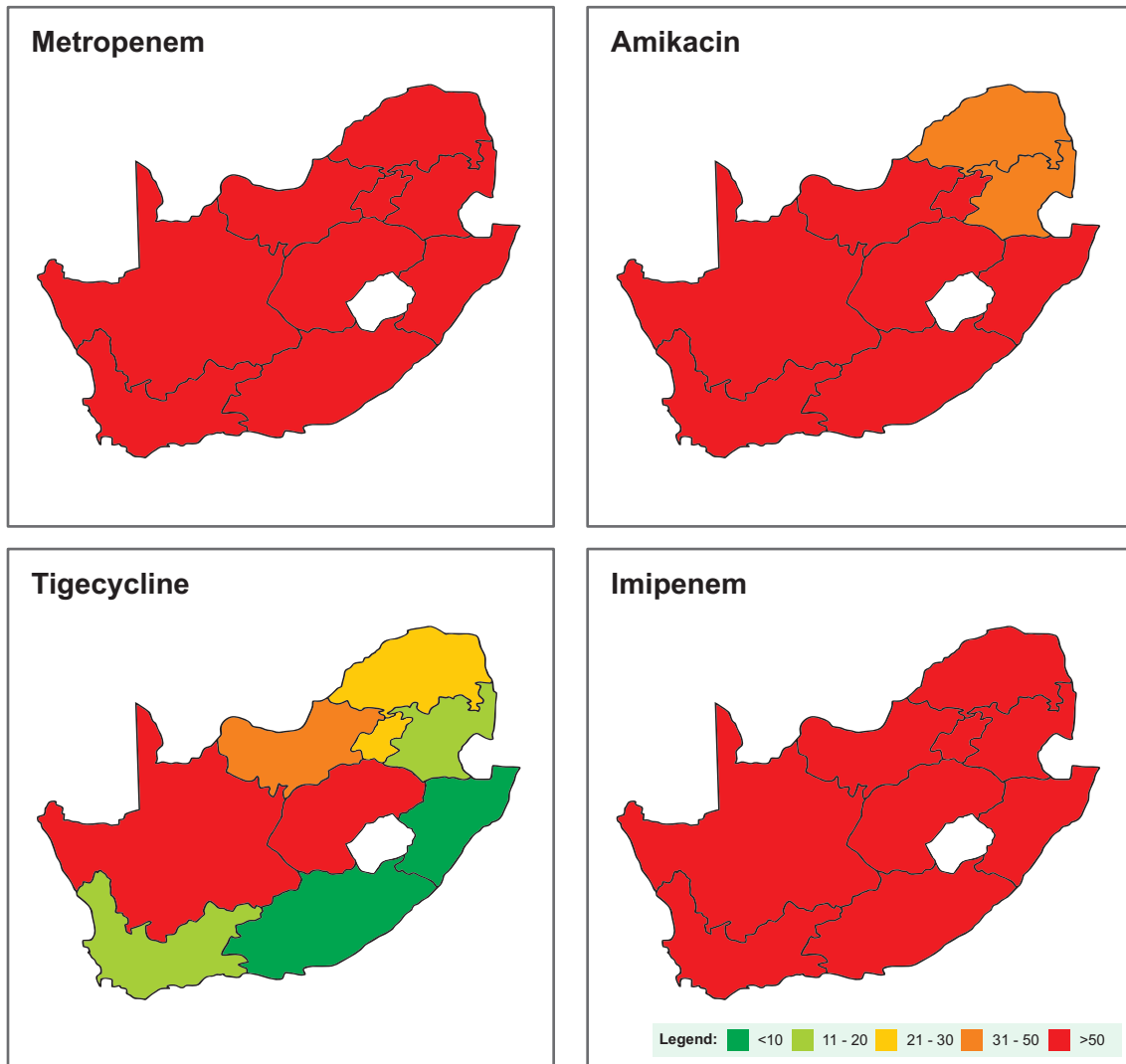
Acinetobacter baumanii

Figure 13. Choropleth map for *Acinetobacter baumannii* by province in South Africa, 2020 (legend shows % non-susceptible ranges)

3.1.2.4 *Staphylococcus aureus*

A consistent decline in MRSA has been observed, from 23% to 18% over the past five years (Figure 14), with resistance varying across the provinces (Figure 15).
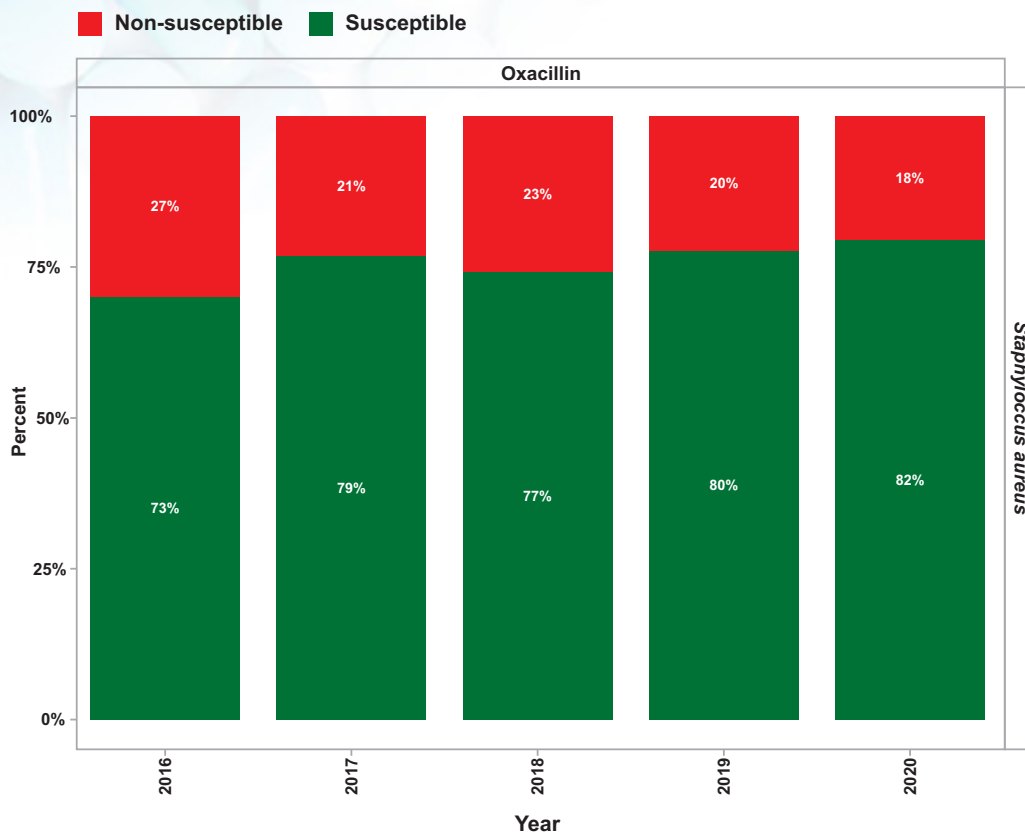
Figure 14. Choropleth map for *Acinetobacter baumannii* by province in South Africa, 2020 (legend shows % non-susceptible ranges)

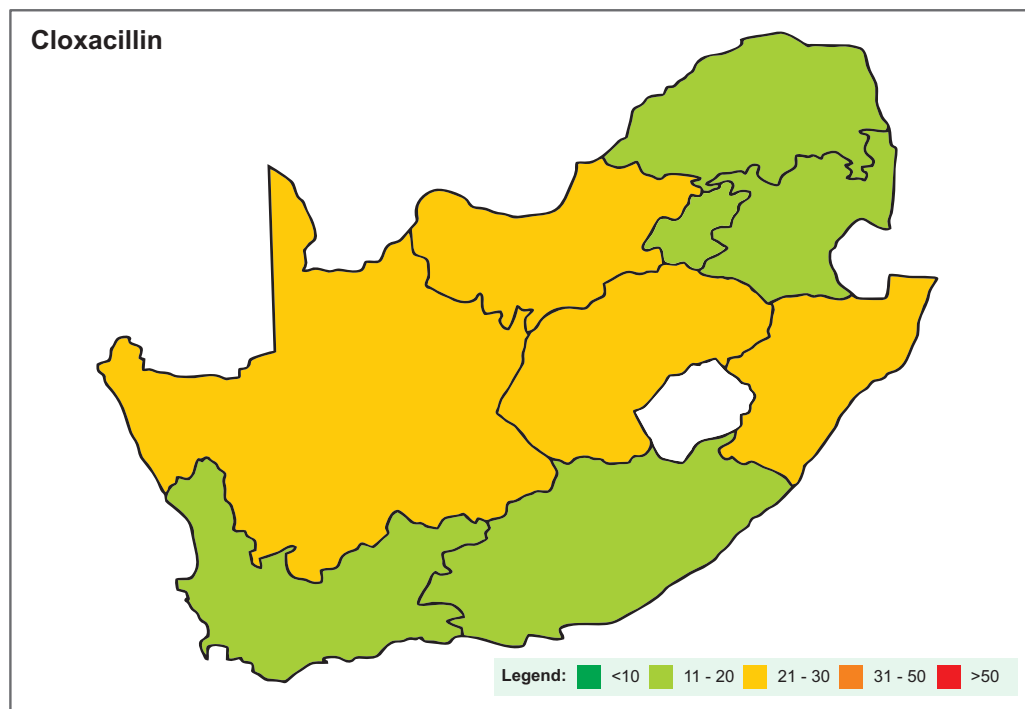*Staphylococcus aureus*

Figure 15. Choropleth map for *Staphylococcus aureus* by province in South Africa, 2020 (legend shows % non-susceptible ranges)

Active surveillance in selected sites in two provinces has shown that just under 8% of MRSA BSIs are community-acquired.[6] This contrasts with the situation in some other countries such as the USA, where more than 50% of MRSA originate in the community.

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

3.1.2.5 *Enterococcus faecalis* and *Enterococcus faecium*

E. faecalis is commonly susceptible to ampicillin (which remains the drug of choice), with resistance of 8% nationally (Figure 16). In contrast, ampicillin resistance in *E. faecium* is seen in more than 95% of isolates in keeping with global distribution (Figure 17). 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. faecium* was recorded in the 2016 and is now present in 1% of blood culture isolates (Figure 17).
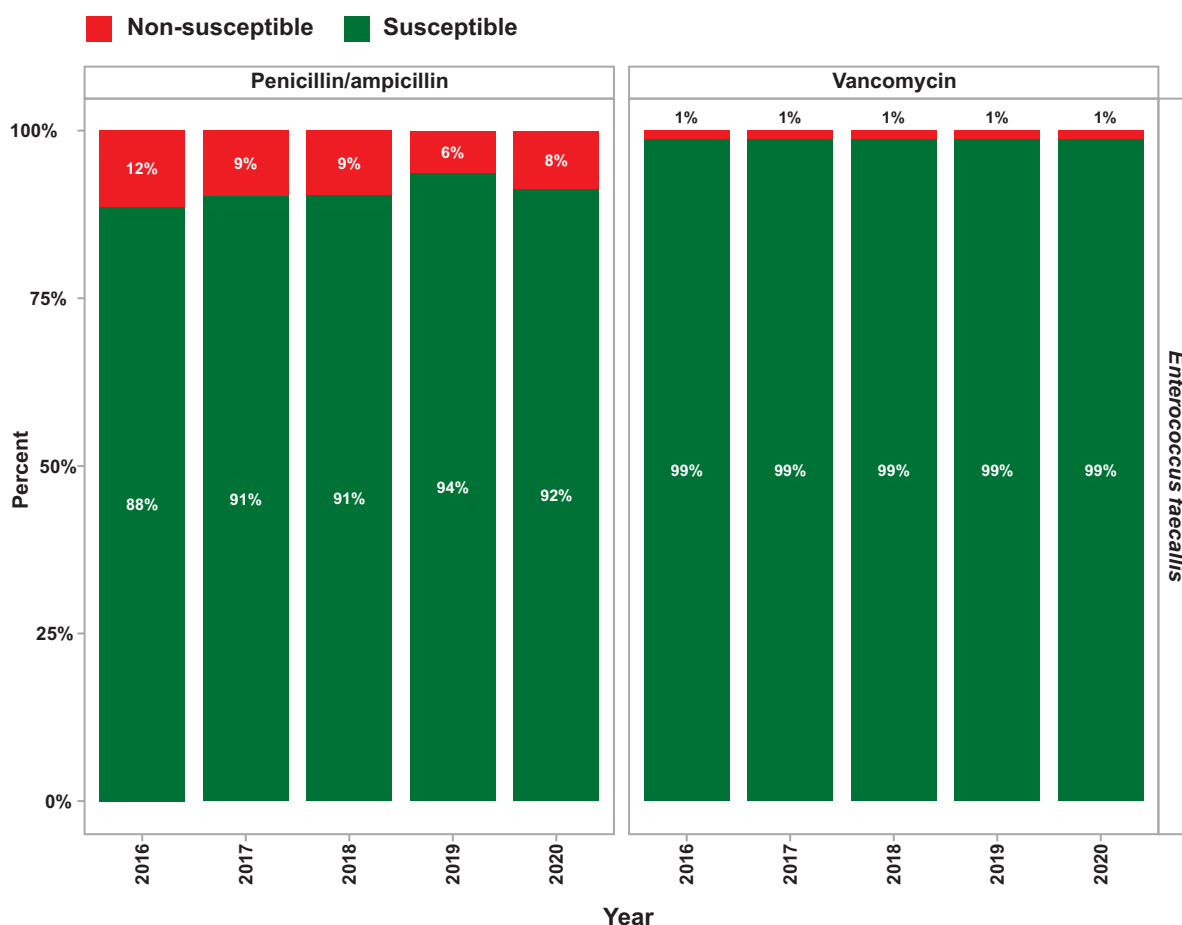

Figure 16. *Enterococcus faecalis* % non-susceptible to ampicillin and vancomycin, 2016 to 2020

