The changing landscape of antimicrobial resistance and use in South Africa: The need for access to new antibiotics: A position paper

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Antibiotic resistance is a global threat, with a disproportionate burden of mortality in low- and middle-income countries. It is increasing in both the public and private healthcare sectors within South Africa, especially in Gram-negative organisms, and is associated with increased use of World Health Organization watch and reserve antibiotics. There is a need for improved access to new antibiotics to treat infections caused by drug-resistant organisms in order to limit side-effects and improve patient outcomes of currently available antibiotics. We propose the responsible introduction of these new antibiotics with both administrative and clinical oversight in order to preserve the longevity of these precious antibiotics.

Keywords: antimicrobial resistance, antimicrobial use, antimicrobial stewardship, antimicrobial access

S Afr Med J 2024;114(10):e2348. https://doi.org/10.7196/SAMJ.2024.v114i10.2348

Described as the silent pandemic, antimicrobial resistance (AMR) was identified in 2017 as one of the World Health Organization (WHO)'s top 10 global healthcare threats.[1] It is estimated that AMR was associated with 4.95 million deaths in 2019, with a disproportionate burden in low- and middle-income countries (LMICs), especially in Africa, where AMR is estimated to be associated with 1.05 million deaths.[2,3] The highest burden is in respiratory followed by bloodstream infections.[3] Neonatal deaths associated with AMR exceeded older age groups in most African countries.[3] Six pathogens are associated with almost 1 million deaths: *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Escherichia coli*, *Staphylococcus aureus*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. *K. pneumoniae* is a more prevalent organism in LMICs compared with high-income countries (HICs), where *E.coli* contributes more significantly to AMR and associated deaths.[2]

The rate at which AMR develops has been linked to overuse of antibiotics; however, there are several other contributory factors, especially in LMICs, including environmental contamination, healthcare transmission and suboptimal diagnostics.[4,5] While consumption of antibiotics in HICs is higher than in LMICs, there has been minimal increase over the last 5 years. This contrasts with LMICs, where consumption of antibiotics continues to rise.[2]

The magnitude of AMR in LMICs can be attributed to numerous factors. Poor hygiene, malnutrition, shortage of clean water and sanitation and poor healthcare systems all contribute to an increased risk of AMR.[5,6] Within the African region, mortality associated with AMR was correlated with quality of and access to healthcare and safe water and sanitation; lower-resourced settings had a higher burden of mortality.[3] Poor laboratory infrastructure in many African countries, resulting in a paucity of population-based AMR surveillance data and the use of empiric v. targeted antimicrobial treatment, likely contributes to AMR and associated mortality.[3] In addition, poor infection prevention capacity due to limited resources, and lack of access to antimicrobials for treatable infections, also contribute to the higher burden of AMR in Africa.[7,8]

South Africa (SA) has not been spared the burden of AMR, with deaths associated with AMR at 17%, almost double those of higher-

income areas such as Western Europe (8.3%), Asia Pacific (9.7%) and North America (10%).[2,3] The WHO adopted the Global Action Plan for AMR in 2015, and shortly thereafter SA developed the SA National Strategy Framework 2017 - 2024, with goals to identify short- to medium-term interventions to preserve antibiotics, improve appropriate antibiotic use and prevent transmission of antibiotic-resistant organisms. In conjunction with this, a ministerial advisory committee (MAC) for AMR was formed in 2016 to advise the health minister on the appropriate approach to improve antimicrobial use.

This article describes the current AMR burden, antimicrobial use and availability within SA. We highlight the need for the introduction of new antibiotics within a suggested framework in order to fill the current gaps experienced in SA.

AMR in South Africa

SA is part of the Global Antimicrobial Resistance and Use Surveillance system (GLASS) and reports on *Enterococcus* spp, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *Enterobacter* spp (ESKAPE) pathogens. These common healthcare-associated pathogens contribute to the AMR burden. Together with these data and surveillance data collected by the SA Society of Clinical Microbiologists (SASCM), there is a good understanding of AMR in healthcare-associated infections. Data from the community setting, however, are lacking.