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.
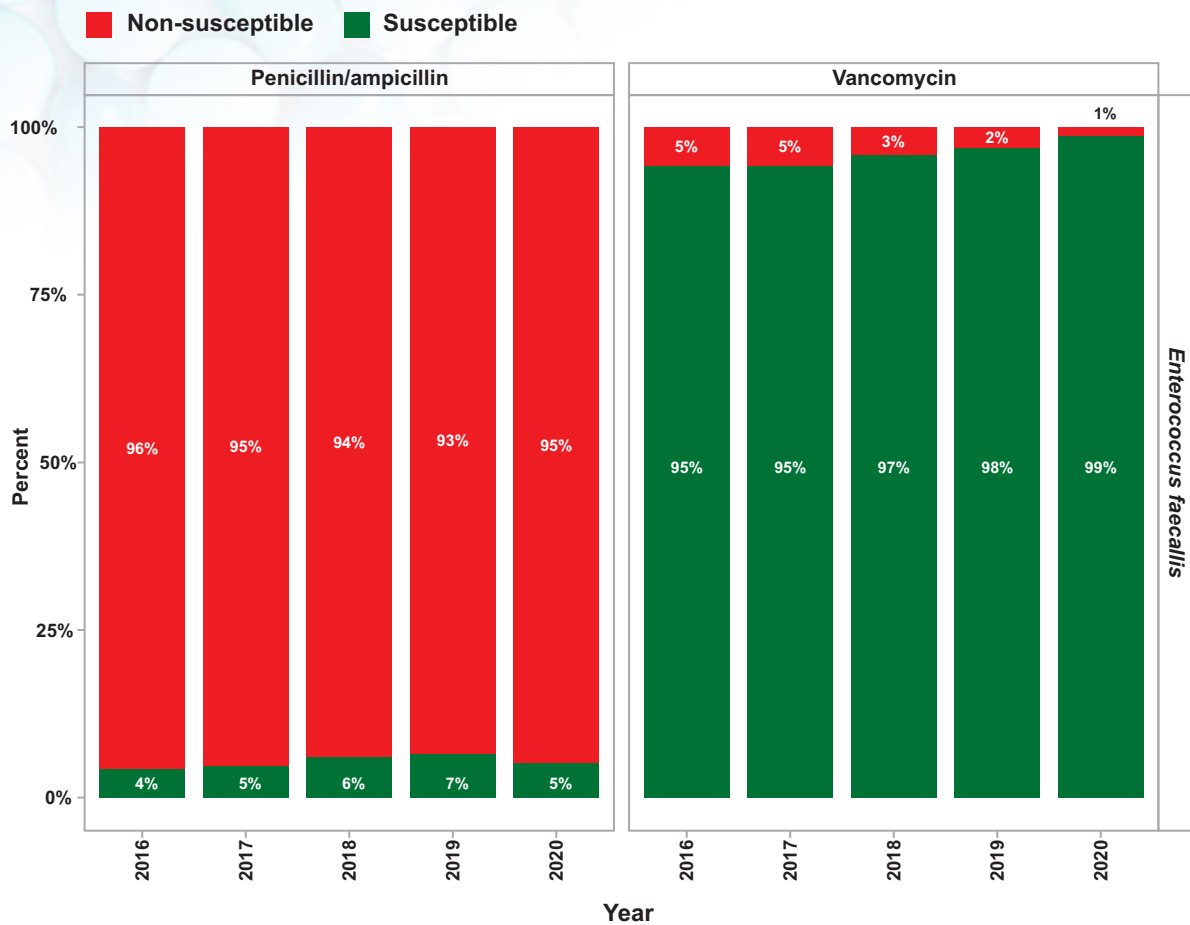
Figure 17. *Enterococcus faecium* **% non-susceptible to ampicillin and vancomycin, 2016 to 2020**

Vancomycin resistance remains uncommon in *E. faecalis* (approximately 1% in 2016), with no change in 2020 (Figure 18). One region (Free State with 3%) reports higher resistance rates to vancomycin in *E. faecium* than the other provinces (Figure 19).
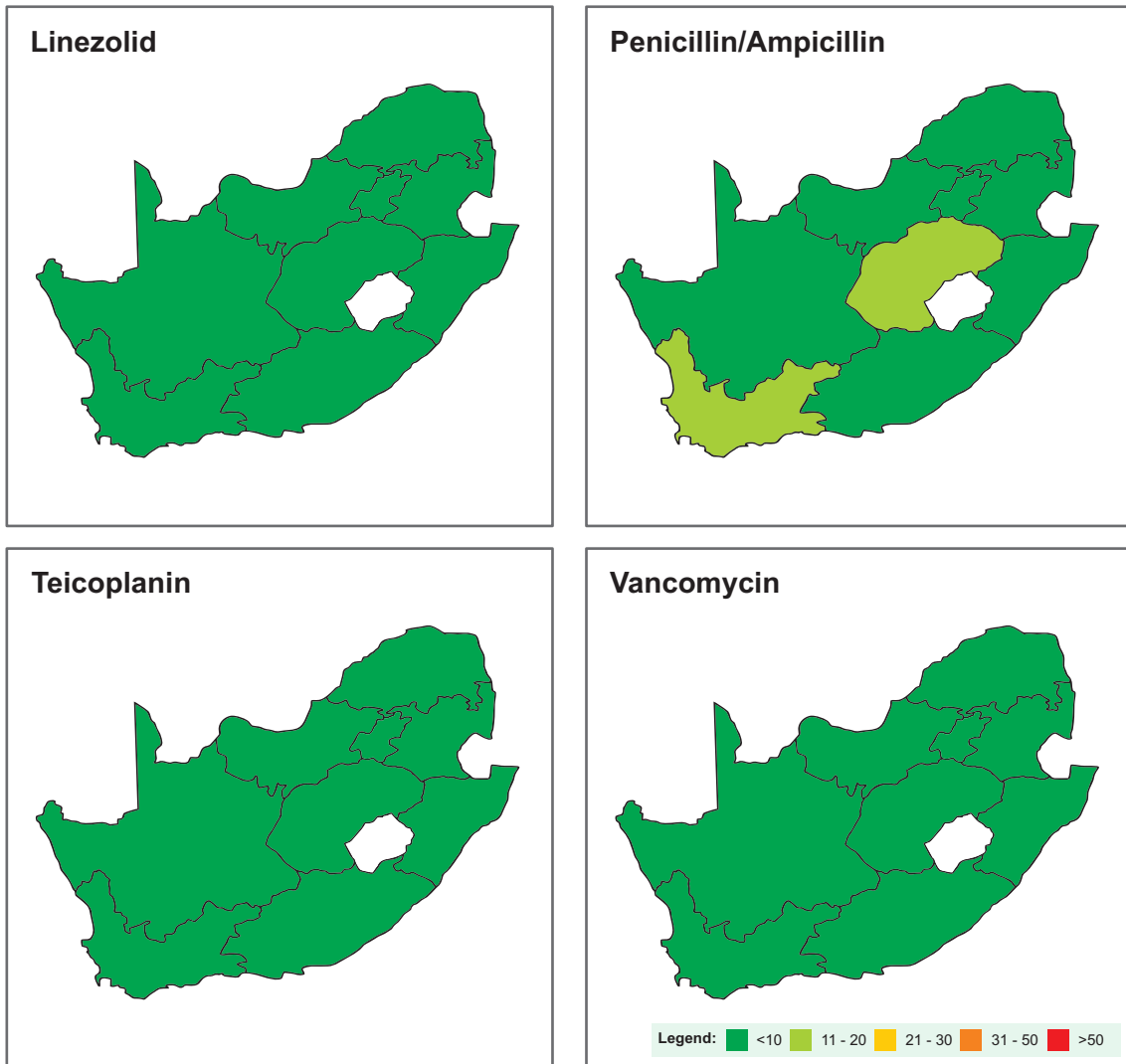
Enterococcus faecalis

Figure 18. Choropleth map for *E. faecalis* by province in South Africa, 2020 (legend shows % non-susceptible ranges)
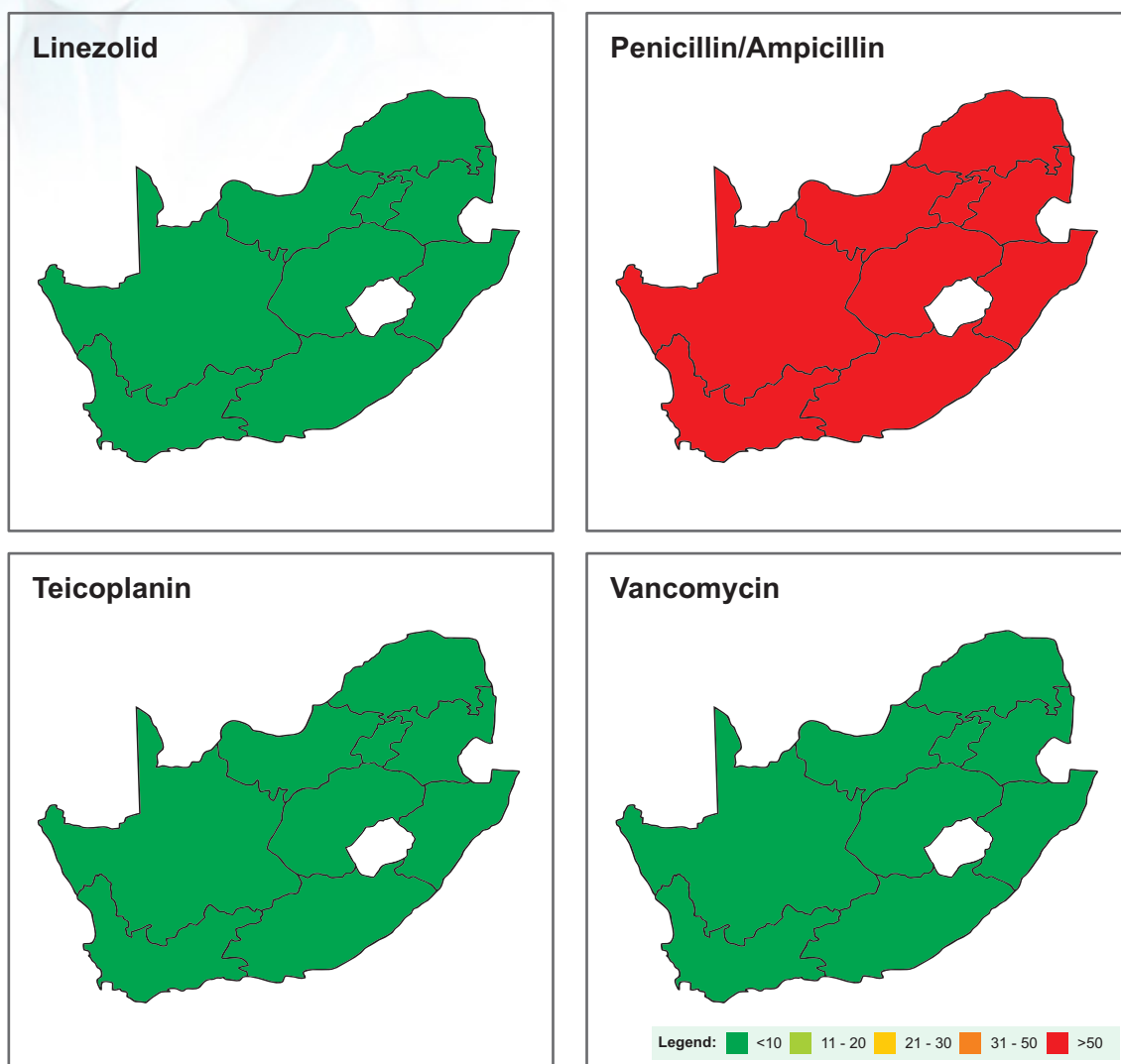
Enteroccus faecium

Figure 19. Choropleth map for *E. faecium* by province in South Africa, 2020 (legend shows % non-susceptible ranges)

3.1.3 *Streptococcus pneumoniae* report to WHO GLASS

S. pneumoniae data are collected through the NICD GERMS-SA laboratory-based surveillance system (see Annexure A for details). South Africa, through the NICD as the national coordinating centre, also participates in the WHO GLASS. These data are obtained from blood culture isolates collected and includes both public and private sector data. Certain sites perform enhanced surveillance where more details about the patient (e.g., demographics, age, gender, source of specimen, type and infection and site, and patient outcome) are collected.

To fulfil GLASS requirements, tier 1 laboratory-based surveillance is used for AMR data from GERMS-SA[7] and reported for *S. pneumoniae.* In a 2020 study of 368 *S. pneumoniae* isolates, resistance to 3rd generation cephalosporins was 1%, and intermediate susceptibility was 3%. Resistance to penicillin and trimethoprim-sulfamethoxazole was 4% and 27% respectively (Figure 20).

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[7]   GERMS 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.
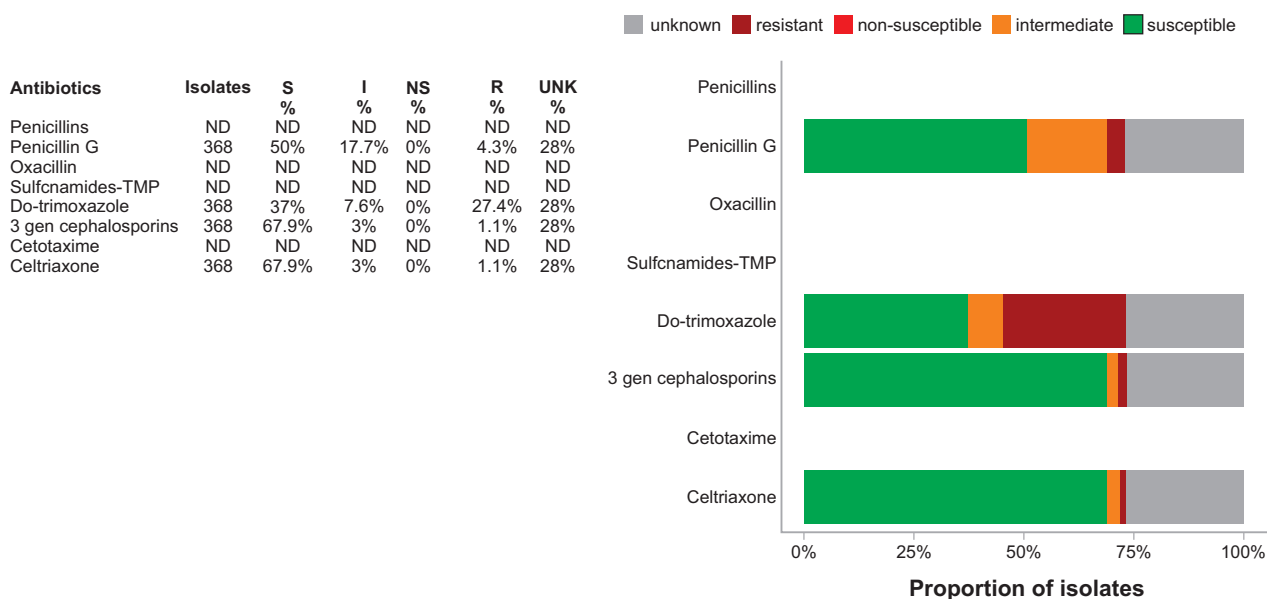
Antibiotics	Isolates	S %	I %	NS %	R %	UNK %
Penicillins	ND	ND	ND	ND	ND	ND
Penicillin G	368	50%	17.7%	0%	4.3%	28%
Oxacillin	ND	ND	ND	ND	ND	ND
Sulfcnamides-TMP	ND	ND	ND	ND	ND	ND
Do-trimoxazole	368	37%	7.6%	0%	27.4%	28%
3 gen cephalosporins	368	67.9%	3%	0%	1.1%	28%
Cetotaxime	ND	ND	ND	ND	ND	ND
Celtriaxone	368	67.9%	3%	0%	1.1%	28%

Figure 20. *Streptococcus pneumoniae* susceptibility profile from WHO GLASS submission 2020

3.2 Antimicrobial resistance in animals

3.2.1 South African cattle feedlots – Surveillance for antimicrobial resistance, 2021

The surveillance programme for South African cattle feedlots is an industry-driven initiative to support feedlot consultants in making informed decisions about AMU in the feedlots. The industry feeds up to 50 000 cattle at any one time countrywide. Cattle in most of the yards could be standing as long as 180 days (60 days backgrounding and 120 days in the feedlot). The bacteria included in the surveillance are involved in bovine respiratory tract infections, and all samples were collected via trans-tracheal aspirates.

Bovine respiratory disease remains the number one cause of morbidity and mortality in feedlots. The first line antimicrobial for treatment of respiratory disease remains florfenicol (an animal only antimicrobial). Antibiotics that show a high level of resistance (Table 1) are currently not used at all, or used very seldom, including erythromycin, lincosamides, tilmicosin, aminoglycosides and cephalosporins.