As with other LMICs, the greatest mortality from AMR is associated with *K. pneumoniae* infections.[3] In addition, the number of bloodstream infections caused by *A. baumannii* is increasing, and now ranks third after *K. pneumoniae* and *S. aureus* in the public sector, surpassing *E. coli*.[9] *A. baumannii* easily develops resistance to antimicrobials and has been linked to several outbreaks in SA, especially in the neonatal setting.[10-12] In the private sector, *E. coli* remains a significant pathogen, ranking second after *K. pneumoniae*, while *A. baumannii* is less frequent and ranks sixth.

Recent data from academic hospitals in SA showed a 36% crude mortality rate for carbapenem-resistant *Enterobacterales* (CRE) bacteraemia, with *K. pneumoniae* the most frequently isolated pathogen (80%). The most common carbapenemase gene associated with resistance was oxacillinase-48 (*bla*OXA-48-like), accounting for 73%. The metallo-β-lactamases, New Delhi metallo-β-lactamase (*bla*NDM) and Verona integron-encoded metallo-β-lactamase (*bla*VIM) contributed 21% and 1%, respectively.[13]

Surveillance data on bloodstream isolates (BSI) from SASCM for the period 2020 - 2023 highlight the concerning trend towards increasing resistance in selected ESKAPE organisms (Table 1). The data for *K. pneumoniae* indicate that for 2023, almost 75% of all BSI isolates are extended spectrum beta-lactamase (ESBL)-producing across both public and private sectors. Carbapenem resistance rates in *K. pneumoniae* isolates from the public sector have increased from 14.7% in 2020 to 32.3% in 2023, and in the private sector this rate now appears stable at >40%. Tigecycline susceptibility data for BSI in the private sector have been included since 2022, with susceptibility rates of 60.8% (3 302 isolates tested) and 65.5% (3 776 isolates tested) for the years 2022 and 2023, respectively. Results for tigecycline should be interpreted with caution, as currently there are no interpretive guidelines that exist for all *Enterobacterales* species.

Resistance to carbapenems in BSI isolates of *P. aeruginosa* and *A. baumannii* highlights the significant selective pressure exerted by carbapenem usage, with resistance exceeding 80% in some instances. This is exemplified by the dramatic increase in resistance to carbapenems of *A. baumannii* isolates from the private sector during the height of the COVID pandemic (in 2021, 83% resistance to meropenem). This has subsequently declined to pre-pandemic levels at ~60% resistance. Furthermore, colistin susceptibility dropped from 90% in 2020 to 83.3% in 2021, subsequently increasing to 94.7% in 2023. In the public sector, *A. baumannii* isolates' resistance to carbapenems remains high at ~80%. The increasing prevalence of *A. baumannii* isolates, especially in the public sector, plus the high associated carbapenem resistance, are particularly concerning, as there is a lack of effective antibiotics to treat these infections, and associated mortality is high. A Gauteng tertiary hospital reported a 47.9% in-hospital mortality rate in patients with *A. baumannii* bacteraemia in 2019/2020.[14] Eighty percent of isolates showed multidrug resistance, and 8% showed resistance to colistin.[14] This high resistance rate is in keeping with national surveillance data for 2017 - 2019 that showed that 75% of isolates were extensively drug-resistant, and 4% were resistant to colistin.[15]

In terms of the Gram-positive ESKAPE pathogens, resistance appears to be stable, with methicillin-resistant *Staphylococcus aureus* (MRSA) rates of ~18% and 12%, in the public and private sector, respectively. Vancomycin-resistant enterococci (VRE) rates have been low (range: 1 - 1.7% for the period 2020 - 2022), although there is a concerning signal from data for 2023 that show a marked increase in VRE to 3% across both sectors.

Interpretation of these aggregated surveillance data must be considered in the context of the antimicrobial susceptibility testing (AST) landscape, with laboratories in SA using different breakpoint guidelines. Since 2017, with the introduction of European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines by some laboratories and continued use of Clinical & Laboratory Standards Institute (CLSI) guidelines by others, interpretive clinical breakpoints are not always comparable. This has important implications for interpretation of surveillance data. Furthermore, standardisation of approaches to AST is lacking, and different protocols and algorithms are employed, resulting in different levels of accuracy and reliability. Based on this for purposes of ESBL and CRE determination, SASCM has chosen to only look at specific indicator antibiotics rather than detailed phenotypic or genotypic detection methods. Further detail on these issues can be found on the Federation of Infectious Diseases Societies of Southern Africa (FIDSSA) website (https://www.fidssa.co.za/federation-members/sascm-surveillance-data).