Feedlot veterinarians have moved away from prophylactic use of antibiotics in the feedlots, but metaphylactic use is regularly practiced because of the unique dynamics of bovine respiratory disease. The cattle feedlot industry would not be able to produce meat sustainably without metaphylactic AMU during critical periods of the feeding programme. Notwithstanding, the 2021 resistance data do not show any major shift or trend towards resistance when compared with the preceding number of years.

Table 1. Surveillance of AMR in cattle feedlots

	Mannheimia haemolytica	*Pasteurella multocida*	*Histophilus somni*	*Salmonella phimurium*
Penicillin	1/20(5%)		1/21(5%)	2/2
Ampicillin	1/20(5%)		1/21(5%)	
Amoxycillin				
Amoxycillin/ Clavulanic acid				
Cephalosporin 1st gen				2/2
Cephalosporin 2nd gen				2/2
Cephalosporin 3rd gen				
Tetracycline	2/20(10%)	18/32(56%)	7/21(33%)	
Fluoroquinolones				
Erythromycin	6/20(30%)	17/32(53%)	3/21(14%)	2/2
Clindamycin/ lincomycin	20/20(100%)	32/32(100%)	14/21(67%)	2/2
Gentamicin		4/32(13%)	2/21(10%)	2/2
Amikacin	3/20(15%)	12/32(38%)	7/21(33%)	2/2
Kanamycin	3/20(15%)	5/32(16%)	13/21(62%)	2/2
Florfenicol	1/20(5%)	1/32(3%)		
Sulfamethoxazole/ trimethoprim	2/20(10%)	2/32(6%)	3/21(14%)	
Tilmicosin	1/20(5%)	13/32(41%)	2/21(10%)	
Tildipirosin		12/32(38%)	2/21(10%)	
Gamithromycin		12/32(38%)	1/21(5%)	
Ceftiofur				
Cefquinome				

(Percent resistance indicated in brackets. Where no results are reported, no resistant strains were recorded)

Mannheimia haemolytica 20 strains; *Pasteurella multocida* 32 strains; *Histophilus somni* 21 strains; *Trueperella pyogenes* 3 strains; *Salmonella Typhimurium* 2 strains

All 3 *Trueperella pyogenes* strains showed no resistance against the panel of antibiotics

3.2.2 Antimicrobial susceptibility data from horses

The following data reflect results of all clinical specimens submitted for bacterial culture and antimicrobial sensitivity (n=145) by a single horse clinic in the Western Cape in the period March 2021 to March 2022. The clinic uses an in-house microbiology laboratory. Antimicrobial susceptibility was determined by the Kirby-Bauer disk diffusion method using Clinical & Laboratory Standards Institute (CLSI) guidelines. Bacterial identification to species level is often limited in this laboratory so bacteria have been grouped to reflect results produced by the laboratory and to try and generate meaningful numbers in the groups. Bars in the graphs are colour coded to reflect the European Medicines Agency categorisation of antibiotics for veterinary use as shown in the key (Table 2).

Table 2: Key to antibiotic classification based on European Medicines Agency

Category	Definitions
Category A - Avoid	• Antibiotics in this category are not authorised as veterinary medicines in South Africa • Should not be used in food-producing animals • May be given to companion animals under exceptional circumstances
Category B - Restrict	• Antibiotics in this category are critically important in human medicine and use in animals should be restricted to mitigate the risk to public health • Should be considered only when there are no antibiotics in Categories C or D that could be clinically effective • Use should be based on antimicrobial susceptibility testing, wherever possible
Category C - Caution	• For antibiotics in this category there are alternatives in human medicine • For some veterinary indications, there are no alternatives belonging to Category D • Should be considered only when there are no antibiotics in Category D that could be clinically effective
Category D - Prudence	• Should be used as first line treatments, whenever possible • As always, should be used prudently, only when medically needed

The following graphs (Figure 21, Figure 22) represent the susceptibility of *E. coli, Klebsiella*, Enterobacterales, *Pasteurellaceae*, *Pseudomonas*, *Staphylococcus*, *Streptococcus*, *Corynebacterium*, *Actinobacteria*, *Rhodococcus*, *Neisseria*, and *Salmonella* to antibiotics (i.e., Penicillin G, Amoxicillin + clavulanic acid, Ceftofur, Imipenem, Chloramphenicol, Doxycycline, Erythromycin, Enrofloxacin, Gentamicin, Trimethoprim + sulfamethoxazole).
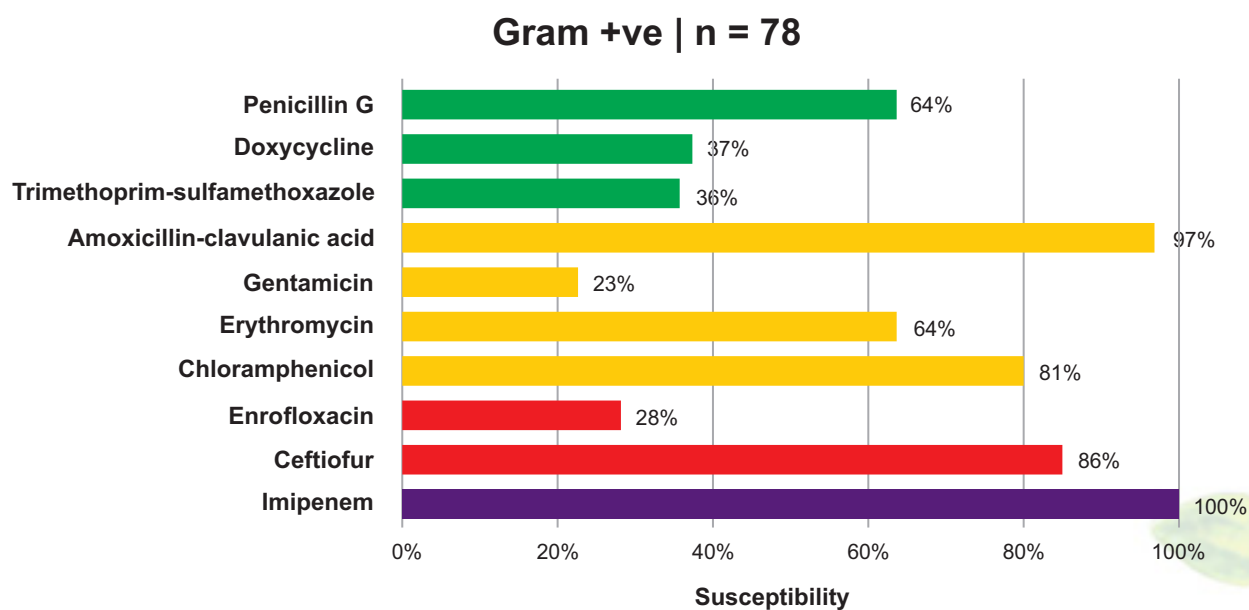
Gram +ve | n = 78

Figure 21: Antibiotic resistance in Gram positive organisms
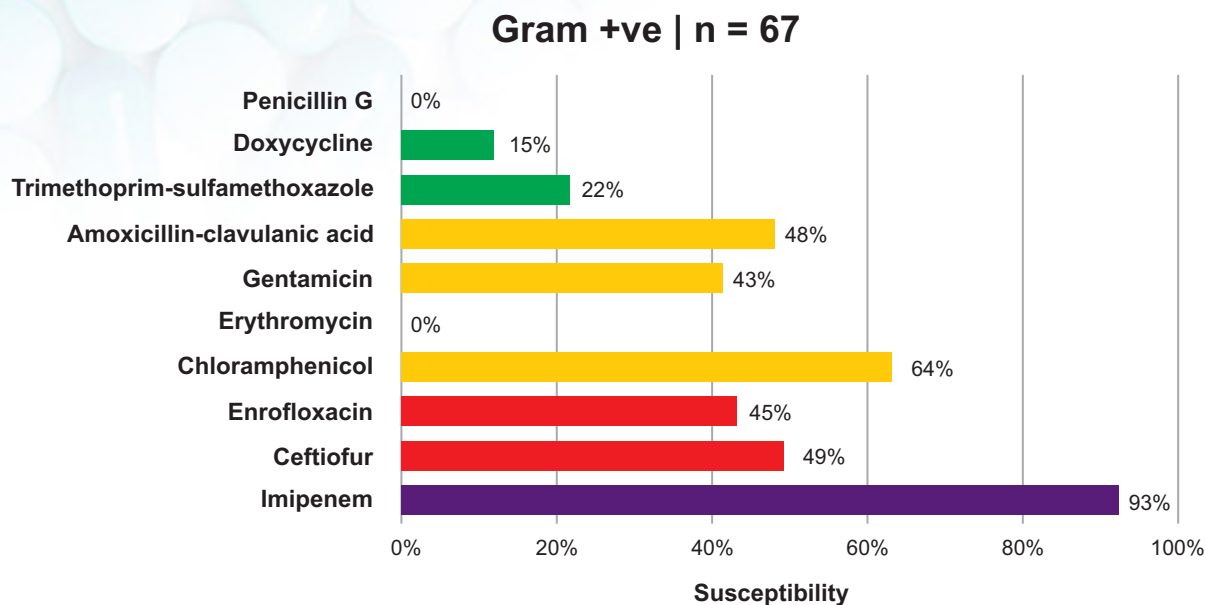
Gram +ve | n = 67

Figure 22: Antibiotic resistance to Gram negative organisms

4. USE OF ANTIBIOTICS IN THE HUMAN AND ANIMAL SECTOR

4.1 Definitions of antimicrobial procurement and use data

Antimicrobial Procurement Data

Aggregated data sets of antimicrobial products or active APIs procured or imported into South Africa. This data relates to total volumes and serves as a proxy for antimicrobial use, as it is more easily available and transparent than aggregated medicine use data.

Antimicrobial Use Data

Data sets of antimicrobial products prescribed, dispensed, or administered to patients or animals. Aggregated national South African antimicrobial use data in humans is not currently easily accessible due to lack of electronic systems and integration thereof, as well as strict patient data law under the Protection of Personal Information (POPI) Act.

4.2 Antimicrobial use data

As the National Department of Health (NDoH) moves towards National Health Insurance, its vision is to make medicine use data more visible and transparent, while maintaining requirements under the POPI Act, using electronic systems for prescribing, dispensing, stock management and the management of medicine master data. According to the WHO's pharmaceutical value chain, dispensing data is the gold standard for measuring AMU (Figure 23). However, currently only procurement data from a national perspective is available (Figure 23).

Pharmaceutical value chain indicating potential data sources for surveillance of antimicrobial consumption and use
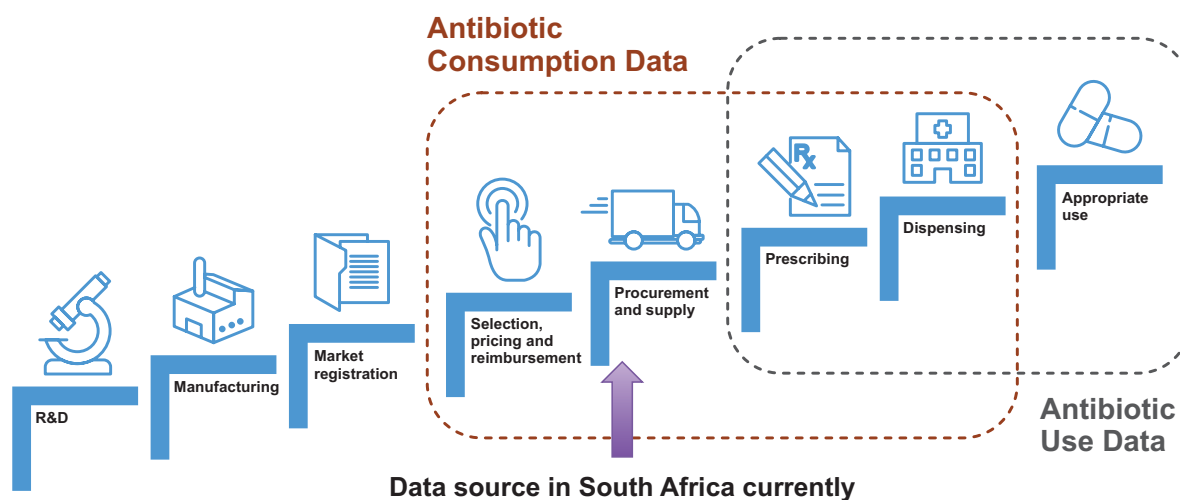
Figure 23. WHO Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries. A practical toolkit. Geneva: World Health Organisation; 2019. Licence: CC BY-NC-SA 3.0 IGO

4.3 Data collection

Procurement-related human antimicrobial data was collected at the product level and comprised International Non-Proprietary Name (INN), strength, dosage form and pack size, together with respective number of packs procured. Procurement data was made available for the public health sector, and analysed using DDD, which is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD is assigned per route of administration within an Anatomical Therapeutic Chemical (ATC) code and is normally based on monotherapy. The DDD provides a fixed unit of measurement independent of price and dosage form, enabling monitoring of use.[8] The DDD allows medicine use to be measured in a simplified manner and for standardised comparisons to be made between usage of products with different dosing regimens. DDDs were taken from the WHO definitions (available from www.whocc.no/atc_ddd_index/), using 2019 values.

An improved classification of import tariff codes by SARS since 2017 has allowed import data on antimicrobial products to be accurately split between human and animal health sectors as well as to break this down into the ATC classes of antibiotics.

Animal antimicrobial procurement data was collected according to antimicrobial class together with respective kilograms of product procured and was disaggregated from all animal species to food-producing animals and companion animals, as well as whether the indication was for therapeutic use or growth promotion.

For import-related human and animal procurement data, the INN of antimicrobial products and active ingredients were collected, together with volumes entering the country.

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[8]   World Health Organisation Collaborating Centre for Drug Statistics Methodology. DDD Definition and General Considerations. (https://www.whocc.no/ddd/definition_and_general_considera/ - accessed 27/10/2017)

4.4 Antibiotics monitored

The review of antibiotics follows the recommendations of the Guidelines on Implementation of the Antimicrobial Strategy in South Africa: One Health Approach and Governance document[9], which recommends the monitoring of the following products as part of AMU reporting at the national level of healthcare:

- All (J01 antibiotics)
- Ratio of broad to narrow spectrum penicillins (J01CA + J01CR vs J01CE + J01CF)
- Specific ATC classes:
    - Carbapenems (J01DH)
    - Vancomycin (J01XA01)
    - 3rd Generation cephalosporins (J01DD)
    - Fluoroquinolones (J01MA)
    - Macrolides (J01FA)
- Specific antibiotics:
    - Trimethoprim + sulfamethoxazole (J01EE01)

Table 3 shows the indicators related to AMU at a national level.