Antimicrobial use in South Africa

Antimicrobial usage (AMU) data in LMICs is poorly reported and typically relies on import data or bulk dispensing from central medical stores. This is a crude measure of antibiotic use, and direct prescription and dispensing data from doctor to patient would provide more reliable AMU data. These are only available in high-resourced settings.

AMU in SA was estimated at 17.9 defined daily doses (DDD) per 1 000 population per day.[16] This is slightly higher than other BRICs (Brazil, Russia, India and China) countries (range 8 DDDs/1 000 population (China) - 15 DDDs/1 000 population (Russia), but is still lower than HICs, which have an AMU of 20.8 DDDs per 1 000 population.[16]

The 2023 SA Report on AMU and AMR gives an annual growth of 50% for antibiotic consumption over the 3-year period between 2020 and 2022.[9] Private sector use increased by 64% over this time period. Public data exclude non-tender items, buyouts and section 21 data. Private data exclude primary care prescribing and retail dispensing, and represent only two-thirds of private hospitals, as not all groups shared their data.

In 2017, the WHO introduced the AWaRe categorisation for antibiotics as a tool to support antibiotic stewardship at a local to

global level. A country-level target of at least 60% use of access antibiotics by 2023 was proposed. SA antibiotic consumption according to the WHO AWaRe categories was estimated at 75.6% access, 23.5% watch and ~1% reserve antibiotics in 2019.[16] This contrasts with the SA Report on AMU and AMR, which showed use of 48% access, 52% watch and ~0.03% reserve antibiotics for the period 2020 - 2022.[9] This report should be interpreted with caution, as reserve drugs such as tigecycline, ceftazidime-avibactam (CA) and ceftolozone-tazobactam are not on tender, and colistin is only available by SAHPRA section 21 approval; therefore reserve antibiotic use is likely underestimated. In addition, global and national shortages of access antibiotics such as parenteral penicillin and cloxacillin may drive use towards watch antibiotics. This highlights the need for reliable supply chain management for all antibiotics.

While consumption of reserve antibiotics between 2020 and 2022 increased in the public sector by 40%, there was a 20% decrease in reserve antibiotic use in the private sector.[9] However, data from a single private site showed an increase in use of CA, from an average of 51 DDDs per quarter for 2022 to 101 DDDs per quarter for 2023 (personal communication, Warren Lowman).

Point prevalence studies (PPS), despite their limitations, may give a better understanding/description of antibiotic use, as these rely on bedside prescribing and include all prescribed antibiotics, including non-tender and section 21 antibiotics. There have been a number of PPSs in SA, mainly in the paediatric hospital population. A PPS of paediatric departments in three academic hospitals found 55.2% use of access, 39.2% watch and 3.8% of reserve antibiotics.[17] Different prescribing patterns were described across the three hospitals, with carbapenem prescription ranging between 10.9% and 19.2%. Reserve antibiotics use was associated with hospital-acquired infections (HAIs) in neonatal and paediatric intensive care units (ICUs).[17] If one considers the impact of age, antimicrobial prescription rates as well as use of watch and reserve antibiotics were higher in neonates/infants as compared with 6- 12-year-olds (in press). A larger PPS including 18 public hospitals showed that almost half (49.7%) of patients surveyed were receiving antibiotics. The majority were access (55%), and 3% were receiving reserve antibiotics.[18] A recent national PPS driven by the MAC for AMR and infection prevention and control (IPC) technical working group included data from 52 (majority public) hospitals, and found an overall use of 64% access, 34% watch and 2% reserve antibiotics. As expected, reserve antibiotic use was higher in ICUs (6%).

Data on HAIs in SA are scarce, the national PPS showed that 7.1% of patients on antibiotics were being treated for an HAI, with paediatric and neonatal rates higher compared with adult rates (12.5% v. 5%). HAI rates were higher in the ICU setting, with up to 23% of patients admitted to ICUs being treated for HAIs.[9] Almost a third (30.8%) of all antibiotics were prescribed for HAIs. Higher rates of 45.3% were reported by a paediatric PPS. The incidence risk ratio (IRR) of HAIs was higher in neonates and adolescents (IRR 2.13; 95% confidence interval (CI) 1.23 - 3.70, and IRR 2.32; 95% CI 1.46 - 3.70, respectively) when compared with children 6 - 12 years of age.[19] These data highlight the importance of IPC measures, as HAIs drive antibiotic use in the hospital setting.

Antibiotic access in South Africa

Current registered antibiotics

Reserve antibiotics available in SA are shown in Table 2. Although registered in SA, the majority are not part of the essential medicines list (EML), and hence not on tender. This leads to both higher costs as well as less predictable access. Antibiotics that are not registered can only be accessed via section 21, and therefore carry significant additional administrative work for both prescriber and dispenser. In addition, the lack of an established supply chain may lead to delayed access, which may limit successful treatment outcomes. The most commonly used available antibiotics for drug-resistant Gram-negative infections, the highest burden of AMR, are described below.

Colistin

Colistin is commonly used for extensively drug-resistant organisms. Its side-effects, especially renal toxicity, require frequent dose adjustment, especially in ICU patients with comorbid conditions, including renal impairment. Colistin pharmacokinetics and dosing are challenging as it is a prodrug, and hence conversion to its active form is associated with interpatient variability. Guidelines have been developed for colistin dosing both in adults and paediatrics, with loading doses now recommended for both groups. In addition, renal adjustment doses have been reviewed.[20,21] Furthermore, routine susceptibility testing poses a challenge, with broth microdilution, the recommended method, only available at selected laboratories. This, combined with revision of polymyxin breakpoints, which state that polymyxins should not be used as stand-alone therapy and are unlikely to be effective in treatment of pneumonia, cast significant doubt on the clinical efficacy of polymyxins.

These factors, together with the availability of new antibiotics with improved outcomes, have resulted in colistin being largely discarded as a first-line recommendation in treatment guidelines for difficult-to-treat resistant Gram-negative bacteria.[22,23] It remains an important option within SA due to lack of alternatives, with the guidelines mentioned above optimising its use.

Tigecycline

Tigecycline is useful for drug-resistant intra-abdominal and skin and soft-tissue infections, although it is considered unreliable in HAI pneumonias. Tigecycline has a high volume of distribution and poor serum concentrations, which make it less effective in primary bloodstream infections. This limits its clinical utility in many HAIs, especially as monotherapy.[24] More recent meta-analyses have shown that high-dose tigecycline is associated with superior clinical and microbiological cure rates, reduced mortality and comparable adverse effects, compared with standard doses.[25,26] Use in children aged <8 years remains problematic owing to the tooth and bone side-effects of tetracyclines and lack of dosing guidelines, especially in neonates.

The very broad spectrum of activity of tigecycline also makes this agent a counterintuitive targeted treatment option for monomicrobial infections from the perspective of antimicrobial stewardship.

New beta-lactam beta-lactamase inhibitors (BLBLIs)

In 2022, CA and ceftolazone-tazobactam were registered in SA. Recommendations for their use were published shortly after their introduction, with the aim of helping to steward the use of these two important antibiotics.[23]

CA has particular use in treating CREs associated with *bla*OXA-48-like genes prevalent in *K. pneumoniae* in SA. There has been increasing experience across both the public and private healthcare system in the use of this antibiotic. CA is readily available in the private sector; however, use in the public sector is limited to hospitals with access to carbapenemase testing as well as antibiotic susceptibility testing to CA. CA has been shown to have both higher clinical cure rates (71% v. 51%, p=0.004) and lower occurrence of acute kidney injury (15% v. 33%, p=0.002) when compared with colistin.[27] A recent systematic review and meta-analysis of observational studies compared the efficacy of CA with other antibiotics for carbapenem-resistant *K.*

pneumoniae infections. Statistically significant differences in favour of CA for clinical success (odds ratio (OR) 3.55, 95% CI 2.42 - 5.19, $p<0.00001$) and 28-day mortality (OR 0.38, 95% CI 0.21 - 0.71, $p=0.002$).[28] In children, only two randomised controlled clinical trials describing safety and efficacy of CA have been published. These include children ≥3 months of age with complicated urinary tract infection (UTI) and intra-abdominal infection in well-resourced settings.[29,30] The use of CA outside these age and clinical indications, including in neonates, is based on pharmacokinetic modelling studies, extrapolation of clinical trial data and case reports.[31–33] It is expected that the same improved outcomes with CA will be seen in SA, as evidenced by anecdotal reports of favourable outcomes.[33] However, with its increasing use, there is need for published CA usage and outcome data for the SA setting.