Table 3. Indicators Related to AMU

National Output	Measure Unit	Numerator	Denominator
Ratio of broad to narrow spectrum antibiotics Broad spectrum ATC: J01CA + J01CR Narrow spectrum ATC: J01CE + J01CF	Ratio	(J01CA + J01CR): (J01CE + J01CF)	J01CA + J01CR + J01CE +J01CF
Consumption of all J01 antibiotics, and specific ATC antibiotics such as carbapenems, vancomycin, 3rd generation cephalosporins, fluoroquinolones, macrolides in DDD's per 1000 inhabitants	Consumption of: • All J01 antibiotics • Specific ATC classes: - Carbapenems (J01DH) - Vancomycin (J01X) - 3rd generation cephalosporins (J01DD) - Fluoroquinolones (J01MA) - Macrolides (J01FA) - Trimethoprim - sulfamethoxazole (J01EE01)	Consumption in DDD's for each antimicrobial	South African population utilising public health care

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[9]   National Department of Health. 2017. Guidelines on Implementation of the Antimicrobial Strategy in South Africa: One Health Approach & Governance. (http://www.health.gov.za/index.php/antimicrobial-resistance - accessed 06/11/2019)

4.5 Data sources

4.5.1 Animal

National AMU data for animals was made available from the OIE reports submitted by the Department of Agriculture, Land Reform and Rural Development (DALRRD). This contained data disaggregated according to growth promotion and therapeutic use, as well as types of animals (companion or food-producing).

4.5.1.1 Human

- Public sector

Prescribing in the public health care sector is guided by the Standard Treatment Guidelines (STGs) and Essential Medicines List (EML), available for all 3 levels of care (primary, hospital, and tertiary (specialist) levels). Products on the EML are procured on state tender, offering economies of scale prices for healthcare facilities. Products on tender are monitored nationally through the RSA Pharma database, however, provinces and facilities can procure non-EML products as buy-outs (for their own cost and management), which do not reflect on RSA Pharma.

- Private sector

New to this report is the inclusion of a portion of private sector procurement data which reflects AMU data measured in DDD's used in acute care hospitals. This data was collected because of collaborations with private hospital groups to provide their AMU data via their pharmacy dispensing programmes. For the acute hospital setting three out of the five big groups affiliated to the Hospital Association of South Africa provided their data - Lenmed, Life Healthcare, and Mediclinic. This data, spanning from 2018 to 2020, was combined and the same evaluation was used as for the RSA Pharma data.

4.5.1.2 Animal and human import data

SARS data includes import data volumes and rand value of human and animal antibiotics and was collected from 2017 to 2020.

4.6 Results

4.6.1 Antimicrobial use estimates through South African import data

Between 2018 and 2020 there was a 28.6% increase in antibiotics imported for animals to 2,48 tons, and a 26.3% increase in human antibiotics imports to 1.7 tons, resulting in a total estimated import of 4.2 tons. This includes finished products as well as the Active Pharmaceutical Ingredient (API) products (Figure 24).

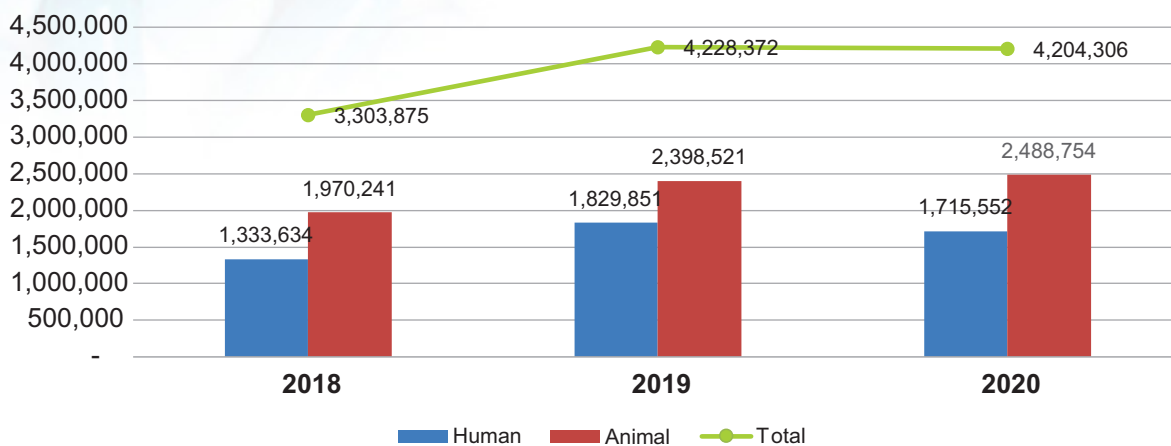**PROCUREMENT OF ANTIBIOTICS FOR HUMAN AND ANIMAL HEALTH (kgs)**

Figure 24. Procurement of antimicrobials for human and animal health in kgs for the period 2018 to 2020 (Source SARS import data)

Animal procurement makes up almost 60% of total procurement tonnage and this has remained constant since 2018 (Figure 25).
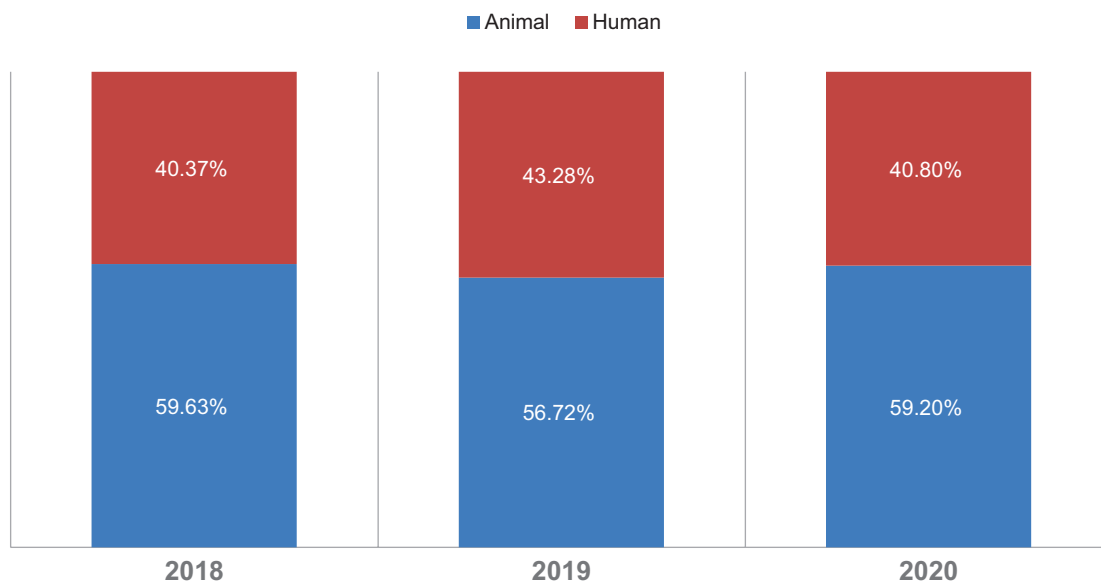

Figure 25. Relative antimicrobial procurement by species 2018 to 2020 (Source SARS import data)

The human health sector procures 1.78 times more penicillins than animal health, whilst most antibiotics procured for animals are either tetracyclines, macrolides or "unclassified as other antibiotics" (Table 4). The latter include polypeptides and ionophors, which are not used in humans.

Table 4. Total volume of all antibiotics and medicaments imported into South Africa (2018 to 2018, in tons)

|	HUMAN TONNAGE PROCURED			ANIMAL TONNAGE PROCURED		
	2018	2019	2020	2018	2019	2020
Antimicrobial						
Broad spectrum	542,308	456,803	541,056	6,933	583,367	553,209
Narrow spectrum	81,872	145,658	263,930	323	13	6
TOTAL penicillins	**624,180**	**602,461**	**804,987**	**7,256**	**583,381**	**553,214**
Streptomycins	375	585	425	1,638	46	8
Tetracyclines	39,552	54,875	57,546	946,715	564,765	782,615
Amphenicols (Chloramphenicol in humans)	11,788	382	3,837	257	33	116
Erythromycin	13,090	7,810	6,376	32	2	1
Macrolides	52,403	49,003	63,807	67,510	93,432	105,278
Cephalosporins	202	142,667	6,295	2,045	2,394	48
Sulfamethoxazole + Trimethoprim*	11,245	914	18,331	1,252	0	1
Fluoroquinolones*	890	29,240	15	-	-	-
Aminoglycosides	984	9,185	1,470	30,615	1	9
Other beta-lactams	62	325	4	226,243	161,485	273,232
Other antibiotics	578,864	932,405	752,459	686,678	992,984	774,232
TOTAL	**1,333,634**	**1,829,851**	**1,715,552**	**1,970,241**	**2,398,521**	**2,488,754**

* A complete data set for sulfamethoxazole + trimethoprim and fluoroquinolones were not available at time of publication, and these amounts as they stand are expected to be a great underestimation of actual usage

### 4.6.2 Antimicrobial use in animals that are significant for humans

The WHO and the OIE have emphasized that it is important for the animal health sector to apply risk management options when considering the use of antibiotics that are critically or highly important for humans. In other words, where humans and animals use shared class antibiotics such as tetracyclines, macrolides, polymyxins and aminoglycosides, the risk management options should allow an appropriate balance between animal, human and public health considerations.[10] Some of these, for example colistin, are regarded as last resort antibiotics for treatment of multi-drug resistant bacterial infections in humans, and can only be considered for animal use if laboratory tests indicate that no other antimicrobial is available for a particular infection. Figure 26 shows the sale of antibiotics for animals, split by class.

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[10]   WHO Critically Important Antibiotics for Human Medicine, 5th Revision, 2016

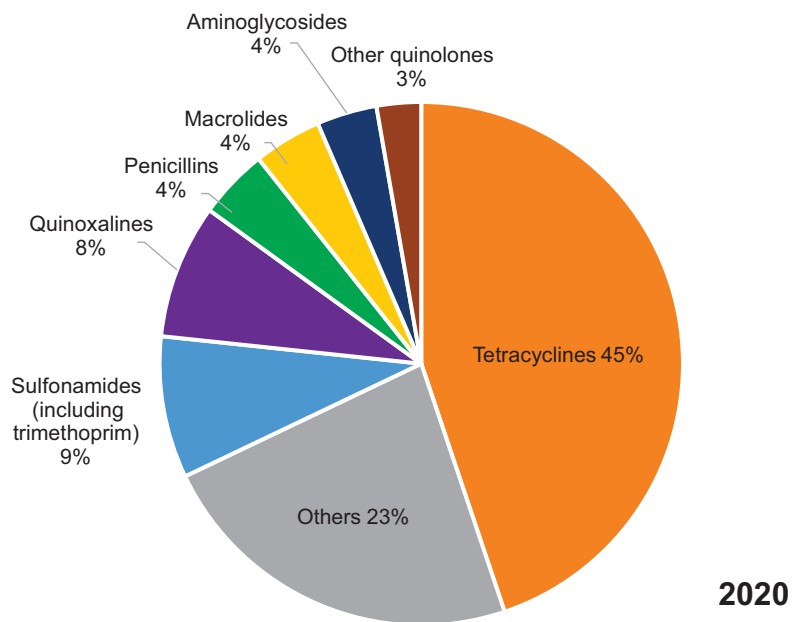## Split of antimicrobial sales by class for animals
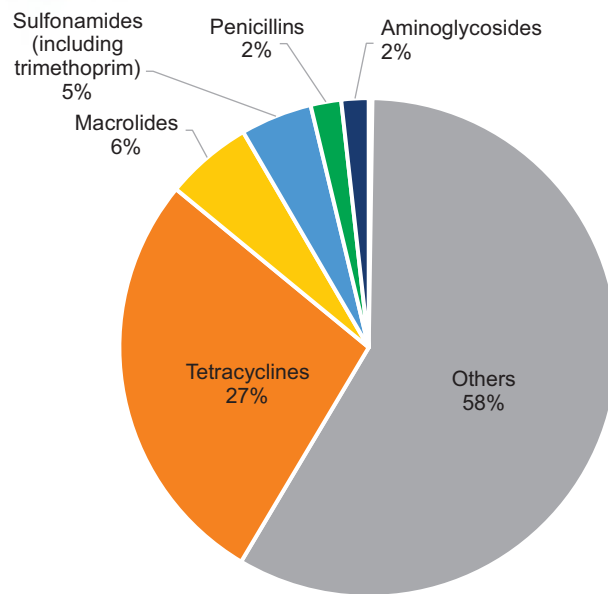
2014
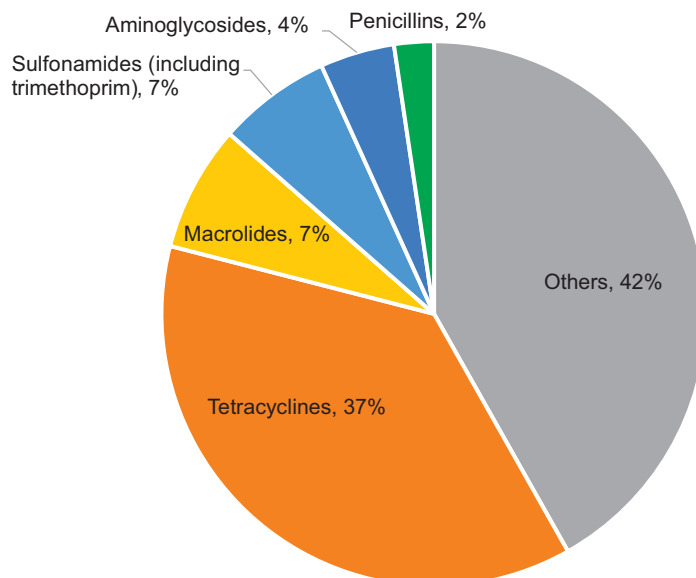
2016

Figure 26. Pie charts showing split of antimicrobial sales by class for animals in 2014, 2016 and 2020

(Data provided by the South African Animal Health Association and reported as part of OIE report 9,10)

Table 5. Comparison between 2014, 2016 and 2020 reported antibiotics used in animals in South Africa

Overall Amount: Growth Promotion + Therapeutic Use	2014	2016	2020
Antimicrobial Class	All animal species (kg)	All animal species (kg)	All animal species (kg)
Aminoglycosides	14 925	18 848	14 078
Amphenicols	3 530	2 958	4 114
Arsenicals	0	0	0
Cephalosporins (all generations)	418	826	297
1-2 gen. cephalosporins	408	248	250
3-4 gen cephalosporins	10	578	47
Fluoroquinolones	0	6 859	2 822
Glycopeptides	0	0	0
Glycophospholipids	0	303	277
Lincosamides	0	159	0
Macrolides	47 757	31 879	15 929
Nitrofurans	0	0	0
Orthosomycins	3 733	1 788	1040
Other quinolones	3 453	0	10 385
Penicillins	16 737	10 055	16 393
Pleuromutilins	7 745	4 481	3 187
Polypeptides	295	140	78
Quinoxalines	3 839	0	31 383
Streptogramins	0	533	0
Sulfonamides (including trimethoprim)	39 264	28 708	35 289
Tetracyclines	231 392	158 519	194 836
Others	469 037	159 451	77 151
Total kg	**842 125**	**425 507**	**407 428**

Table 5 shows a steady decline in quantities of antibiotics used in animals during the past 6 years, notwithstanding the increase in tonnage procured as reflected in Table 2. Tonnage procured does not necessarily reflect the quantities of antibiotics sold and finally used. A major reason for a decline in AMU in animals is the phasing out of antibiotic growth promoters since 2019. The reasons for a significant decline in the use of growth promoters are two-fold. Firstly, multinational pharmaceutical companies based in the northern hemisphere have voluntarily started phasing out claims for prophylaxis and growth promotion in the package inserts of their products. Secondly, an agreement was reached between the Registrar of Stock Remedies and SAAHA and its members, which represent most pharmaceutical companies supplying the animal production industries, to remove all claims for antibiotics of prophylaxis and growth promotion. This has effectively eliminated medically important antibiotics for growth promotion in South Africa. No antimicrobial drug will receive marketing authorization in South Africa in future with claims for prophylaxis and growth promotion.

Where sub-therapeutic antimicrobials are administered to young growing animals in water or feed to improve utilization of feed and weight gain when suffering from low-grade, subclinical bacterial-induced inflammation in the gut, it will include members of the class orthosomycins, polypeptides, quinoxalines and ionophors, all of which are currently used only in animals.

4.6.3 Poultry *E. coli* surveillance data for 2021

The poultry surveillance programme for *E. coli* resistance to antimicrobials is a poultry industry-driven initiative, supported by poultry veterinarians to control the development of AMR in commercial poultry and provide data for poultry veterinarians to apply AMS in the industry.

E. coli is the bacterium of choice for surveillance as it is both a commensal/indicator organism and poultry pathogen that enables detection of the emergence of resistance on intensive production units and monitoring the outcome of interventions implemented to reduce the need for antimicrobial drugs.

The isolated and identified strains were collected under the guidance of poultry veterinarians on poultry production farms throughout the country and are representative of countrywide trends. Samples were collected during necropsies from either air sacs, pericardia, liver abscesses or necrotic lesions in the femoral joints.

When the minimum inhibitory concentrations (MICs) of a particular antimicrobial shows an upward trend, the attending poultry physician will prescribe a different antimicrobial class. The result of this approach is that major, long-term increases were not recorded during the past decade, and when data from previous years are compared, resistance patterns for some units will be better because of the interventions. An example of such a trend is for colistin, an antibiotic that was withdrawn from veterinary use in 2016. The MIC values for colistin during 2014 and 2015 showed a meaningful upward trend, and in 2015 about 20% of strains yielded MICs equal to or higher than the clinical breakpoint of 4 ug/ml. This year's report identified only 3.6% of *E. coli* strains resistant to colistin.

When the 2021 MIC data are compared with the results documented in the 2007 national veterinary surveillance programme, resistance rates for oxytetracycline and trimethoprim are slightly down. The MICs for neomycin are down, and for quinolones are similar.

MIC distribution and percentage of resistant strains of 332 pathogenic *E. coli* strains collected by V-Tech during 2021 in South Africa

Antimicrobial	% Resistant	Distribution of MICs (Ug/ml) in %												
		0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
Chlortetracycline[1]	79.52%						0.30%	5.72%	14.46%	13.86%	10.84%	1.81%	4.22%	48.80%
Doxycycline[2]	52.11%				3.61%	1.20%	16.87%	13.55%	12.65%	11.45%	13.25%	15.66%	8.43%	3.31%
Enrofloxacin[3]	59.94%	7.23%	0.00%	21.39%	11.45%	13.25%	16.27%	6.33%	7.53%	7.53%	9.04%			
Norfloxacin[4]	21.39%	6.63%	0.00%	16.57%	8.13%	12.05%	15.06%	12.05%	8.13%	5.42%	15.96%			
Florrenicol[5]	9.94%			2.41%	0.60%	10.24%	11.75%	17.17%	36.64%	13.25%	5.72%	1.51%	2.71%	
Fosfomycin[6]	32.83%			4.82%	13.25%	15.06%	10.54%	12.35%	11.14%	6.63%	6.93%	19.28%		
Neomycin[7]	25.30%				15.66%	0.30%	32.53%	12.65%	5.42%	5.12%	3.01%	7.23%	10.24%	
Kanamycin[8]	26.51%				3.01%	0.00%	18.37%	16.27%	24.40%	9.64%	1.81%	2.41%	3.61%	
Colistin[9]	3.61%	5.42%	0.00%	29.82%	23.80%	25.60%	11.75%	0.60%	0.60%	0.90%	1.51%			
Amoxycillin[10]	42.47%		2.41%	0.00%	7.53%	11.75%	6.63%	15.96%	9.94%	3.31%	6.02%	36.45%		
Trimethoprim[11]	35.24%	10.84%	0.90%	30.42%	10.54%	7.53%	4.52%	1.81%	1.51%	8.73%	23.19%			

MIC_{50} is indicated in green and MIC_{90} is indicated in orange. The breakpoint f each antibiotic is indicated by a bold black line.

References:
Ref 1   CLSI. *Performance standards for Antimicrobial Susceptibility Testing.30th ed. SLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2020.*
Ref 2   *The European Committee on Antimicrobal Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 11.0, 2021. http://www.eucast.org*
Ref 3   *The National Antimicrobial Resistance Monitoring System. 2021. http://www.fda.gov/media/108180/download*
Ref 4   *Hao, H/ et al. 'Susceptibility Breakpoint for Enrofloaaxacin against Wine Salmonella spp.', Journal of Clinical Microbiology, 51. (2013), 3070-3072 (p.3071).*

1   Tetracycline breakpoint level is reported in the CLSI and NARMS (Ref 1, Table 2A, page 39)(Ref 3, table 1, page 1).
2   Docycycline breakpoint level is reported as doxycycline in Ref 1 of as tetracycline (Ref 1, Table 2A, page 39)(Ref, table 1, page 1).
3   Paper pubished in the Journal of Clinical Microbiology in 2003, states that enrofloxacin is susceptible at< 0.5mg/ml (ref 4, Hao et al, 2003)
4   The breakpoint level is based on published urinary tract infections in humans (Ref 1, table 2A, page 39)
5   Chloramphenicol breakpoints were used for florfenicol (Ref 1, table 2A, page 40) (Ref 3, table 1, page 1)
6   MICs for fosfomycin were established in a supplemented broth dilution; Resistance level are for urinary tract infection (Ref 2. page 23)
7   Kanamycin breakpoint can also be used for neomycin (Ref 1, table 2A, page 38) (Ref 3, table 1, page 1)
8   Kanamycin breakpoint level is reported in the CLSI (Ref 1, table 2A, page 38) (Ref 3, table 1, page 1)
9   Colistin breakpoint level is reported in the CLSI and NARMS (Ref 1, table 2A, page 38) (Ref 3, table 1, page 1)
10   The breakpoint of ampicillin levels could be used to predict results for amoxicillin (Ref 1, table 2A, page 33, comment 5) (Ref 3, table 1, page 1)
11   The MIC levle of trimethoprim are based on a sulfadiazine: trimethoprim ration of 19:1; only the trimethoprim is reported in the table (Ref 1, table 2A, page 40) (Ref 3, table 2A, page 40) (Ref 3, table 1, page 1)

4.6.4 Antimicrobial residues from National Chemical Residues Monitoring programme in Animal Health

Antibiotic residues are trace amounts of metabolites found in the edible portions of animal products after the animal has received antibiotics. If these are found to be in excess of acceptable limits, it may contribute to the development of antibiotic resistance in the animal or human that consumes the product. A 'withdrawal' or 'washout' period is thus necessary from the time the antibiotic was administered until the animal can be slaughtered, so that the metabolites are diminished within the animal.

Residue testing in South Africa is conducted under the Directorate of Veterinary Public Health within DALRRD, and consists of two national programmes:

1. The NCRMP covers meat from abattoirs in South Africa destined for local consumption as well as export to non-EU countries. The maximum residue levels used are based upon Codex and South African legislation.
2. The National Chemical Residue Control Programme (NCRCP) is a parallel programme targeting farms and establishments specifically registered for export to the EU. The analyses and maximum residue levels for the NCRCP are based on EU legislation, which includes other prohibited substances such as steroids and growth promoters (e.g., antibiotics amongst others).

4.6.4.1 National Chemical Residue Monitoring Programme

The NCRMP is coordinated and funded by the DALRRD under the Meat Safety Act (Act Number 40 of 2000). The objectives of the programme are to verify that official controls are in place at farms and abattoirs and collate data on chemical residues in food products of animal origin for local and export consumption.

Meat samples of kidneys from beef, mutton/lamb, poultry, and pork are sampled with 0,014% of the red meat production of the country being sampled and in poultry, 3 in 10 million birds slaughtered. Results represent 1163 samples taken over the period 2020 to 2021 tested against 24 antimicrobial classes, depending on the species.

Of the total meat samples collected, eighty one percent (81%) received by the laboratory were analysed (Table 6).

Table 6. Number of samples collected by species type and number analysed

Meat products	Beef	Lamb/mutton	Pork	Poultry	Total
Sampled	812	665	458	398	**2333**
Analysed	623	547	394	327	**1891**
	77%	**82%**	**86%**	**82%**	**81%**

Antimicrobial residues were detected in 0.16% (3 out of 1891) of samples analysed, of which were for tetracyclines. Higher detection was observed with tetracyclines in pig kidney samples (2 of the 3 samples). No antibiotics were detected in samples from sheep or poultry.

Table 7. Number of resistant specimens by species type

Samples	Level of Action (ppb)*	Beef	Lamb/ mutton	Pork	Poultry	Total	%
		n = 623	n=547	n=394	n=327	n=1891	
Tetracyclines	600	1	0	2	0	3	0.16
Penicillins	50	0	0	0	0	0	
Sulphonamides	100	0	0	0	0	0	
Macrolides	200	0	0	0	0	0	
Total		**1**	**0**	**2**	**0**	**0**	**0.16**

* MRLS are based on the EU legislation, which are almost exactly aligned to Codex guidelines. Where differences exist between Codex and EU, DALRRD is aligned to the EU levels

The contamination of commercially produced meat in South Africa and exposure of consumers to antimicrobial residues from these products appears to be low. It is possible that the results are an underestimation of the situation in the country due to gross under sampling, largely due to a lack of available funds and capacity constraints within the provincial veterinary public health structures to sample, monitor and follow up establishments with non-compliances.

4.6.5 Human AMU in South Africa compared to global levels

The most recent international report on AMU comes from 2015. South Africa's antibiotic use in 2015 was 9,177 DDD per 1000/population, much higher than seen in other BRICS countries - *Brazil 6,763; Russia 6,069; India 4,950; China 3,060 - although lower than in higher-income countries (e.g., USA 10,298; Canada 7,078; Australia 11,088)* (Figure 27).

USE OF ALL ANTIBIOTICS IN 2015

Source: IQVIA
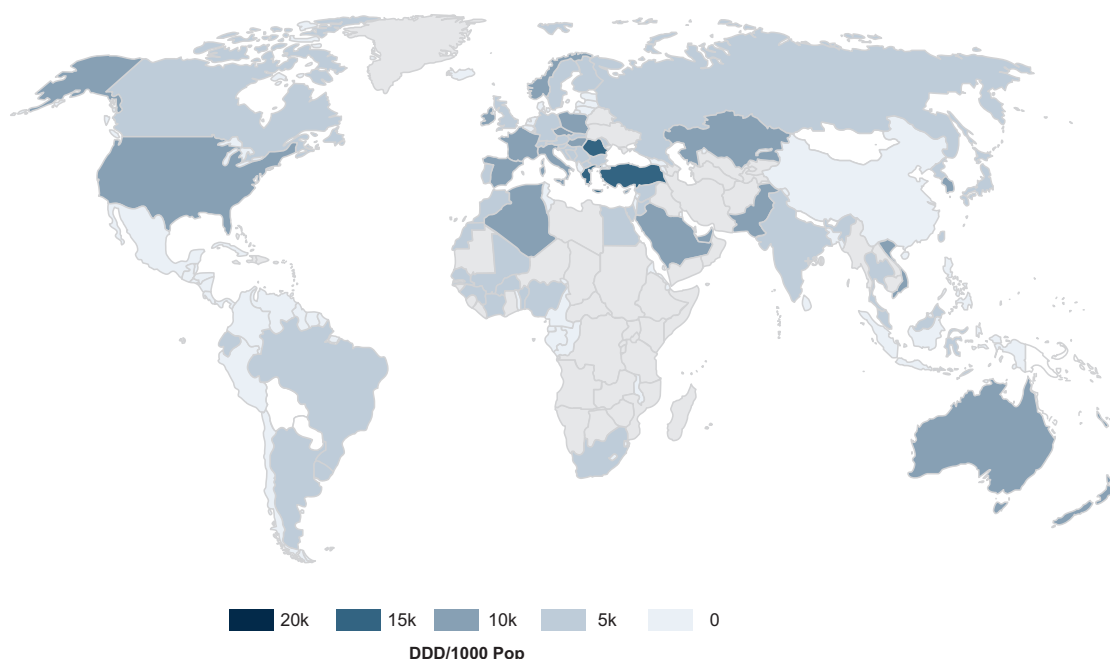
Figure 27. Use of antibiotics across the world 2015 (IQVIA data as presented by ResMaps (CDDEP))

Broad spectrum antibiotics are used extensively in South Africa compared to other countries e.g., 12% higher usage than the UK, and 15% higher usage than Russia, however, the USA usage is 12% higher than that in South Africa. Out of all the countries displayed in Figure 28, South Africa has significantly higher trimethoprim-sulfamethoxazole use, representing the burden of prescribing in the world's largest *HIV* programme, for which trimethoprim-sulfamethoxazole is core to the prevention of *Pneumocystis jirovecci pneumonia* (PJP). The exact quantities that are used for PJP in contrast to other indications cannot be determined currently.

Antibiotic Use in 2015
Source: IQVIA
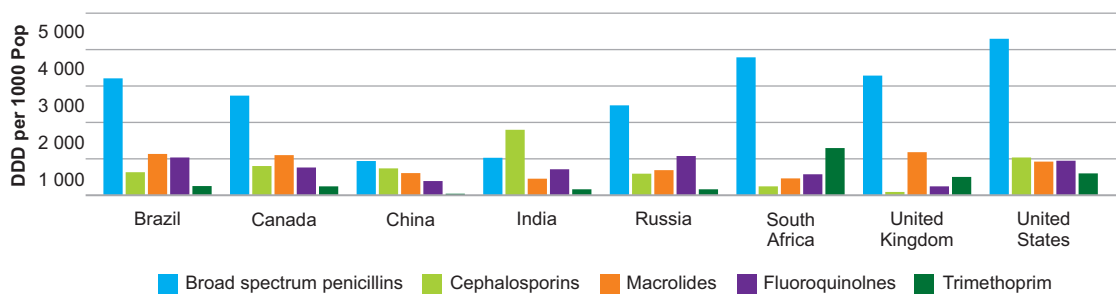
Figure 28. AMU comparison of South Africa compared to BRICS, US and UK ((IMS data as supplied by ResMaps (CDDEP))

4.6.5.1 All antibiotics procured in the public sector

The ribbon chart (Figure 29) shows the procurement of antibiotics by ATC class from 2015 to 2020 in the public sector.

Table 8 gives the description of the ATC class, with an example from each class. ATC classes with less than 10,000 DDDs were excluded from the ribbon chart to make it easier to read.