CA has recently been approved for use in the adult EML for targeted therapy for bloodstream infections in the ICU setting. With its addition to the EML, we expect improved access and decreased cost via the tender process.

Gaps in antibiotic coverage in SA

Antibiotics for metallo-ß-lactamase CRE infections

While CA has improved the options for OXA-48 CRE infections, there are still limited treatment options for CRE infections caused by the metallo-ß-lactamases (MBLs). The optimal therapy for these organisms is poorly defined, and while less common in SA, there is still a need for appropriate options. Aztreonam, a monobactam antibiotic currently not registered in SA, used alone or in combination with other agents, is an effective treatment option in these cases.[34] Because of its clinical effectiveness against MBLs, the new combination of aztreonam-avibactam is currently undergoing clinical trials. While still waiting Food and Drug Administration (FDA) approval, it has recently been granted marketing authorisation by the European Medicines Agency, following phase 3 trials providing safety data, for treatment of Gram-negative infections where treatment options are limited. This new drug combination would provide a more robust option for the treatment of MBL CRE infections within the SA setting.

Table 1. Selected resistance patterns for ESKAPE organisms by healthcare sector (data provided by SASCM)

	2020	2021	2022	2023	2020	2021	2022	2023
Organism	**Public sector**				**Private sector**			
Klebsiella pneumoniae, n	7 484	7 050	7 357	7 402	3 669	4 681	4 318	4 746
CRE, %	14.7	23.7	29.3	32.3	39	44.1	41.8	44.8
ESBL, %	72.8	68.8	73.4	74.3	63.3	66	68.9	73.1
E. coli, n	4 471	4 091	4 477	4 751	3 132	2 881	4 020	4 287
CRE, %	0.6	1.1	2	4.6	0.7	0.7	0.3	0.8
ESBL, %	28.6	11.1	30.1	36	21.6	23.5	26.5	29.1
Pseudomonas aeruginosa, n	1 589	1 740	1 741	1 860	1 125	1 371	1 204	1 243
CRPA meropenem, %	20.2	20.2	21.5	16.9	27.6	24.3	26.2	25.2
Imipenem	25.8	23.7	24.2	25.5	32.6	28.8	28.5	30.7
Acinetobacter baumannii complex, n	4 086	4 994	4 769	5 238	430	879	508	494
CRAB meropenem, %	80.6	82.1	80.2	80.7	67.9	83	65.1	60
Imipenem	80	81.5	78.9	79.1	70.2	84.3	66.7	59.5
Staphylococcus aureus, n	6 275	6 180	6 301	7 129	2 267	2 677	2 652	2 991
MRSA, %	20.1	17.3	17	18.4	11.9	11.6	12.4	12.6
Enterococcus faecium, n	2 419	2 676	2 553	2 637	337	462	438	427
VRE, %	1.3	1	1.7	3	1.5	1.1	1	3.1

ESKAPE = *Enterococcus faecalis* and *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp; SASCM = South African Society of Clinical Microbiologists; CRE = carbapenem-resistant *Enterobacterales*; ESBL = extended-spectrum beta-lactamase-producing *Enterobacterales*; CRPA = carbapenem=resistant *Pseudomonas aeruginosa*; CRAB = carbapenem-resistant *Acinetobacter baumannii*; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant *Enterococcus faecium*.