Ribbon charts (see Figures 29 and 30) show rank changes, with the highest value always displayed on top for each time period. It also displays the changes in rank from period to period, in the case of Figure 29, from year to year.
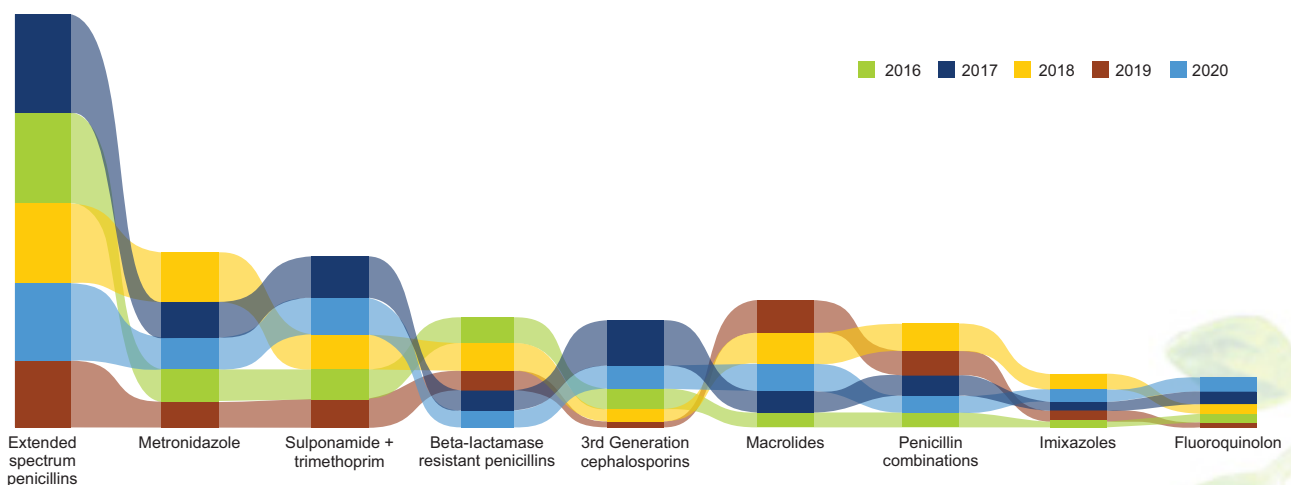
Figure 29. Antimicrobial procurement in South Africa's public health care sector (as DDDs) from 2016 to 2020 (excluding ATC codes with DDDs less than 10,000)

Table 8. ATC class and description of antibiotics analysed

ATC 4th Level	ATC Description	Examples
J01AA	Tetracyclines	Doxycycline
J01CA	Penicillins with extended spectrum	Ampicillin, Amoxycillin
J01CE	Beta-lactamase sensitive penicillins	Phenoxymethylpenicllin
J01CF	Beta-lactamase resistant penicillins	Cloxacillin, Flucloxacillin
J01CR	Combinations of penicillins, including beta-lactamase inhibitors	Amoxycillin and clavulanic acid
J01DB	First generation cephalosporins	Cephalexin, Cefazolin
J01DC	Second generation cephalosporins	Cefoxitin
J01DD	Third generation cephalosporins	Cefotaxime, Ceftazidime, Ceftriaxone
J01DE	Fourth generation cephalosporins	Cefepime
J01DH	Carbapenems	Meropenem, Ertapenem, Imipenem
J01DI	Other cephalosporins and carbapenems	Ceftaroline
J01EE	Combinations of sulfonamides and trimethoprim	Trimethoprim-sulfamethoxazole
J01FA	Macrolides	Clarithromycin, Azithromycin
J01FF	Lincosamides	Clindamycin
J01GB	Other aminoglycosides	Gentamicin, Amikacin, Kanamycin
J01MA	Fluoroquinolones	Ciprofloxacin, Levofloxacin, Moxifloxacin
J01XA	Glycopeptide antibiotics	Vancomycin
J01XB	Polymixins	Colistin
J01XD	Imidazole derivatives	Metronidazole parenteral
J01XE	Nitrofuran derivatives	Nitrofurantoin
J01XX	Other antibiotics	Linezolid
P01AB	Nitroimidazole derivatives	Metronidazole oral only

Extended spectrum penicillins (J01CA, e.g., amoxicillin) accounted for most of the antimicrobial procurement from 2018 (25% of total) to 2020 (28%). Oral metronidazole (P01AB) is the second most procured antibiotics (15% of total in 2018, 11% in 2019 and 12% in 2020), followed by trimethoprim-sulfamethoxazole (J01EE), with 11%, 12% and 13% respectively. This differs from the previous published report due to a change in the DDD value used (ANNEXURE B: Defined Daily Doses for Trimethoprim-sulfamethoxazole).

4.6.5.2 All antibiotics procured in the private sector

Figure 30 shows the procurement of antibiotics by ATC class from 2018 to 2020 in the public sector. This should be used in conjunction with Table 8 which gives the description of the ATC class, with an example from each class. ATC classes with less than 100,000 DDDs were excluded from the ribbon chart to make it easier to read.
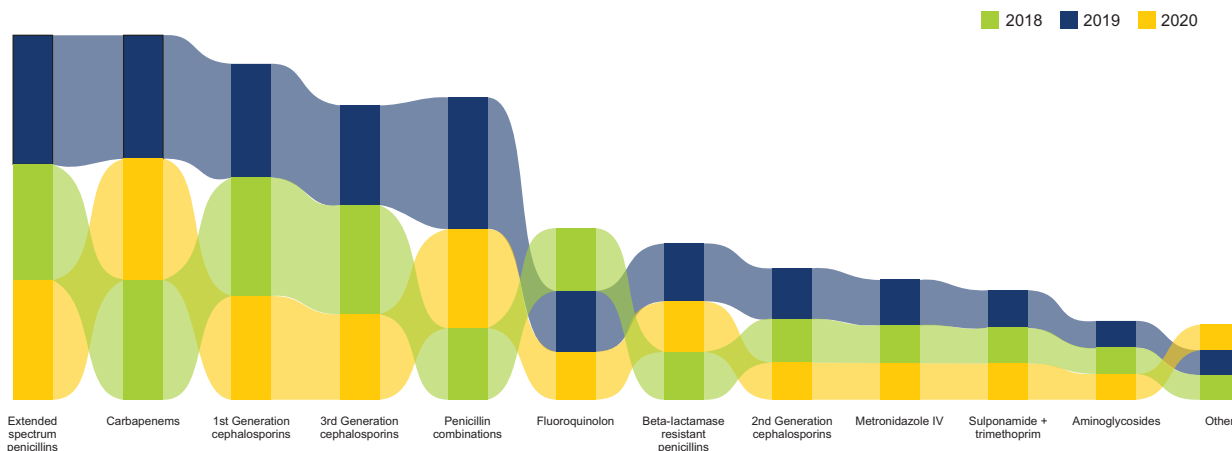
Figure 30. Antimicrobial procurement in South Africa's public health care sector (as DDDs) from 2018 to 2020 (excluding ATC codes with DDDs less than 100,000)

The private sector pattern of AMU is very different to that of the public sector (see also Table 9):

- Extended spectrum penicillins (J01CA, e.g., amoxicillin) accounted for most of the antibiotic procurement from 2018 (40% of total) to 2020 (41% of total).

- Carbapenems (J01DH) are the second most procured antibiotic (20.6% in 2018, and similar 20,1% in 2020),

- The third most used antibiotics are 3rd generation Cephalosporins (J01DD) at 16.3% in 2018 and 13.3% in 2020.

- Macrolides have doubled in proportionate use from 5.3% in 2018 to 11,4% in 2020 and this may reflect in the increase used during the COVID-19 pandemic in South Africa.

4.6.6 Comparison of antimicrobial procurement between public and private sectors

Due to the current disparate data collection processes used for the private and public sectors, the following caveat (Table 9) should be taken into consideration when reading the section on AMU for human consumption.

Table 9. Important caveat to comparing private to public healthcare data

It is important to note that the AMU data between the private and public healthcare sectors cannot be directly compared:

- Private sector data is incomplete (consisting of 3 hospital groups, and excludes all community-level antibiotic prescriptions), and the public sector data includes all procurement for hospital and community level facilities.

- The public sector provides health services for approximately 80% of the population with 20% of the overall health expenditure of the country, and vice versa with regards to the private sector, but it is estimated that the private sector procures the majority of antibiotics in the healthcare sector. The graphs shown below only show procurement as DDDs and doesn't take the populations using the different sectors into account.

ANTIMICROBIAL PROCUREMENT IN PUBLIC AND PRIVATE HEALTHCARE SECTORS
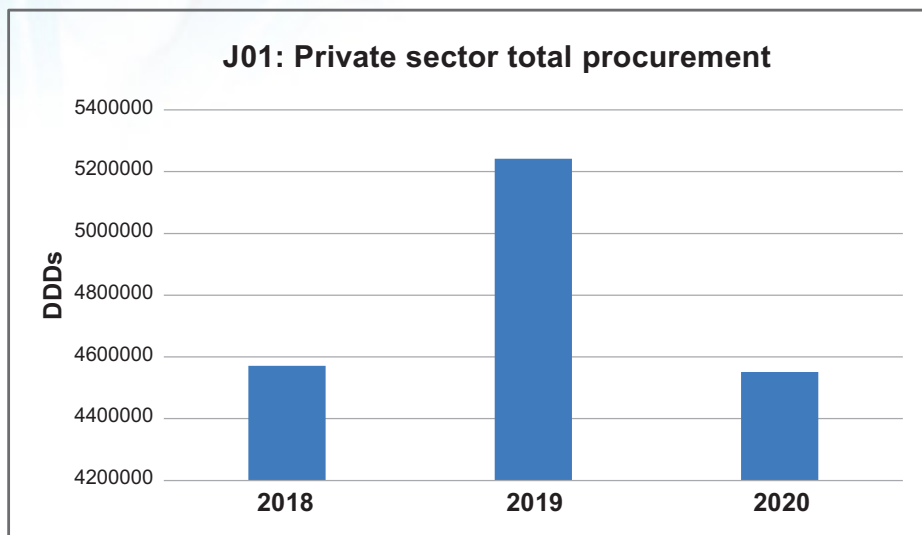
PUBLIC SECTOR
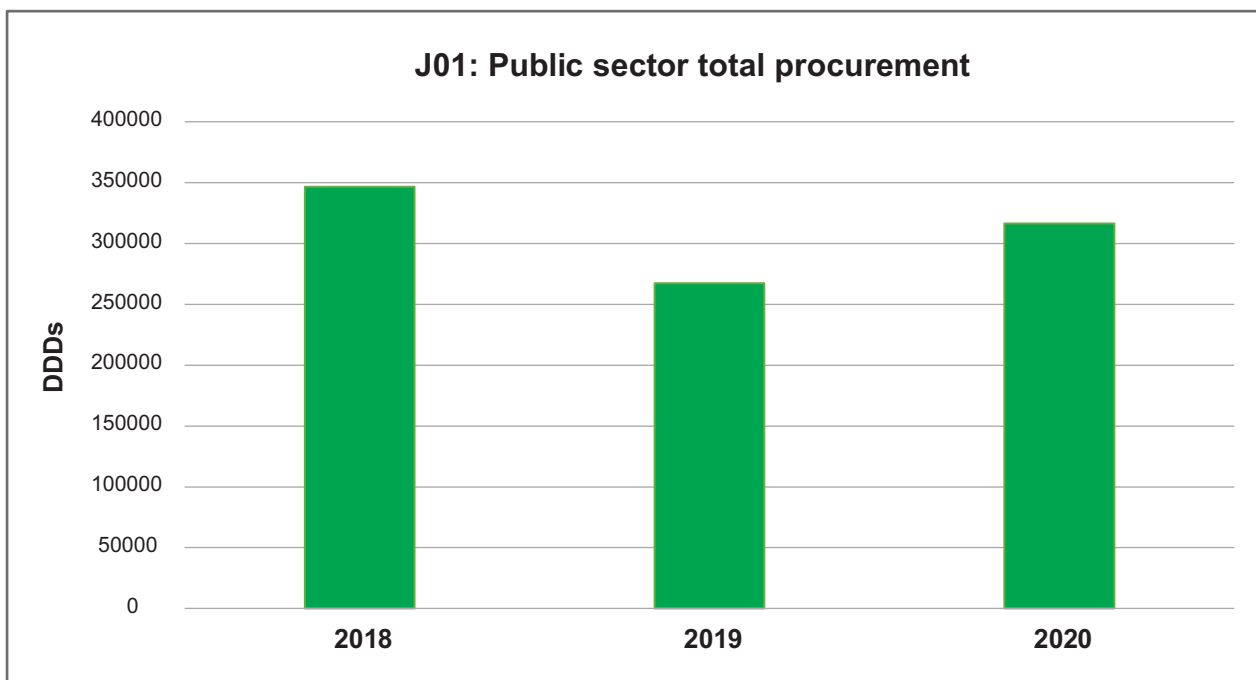
Figure 31. Comparison of total procurement of antibiotics in the J01 ATC class between the private and public healthcare sectors – note the difference in log scale between private and public sector graphs.

Figure 31 shows AMU (as DDDs) in both private and public healthcare sectors. For all 3 years depicted, the public sector procured less than 8% of the total quantity of antibiotics procured for human health i.e, 92% of all antibiotics procured for human health went to the public sector. This could reflect access between the public and private sectors and may also be due to the STGs and EML that guide the use (and restriction of what is available) of medicines, including antibiotics, in the public sector.

4.6.6.1 Procurement of trimethoprim-sulfamethoxazole in comparison to other antibiotics in private and public sectors

TRIMETHOPRIM-SULFAMETHOXAZOLE VS OTHER ANTIMICROBIALS FOR SYSTEMIC USE

Figure 32. Trimethoprim-sulfamethoxazole versus other antibiotics in South Africa: private sector and public sector (as a percentage of DDDs)

The public sector procures about 10% more trimethoprim-sulfamethoxazole than the private sector, however, without a full accounting of private community-based usage, we can only assume that the public sector uses more trimethoprim-sulfamethoxazole than the private sector due to the HIV programme being focused in the public sector (Figure 32).

4.6.6.2 Ratio of broad to narrow spectrum penicillins in private and public sectors

Broad spectrum penicillins are those in the ATC classes J01CA (which includes ampicillin, amoxicillin, piperacillin) and J01CR (which includes combinations of beta-lactamase inhibitor with ampicillin, amoxicillin, or piperacillin). Narrow spectrum penicillins are those in the ATC class J01CE (including benzylpenicillin, phenoxymethylpenicillin, benzathine benzylpenicillin) and J01CF (such as cloxacillin and flucloxacillin).

BROAD SPECTRUM AND NARROW SPECTRUM PENICILLIN PROCUREMENT
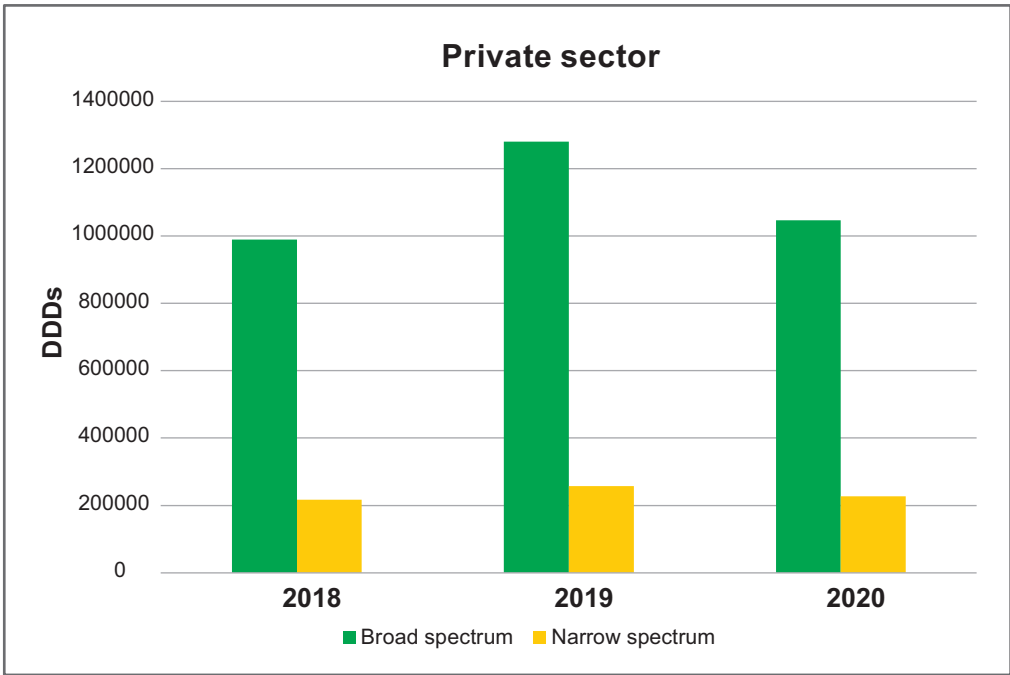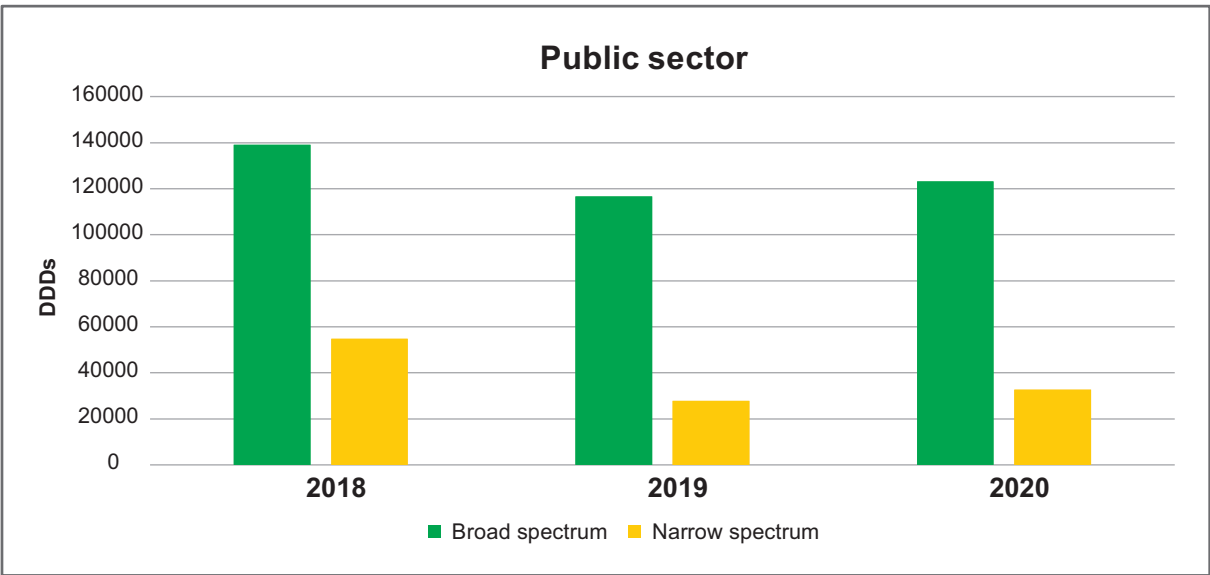
Figure 33. Comparison of the procurement of penicillins between private and public sectors. Note the different log scales used in the Y-axis of the graphs.

Throughout the 3 years, the private sector procured between 88-92% of all the broad-spectrum penicillins in the healthcare sector. In 2018, the public sector procured 20% of the healthcare system's narrow spectrum penicillin, however this decreased to 10 to 13% in the following years. Overall, the public sector procured between 9 to 14% of all penicillins between 2018 to 2020 (Figure 33). Public health facilities can procure products not available on the South African market (e.g., many penicillins) via Section 21 through SAHPRA . These are not captured in this data and may result in a (relatively small) underestimation of penicillin use in the public sector.

4.6.6.3 Comparison of antibiotics (carbapenems, vancomycin, 3rd generation cephalosporins, fluoroquinolones, and macrolides) between private and public healthcare sectors

Figure 34. Comparison of antimicrobial procurement of certain J01 ATC classes between private and public sectors: in comparison with total antibiotics procured per sector

Although there may be many reasons for the observed changes in AMU over the years, there is a lack of definitive evidence to indicate the probable causes for these changes at this moment. It has been proposed that the increase of macrolide use in 2020 (private sector) was due to the COVID-19 pandemic.

The procurement (in DDDs) of carbapenems, vancomycin, 3rd generation cephalosporins, fluoroquinolones, and macrolides were compared to the total antibiotics procured, resulting in the percentage procurement in Figure 34. Note that these are in comparison with the total antibiotics procured for that sector, and this is a comparison of the percentage use of different antibiotics in each sector. Below are assumptions based on the available data (Figure 34).

Carbapenems
- The private sector uses significantly more carbapenems than the public sector (on average 12% more).
- Together with the observed relatively high broad-spectrum penicillin usage, it appears that the broader-spectrum antibiotics are more frequently used in the private sector.

Vancomycin
- Private and public sector procurement is equal and usage in both sectors remains relatively low and stable through the years observed.

3rd Generation cephalosporins
- The use in the public sector jumped from an average of 4% in 2018/2019, to 10% in 2020 and the private sector is showing a decrease from 11% in 2018 to 9% in 2020. Although the reason for this is unknown, one consideration is that it may reflect the movement to carbapenems and other antibiotics to treat multi-drug resistant organisms.

Fluoroquinolones
- Although the procurement of fluoroquinolones in the public sector fluctuates, it has been on a steady decline in the private sector. The public sector, on average, procures 2% less fluoroquinolone than the private sector.

Macrolides
- The public sector procures significantly more macrolides than seen in the private sector (on average, 7% more), although there appears to be a steady increase in procurement in the private sector.

4.6.7 WHO AWaRe Index

The WHO AWaRe Index categorises antibiotics into "Access", "Watch" and "Reserve" groups (Table 10). This index is a tool for AMU surveillance and directing antibiotic stewardship interventions. The aim is to maximise the use of Access antibiotics, which are the first line, narrow-spectrum choice for most infection syndromes, while reducing the use of Watch antibiotics and maximising stewardship of last-resort Reserve antibiotics.

Table 10. Antibiotics categorised into Access, Watch and Reserve groups as per the World Health Organisation

Access	Watch	Reserve
First or second choice empirical treatment. These are the core set of antibiotics that should always be available as they offer the best therapeutic value, minimising potential for resistance	Considered to have a higher toxicity or resistance potential, as either first or second choice antibiotics. These are only indicated for a limited number of disorders and require monitoring due to increased risk of AMR.	These should be considered as a last resort for highly selected patients. These antibiotics are prioritised as key targets for antimicrobial stewardship programmes and require close monitoring.

Some examples include: (The complete lists can be accessed from: https://list.essentialmeds.org/antibiotics/access)		
• Amoxicillin • Amoxicillin + clavulanic acid • Ampicillin • Benzathine benzylpenicillin • Cefalexin • Chloramphenicol • Clindamycin • Cloxacillin • Doxycycline • Flucloxacillin • Gentamicin • Metronidazole • Sulfamethoxazole + trimethoprim	• Azithromycin • Cefaclor • Cefepime • Cefotaxime • Cefoxitin • Ceftazidime • Ceftriaxone • Ciprofloxacin • Clarithromycin • Doripenem • Erythromycin • Kanamycin • Levofloxacin • Neomycin • Piperacillin-tazobactam • Vancomycin	• Colistin* • Fosfomycin (injection) • Linezolid* • Tigecycline* • Cefiderocol • Ceftazidime + avibactam* • Ceftolozane+tazobactam • Daptomycin* • Faropenem • Imipenem + cilastatin + relebactam • Meropenem + vaborbactam • Minocycline* • Polymixin* • Tedizolid

* Indicates RESERVE antibiotics that are registered in South Africa

4.6.7.1 AWaRe classification in the private sector

PRIVATE SECTOR – AWaRe PROCUREMENT

2018: 51% (green), 44% (yellow), 5% (red)

2020: 50% (green), 43% (yellow), 6% (red)
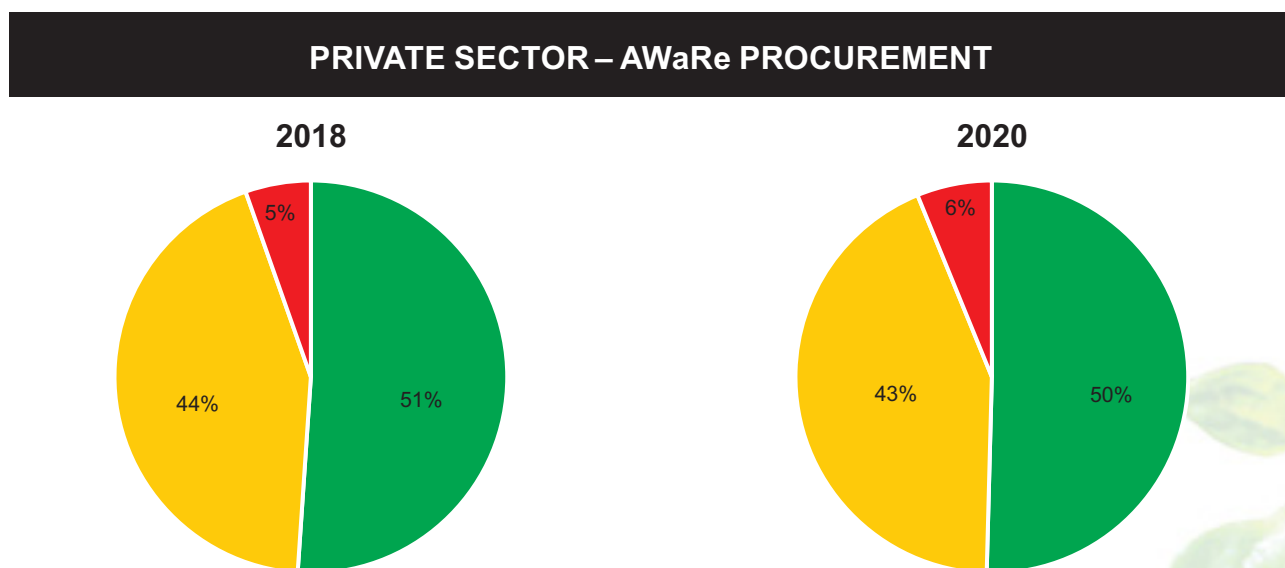
Figure 35. AWaRe classification for the private sector, 2018 compared to 2020 (as % of total DDDs)

The WHO country-level target for AWaRe group antibiotics is for 60% of all antibiotics used to come from the Access group. Procurement of antibiotics in the private sector is noteworthy for its almost equal procurement of Access and Watch antibiotics, and the high level of Reserve antibiotic procurement, especially compared to the public sector (Figure 35). There is extreme concern around the use of Watch and Reserve antibiotics in the private sector, and how that is potentially driving resistance in that sector and in South Africa as a whole.

4.6.7.2 AWaRe classification in the public sector

PUBLIC SECTOR – AWaRe PROCUREMENT
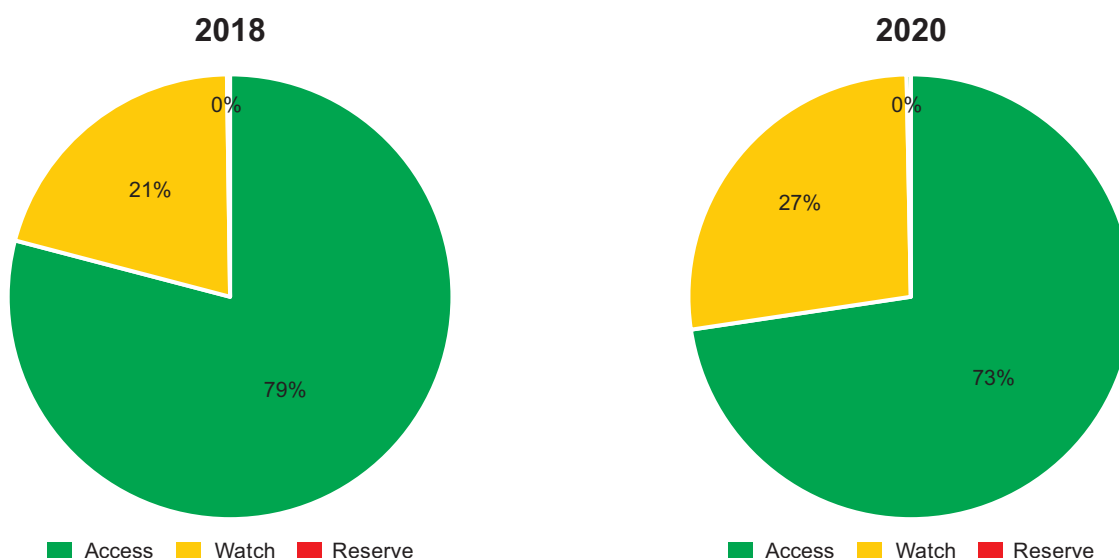
2018

2020

Figure 36. AwaRe classification in the public sector, 2018 compared to 2020 (as a ratio of total DDDs)

In the public sector, there have been reductions in the procurement of Access group antibiotics by 1% from 2018 to 2020, and Watch by 6%, whereas Reserve has increased from a total of 0.13% of antibiotics procured in 2018 to 0.31%. For perspective, in 2015, for every 1 DDD of Reserve antibiotic procured in the public sector, there were 1,993 DDD Access and 602 DDD Watch antibiotics procured. By 2020, this had decreased to 237 Access and 88 Watch antibiotics for every 1 Reserve antimicrobial (Figure 36).

To accurately compare the usage of AWaRe antibiotic procurement between public and private sectors, a more complete set of data from the private sector will be required, as well as the appropriate denominators, in this case, the users of the services utilising private and community pharmacies; and those using public health facilities.

For 2020, 73% of antibiotics procured by South Africa was in the Access group, which is substantially greater than the WHO recommended target of more than 60%. However, the public sector, which procures most medicines, does not have equal access to the Watch and Reserve group of medicines, with only 3 medicines available in the Reserve group. Based on current understanding of bacterial resistance patterns for the commonest pathogens causing community-acquired infections, the MAC-AMR believes that community Access antibiotic group use should be closer to 80%.

5. OVERVIEW OF ANTIMICROBIAL RESISTANCE IN THE ENVIRONMENT

Globally, the increasing use of antibiotics in the healthcare systems and intensive livestock farming has led to increased levels of antibiotic-resistant bacterial populations in the environment, thus exerting selection pressures and inducing the transfer of antibiotic resistance genes to potential human pathogenic bacteria[11]. Numerous studies have highlighted the soil and water environment affected by agriculture, as vital reservoirs and sources of antibiotic resistance[12,13,14]. Pollution of strategic resources such as irrigation water used for fresh produce production increases the risk to the consumer and subsequently leads to a more severe impact on human health, the environment and food security. Contaminated environmental resources have been reported to play an important role in the increased prevalence and dissemination of potential human pathogenic bacteria resistant to multiple antibiotics[14].