Table 2. Reserve antibiotics currently available in South Africa

Antibiotic	Date of registration with SAPHRA (where applicable)	EML	Clinical use
Tigecycline	2007	No	CRE, CRAB
Linezolid	2014	Yes	Gram-positive MRSA, MDR-TB
Ceftaroline	2015	No	Mainly MRSA, some Gram-negative, similar to ceftriaxone/cefotaxime
Daptomycin	2020	No	Gram-positive MRSA, VRE
Ceftazidime-avibactam	2022	Yes, 2024	CRE, OXA-48, KPC
Ceftolozone-tazobactam	2022	No	MDR *Pseudomonas*
Tedizolid	2023	No	Gram-positive MRSA, VRE
Colistin	Not registered (section 21 access)	No	CRE, CRAB
Aztreonam	Not registered (section 21 access)	No	MBL, and in combination with avibactam for multiple beta-lactamases

SAHPRA = South African Health Products Regulatory Authority; EML = essential medicines list; CRE = carbapenem-resistant *Enterobacterales*; CRAB = carbapenem-resistant *Acinetobacter baumannii*; MRSA = methicillin-resistant *Staphylococcus aureus*; MDR-TB = multidrug-resistant tuberculosis; VRE = *Enterococcus faecium*; OXA-48 = oxacillinase-48; KPC = *Klebsiella pneumoniae carbapenemase*; MBL = metalobetalactamase.

Antibiotics for carbapenem-resistant *A. baumannii* (CRAB) infections

Treatment options for CRAB infections in SA are largely limited to colistin and tigecycline. International guidelines recommend combination therapy with ampicillin-sulbactam as the backbone antibiotic for treatment of CRAB.[35] Although a WHO access antibiotic, access in SA is limited through section 21 application, and it is rarely used in the public sector despite the high burden of CRAB. A recent meta-analysis reported that sulbactam in combination with a second agent for serious CRAB infections was associated with reduced mortality, and less nephrotoxicity than polymyxin-based therapy.[36] In the ATTACK study,[37] sulbactam-durobactam, a new BLBLI active against CRAB, had a lower 28-day mortality (19% v. 32%) and was significantly less nephrotoxic compared with colistin (13% v. 38%, $p<0.001$).[37] It was recently registered by the FDA in >18-year-olds for the treatment of hospital-acquired pneumonia. Sulbactam-based combination therapy, with tigecycline, cefiderocol or colistin, based on susceptibility results and site of infection, should be standard of care for serious CRAB infections.[38]

Antibiotics covering CRAB and MBL CRE infections

Cefiderocol, a new siderophore cephalosporin, offers new options for both MBL CRE and CRAB infections. Results from the CREDIBLE study[39] showed that cefiderocol had similar clinical and microbiological efficacy for the treatment of pneumonia, bloodstream and complicated UTIs caused by carbapenem-resistant Gram-negatives when compared with best available therapy.[39] Although not a primary endpoint in the study, there was an increased all-cause mortality in the cefiderocol group, especially in patients with CRAB infections. More recent observational studies on the treatment of CRAB demonstrate more favourable results, with cefiderocol having either lower (55.8% v. 34%, $p=0.018$) or equivalent (55% v. 58%, $p=0.7$) 30-day mortality when compared with colistin.[40,41] In addition, it is associated with lower nephrotoxicity (21% v. 2%, $p=0.003$).[40] While ongoing research is required, cefiderocol appears to be an effective and safe option for difficult-to-treat Gram-negative infections.

While the drivers and needs for AMR in LMICs are multifaceted, and access to first-line antibiotics is often lacking, in SA the well-developed EML and standard treatment guideline programme and robust tender process mean that access to first-line/access antibiotics is generally good. However, as described above, there is a need for improved access to new antimicrobials associated with improved outcomes and better side-effect profiles for MDR infections. The essential component is that these antibiotics must be introduced responsibly to prevent rapid development of resistance and loss of their benefits. CA and cefiderocol, which have an important role to play in carbapenem-resistant organisms, both have a high risk of developing resistance, and therefore stewarding these antibiotics is paramount.[42,43]

Based on the resistance patterns seen in both the private and public sector, and data to support their use, we believe that there is a need for the antibiotics summarised in Table 3 to be available and registered in SA for the treatment of drug-resistant Gram-negative infections. The introduction of these antibiotics should be coupled with the recommendations discussed below. There are important vulnerable population groups when considering access to antibiotics, including children, neonates and pregnant women. When new antibiotics are introduced, registration including all vulnerable groups should be a priority.