Novel and more affordable cutting-edge technologies enable scientists to decipher the complex resistome in microbiomes in multiple sectors within One-Health. Current research will therefore improve our global understanding of AMR genes in terms of origins, transmission and control and further enable scientists to better rank critical AMR genes and their hosts in the One-Health context[15]. It will also provide a clear understanding of sources and selective pressures affecting the emergence, transmission, and evolution of AMR genes. Finally, these tools will provide a basis to elucidate the mechanisms that allow an organism to overcome taxonomic barriers in AMR genes transmission.

Recently, ESBL- and carbapenemase-producing Enterobacterales have been reported as serious and urgent health threats[16]. These pathogens have been identified in the health care system, the agroecosystem including wastewater, irrigation water, soil, vegetable crops and animal husbandry[16,17,18,19]. However, surveillance and information about the dissemination of these multidrug-resistant microbes within the water-plant-food interface remain limited in South Africa because of lack of capacity and integration.

South African environmental antibiotic resistance surveillance studies include the identification and characterisation of multidrug-resistant potential foodborne pathogens from fresh produce and irrigation water. Beharielal et al. (2018) reported high percentages of resistance for streptomycin (95%) and amoxicillin-clavulanic acid (32%) in *E. coli* isolates (n=155) from fresh produce and irrigation water samples in KwaZulu-Natal. Similarly, Ratshilingano et al. (2021) reported multidrug resistance in 64.7%

[11]   Manyi-Loh, C., Mamphweli, S., Meyer, E., and Okoh, A. (2018). *Antibiotic use in agriculture and its consequential resistance in environmental sources: Potential public health implications*. doi:10.3390/molecules23040795

[12]   You, Y., and Silbergeld, E. K. (2014). Learning from agriculture: Understanding low-dose antibiotics as drivers of resistome expansion. *Front. Microbiol*. 5, 1–10. doi:10.3389/fmicb.2014.00284

[13]   Richter, L., du Plessis, E. M., Duvenage, S., and Korsten, L. (2020). Occurrence, Phenotypic and Molecular Characterization of Extended-Spectrum- and AmpC- β-Lactamase Producing Enterobacteriaceae Isolated From Selected Commercial Spinach Supply Chains in South Africa. *Front. Microbiol*. 11, 1–10. doi:10.3389/fmicb.2020.00638

[14]   Larsson, D. G. J., Andremont, A., Bengtsson-Palme, J., Brandt, K. K., de Roda Husman, A. M., Fagerstedt, P., et al. (2018). Critical knowledge gaps and research needs related to the environmental dimensions of antibiotic resistance. Environ. Int. 117, 132–138. doi:10.1016/j.envint.2018.04.041.

[15]   Kim, D. W., and Cha, C. J. (2021). Antibiotic resistome from the One-Health perspective: understanding and controlling antimicrobial resistance transmission. Exp. Mol. Med. 53, 301–309. doi:10.1038/s12276-021-00569-z.

[16]   CDC (2019). Antibiotic resistance threats in the United States. Atlanta. GA Available at: https://www.cdc.gov/drugresistance/biggest_threats.html

[17]   Njage, P. M. K., and Buys, E. M. (2014). Pathogenic and commensal Escherichia coli from irrigation water show potential in transmission of extended spectrum and AmpC β -lactamases determinants to isolates from lettuce. *Microb. Biotechnol*. 8, 462–473. doi:10.1111/1751-7915.12234.

[18]   Richter, L., Du Plessis, E. M., Duvenage, S., and Korsten, L. (2019). Occurrence, Identification, and Antimicrobial Resistance Profiles of Extended-Spectrum and AmpC β-Lactamase-Producing Enterobacteriaceae from Fresh Vegetables Retailed in Gauteng Province, South Africa. *Foodborne Pathog*. Dis. 16, 421–427. doi:10.1089/fpd.2018.2558.

[19]   Ebomah, K. E., and Okoh, A. I. (2020). An African perspective on the prevalence, fate and effects of carbapenem resistance genes in hospital effluents and wastewater treatment plant (WWTP) final effluents: A critical review. *Heliyon* 6, e03899. doi:10.1016/j.heliyon.2020.e03899.

of the commensal *E. coli* isolates (n=51) analysed from leafy green vegetables and irrigation water in Gauteng and the North-West Provinces. Moreover, Richter et al. (2020) investigated the prevalence of ESBL-producing Enterobacterales in spinach production systems in Gauteng Province. The authors reported that 14.58% of the samples (irrigation water, soil and spinach) (n=288) were found to be contaminated with ESBL/AmpC-producing Enterobacterales[16]. This included 15.28% (11/72) water and 12.12% (16/132) harvested- and processed spinach, while 25% (15/60) retail spinach samples were found to be contaminated with an increase in isolate abundance and diversity in both scenarios[16]. The abovementioned studies highlight the importance of pre-and post-harvest hygiene practices, as antibiotic-resistant potential pathogens were isolated from fresh produce and within the production environment.

Surveillance of AMR in agroecosystems should be an integral part of national monitoring programmes inform risk analysis, develop and implement mitigation strategies, guidelines and direct policy changes The threat of AMR in the water and the subsequent irrigated crops has been shown in several studies in South Africa and should be regarded as an integral part of future One Health study programmes to determine the potential risk associated with the presence of antimicrobial-resistant bacteria (ARB's) and further AMR genes.

6. FUTURE PLANS FOR SURVEILLANCE

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

As part of the work on improving the availability and quality of data on AMU and therefore improve decision making and actions to reduce inappropriate use, a mapping exercise was undertaken to identify current and future sources of AMU data (Figure 37). Please note items in Figure 37 marked with an Asterix (*) are future sources being investigated for future reports. These include:

1. Private sector primary care setting AMU reported as part of retail pharmacy reports with IQVIA.
2. Increase hospital groups reporting and consistency of data for acute hospital setting.
3. Investigate RxSolutions for dispensing data from public sector to better reflect use of antibiotics in the various healthcare settings in the public sector.

AMU DATA MAP – KEY SOURCES FOR 2021
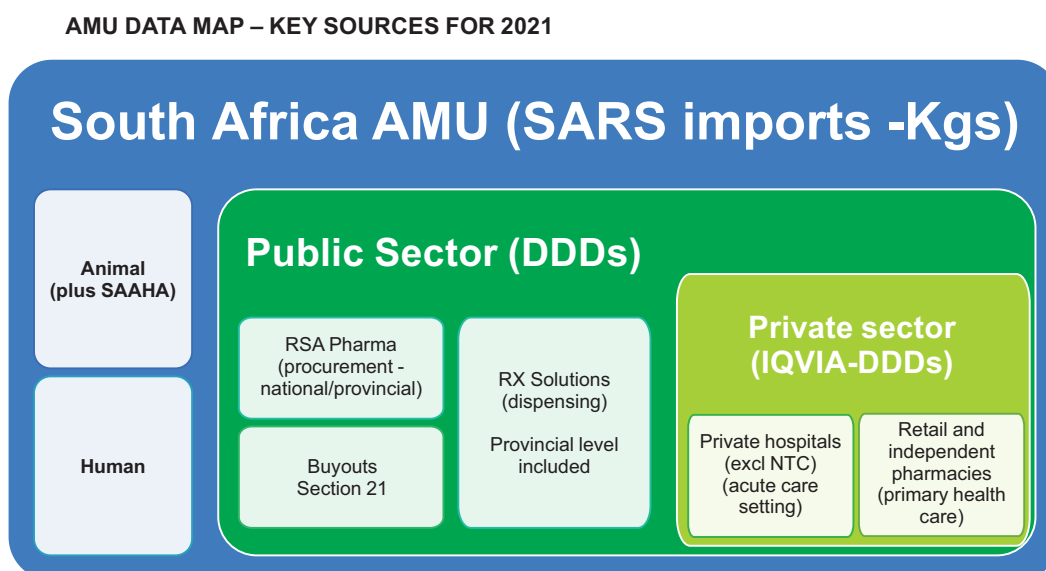
Figure 37. Data map of sources of AMU data in South Africa

Currently national level data is collected from imports into the country using SARS data. This reflects human and animal imports in kilograms per year and in additional SAAHA data on animal use in the sector will be more formalised.

The following plans are being put in place for future surveillance reporting:

- A national veterinary AMR surveillance programme is being developed in collaboration with various stakeholders. Bacterial isolates collected via the veterinary food safety surveillance programme will be tested for resistance to antibiotics of significance.
- The OIE surveillance programme for quantities of antibiotics used in livestock is an incremental programme that includes more detailed information as Member States make use of the more advanced options for reporting. The objective is to comply with the most advanced reporting option, that includes quantities of antibiotics used in kg per antimicrobial class, therapeutic and growth promotion use, use per animal species/farming enterprise, and the routes of administration of antibiotics.
- The antimicrobial residue monitoring programme will be transitioning to a risk-based sampling plan which reflects testing for antimicrobials of interest by species and includes some veterinary compounds that are registered but not previously tested. The maximum residue limits will be amended to the updated Codex Alimentarius Commission guidelines and the programme expanded to represent meat production in the country including rural farming operations.
- Human AMR surveillance will continue improving data quality for surveillance purposes and expand surveillance to other specimen types, such as urine.
- During 2021 funding was approved through DALRRD to develop and implement a national veterinary surveillance programme for bacterial resistance against antimicrobial drugs. The surveillance programme will be coordinated by the bacteriology section of the Agricultural Research Centre's Onderstepoort Veterinary Research facility. The aim is to cover all 9 provinces and to focus on indicator and food-chain bacteria from food-producing animals as target bacteria, and to record the resistances quantitatively by means of minimum inhibitory concentrations.

From the environmental sector, the following recommendations for future research focus areas/activities have been recommended[20]:

- It is important to include Plant Health as part of a holistic One Health approach to develop and implement mitigation strategies.
- The occurrence and characterisation of chemical pollutants should also be investigated since resistance to chemicals exists in agricultural environments. In addition, chemical disinfectants need longer contact times, higher doses and have several disadvantages such as persistent use and use for aspects beyond their registered use i.e., plant disease control.
- There is a national need to map out the potential contributors to the growing AMR problems i.e., sewage plants, the mining sector, animal husbandry etc.
- Investigate treatment options to ensure safe water and fresh produce. All disinfection treatments are influenced by the water quality i.e., organic pollutants etc.
- Risk assessment of results obtained to date should be done to determine the risk associated with potential human pathogenic bacteria isolated from the water-plant-food-public health interface.
- Education is key to educating the public, farmers, retailers (formal and informal) municipalities, advisory boards, and policymakers.
- Food safety is an integral part of food security, and issues such as how AMR can be addressed without compromising food security in the country should be considered.

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[20]   du Plessis, E. M., Duvenage, S., Korsten, L., and Sigge, G. (2021). Measurement of water pollution determining the sources and changes of microbial contamination and the impact of food safety from farming to the retail level of fresh vegetables. Water Research Commission.

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    - Marc Mendelson* (Chairperson: MAC-AMR); Moritz van Vuuren* (Vice-Chairperson: MAC-AMR); Mphane Molefe*; Olga Perovic*; Chetna Govind* (Chairperson: Surveillance Technical Working Group); Kim Faure*; Adrian Brink, Barney Kgope, Belinda Makhafola, Ben Durham, Catriona Lyle, Gary Reubenson, Guy Richards, Heather Finlayson, Mphane Molefe, Mukesh Govind, Portia Nkumbule, Richard Gordon, Shaheen Mehtar, Andrew Whitelaw, Husna Ismail, John Black, Martlie Mocke-Richter, Memela Makiwane, Michelle Gizjelaar, Natalie Schellack and Nenene Qekwana.

    - Secretariate: Ruth Lancaster* and Janine Jugathpal.

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- Special thanks go to the private hospital groups Mediclinic, Life Healthcare and Lenmed groups, for providing their antimicrobial procurement data for this report.

7.1 Queries or comments

Queries or comments relating to this document can be addressed to the MAC-AMR Secretariat, Dr Ruth Lancaster, at Ruth.Lancaster@health.gov.za.

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ANNEXURE A: BACKGROUND TO THE EXISTING SURVEILLANCE SYSTEM

- **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 and private sector laboratories where previously these reports were released individually by the SASCM.

There are two tiers of surveillance:

1. Laboratory based AMR surveillance which collects laboratory and clinical data from a selection of sentinel sites consisting primarily of academic and large referral laboratories in the public sector.

2. Electronic surveillance 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 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 programme for quality checks and all private laboratories and the majority of NHLS laboratories are South African National Accreditation Society accredited.

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

- **Case definitions used:**

Patients with BSIs 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 antimicrobial 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.

- **Limitations to the data source**

Some key limitations to the data include:

- Lack of standardization 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.

- **World Health Organisation Global Antimicrobial 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 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 harmonized 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[21], 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 programme 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 programme 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 antimicrobial treatment is not recommended.

- **Human Antimicrobial Use Data Sources**

There are three existing sources of AMU 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 AMU to be formulated:

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[21]   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/

- SARS import data, which contains the volume of antibiotics (in kgs) and rand value imported into the country (as either the final product or as the Active Pharmaceutical Ingredient). This data does not distinguish between antibiotics for use in humans or animals due to the current limitations on the tariff coding system. They also exclude any antibiotics produced in South Africa and those procured in terms of Section 21 of the Medicines and Related Substance Act 101 of 1965.

- Quintiles IMS/IQVIA (formally known as IMS Health) contains standard units per 1000 population of antibiotics supplied by the pharmaceutical manufacturers in the country to both the public and private sectors. It provides insights into the usage patterns by antimicrobial class for both sectors, and tracks usage from previous years as far back as 2000. Obtaining comprehensive datasets of private AMU are under discussion.

- The RSA Pharma database, and in the future the ABC analysis of this data, 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 (buyouts) and Section 21 purchases made by provinces and institutions.

- **Animal Antimicrobial Use Data**

  A process was started by the OIE in 2012 that required all Member States to provide AMU data on an annual basis. The first year of reporting was 2013 which South Africa could not comply with. At the request of DALRRD, the South African Animal Health Association SAAHA, which represents 80% of all pharmaceutical companies that provide antibiotics in the animal health domain, agreed to provide use data in volumes per antimicrobial class starting in 2014. No data were collected in 2017 and 2019 and the 2020 data represent the fifth year that data have been submitted to the OIE.

ANNEXURE B: DEFINED DAILY DOSES FOR TRIMETHOPRIM-SULFAMETHOXAZOLE

Trimethoprim-sulfamethoxazole is a co-formulation of trimethoprim and sulfamethoxazole, and comes in various formulations (tablets, oral liquid and intravenous solutions). The DDD for trimethoprim-sulfamethoxazole is not available on the WHO Collaborating Centre for Drug Statistics Methodology website[22].

For the 2018 Surveillance Report[23], the DDD for trimethoprim-sulfamethoxazole was internally standardised at 400mg for all formulations. This was based on the trimethoprim component for this co-formulation.

However, engagement with the WHO towards the end of 2018 provided updated DDDs, based on formulation type (Table 11). These units were used for this annual surveillance report.

Table 11. Defined Daily Doses for trimethoprim-sulfamethoxazole co-formulation, as per communication with WHO

Drug	Strength	Strength Unit	Unit	DDD	DDD Unit*
Trimethoprim-sulfamethoxazole	240	mg/5ml	100ml bottle	20	UD
Trimethoprim-sulfamethoxazole	240	mg/5ml	50ml bottle	10	UD
Trimethoprim-sulfamethoxazole	480	mg	tablet	4	UD
Trimethoprim-sulfamethoxazole	480	mg/5ml	vial	4	UD

*UD – Unit dose

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