Registration of new drugs for children and neonates is often delayed, as studies typically follow those in adults. As a result, the new drugs are often used off-label in paediatrics. Antibiotic use and resistance are high, especially in preterm neonates, therefore there is a need for greater focus on drugs suitable in this age group, considering their immature immune system and rapidly changing renal function in the first days of life. The formation of the Neonatal Sepsis Task Group and collaborations such as the NeoSep study (ISRCTN48721236) are encouraging, and will aid in decreasing neonatal mortality rates from sepsis.[44]

Antibiotic choices are limited during pregnancy and lactation, and further work is needed on emphasising early investigation and appropriate treatment of sepsis to reduce the impact on maternal health. Work on AMR during pregnancy has focused largely on sexually transmitted diseases and urinary tract infections (UTIs) in SA. Pregnant women are at an increased risk of UTIs, the majority caused by *E. coli*, with increasing ESBL rates. *K. pneumonia*e, the third most common cause, demonstrates increasing carbapenem resistance.[45] Commonly used drugs for UTIs such as aminoglycosides and fluoroquinolones, as well as colistin and tigecycline used for MDR infections, are not recommended in pregnancy. There is a need for ongoing focus for appropriate and safe drugs for use in pregnancy.

Current stewardship practices in SA: private and public

In many SA institutions, both public and private, there are robust and active antimicrobial stewardship programmes. The majority of the private groups have clinical or ward pharmacists who assist with stewardship activities. Within the public sector, many provinces have stewardship committees and are training champions within these hospitals to drive stewardship activities.

Many public sector hospitals, especially tertiary institutions, have authorisation policies for the prescription of precious broad-spectrum antibiotics such as the carbapenems. With the recent launch of the new BLBLI agents, similar strict measures have been instituted to ensure the judicious use of these new agents. These include motivations to the pharmacy and therapeutics committee and restricted access under microbiological or infectious diseases approval. This in-depth attention to antimicrobial stewardship is not always available at district and regional public sector hospitals, with some healthcare staff reporting limited educational activities surrounding antimicrobial stewardship, and only 50% reporting successful local antimicrobial stewardship programmes.[46] Within the private sector groups, these stewardship activities include completion of BLBLI checklists requiring both microbiological or infectious disease input, and then signed off by regional clinical pharmacists, and clinical pharmacists within other groups monitoring the appropriate use of these new agents and instituting interventions when these agents are inappropriately used.

Funders are requesting letters of motivation to be written as well as submission of culture and blood results to ensure the appropriate and judicious use of these new agents before agreeing to fund new agents. However, for the most part, clinicians working in private hospitals work independently with no regulation of antibiotic prescribing.

These current governance policies should act as a framework for introduction of new antibiotics into the SA market.

Recommendations for framework for responsible introduction

Antimicrobial resistance exerts a significant burden, not only in terms of morbidity and mortality, but also a significant financial burden on healthcare systems. It is estimated that HAIs occurring in eastern and southern Africa cost USD6.1 million, or 1.14% of the combined gross domestic product.[47] The HIV, tuberculosis and sexually transmitted infections directorate, covering other high-burden diseases in SA,

has had good success maintaining international standards via the introduction of new drugs and national standard treatment guidelines. Antimicrobial stewardship requires the same governmental backing in terms of human and financial resources to guide the introduction of new clinically relevant drugs into SA. This can be accomplished by the development of a new One Health antimicrobial resistance directorate with dedicated human and financial resources to lead policy implementation around antimicrobial resistance. Built on the already developed framework of the MAC on antimicrobial resistance, it should include representation from strategic stakeholders, including the Department of Health, private institutions, laboratory providers and public health authorities, as well as representation from One Health colleagues, public communications, information technology and data support. Antimicrobial resistance requires both clinical and administrative expertise and drive. Figs 1 and 2 outline holistic interventions addressing both these areas that a new directorate should oversee and support. These interventions should be considered for implementation when drafting the new SA national framework in

Table 3. Priority antibiotics for consideration in South Africa considering current antibiotic resistance patterns

Antibiotic	Bacterial targets	Comments	Priority
Ampicillin-sulbactam or sulbactam-durlobactam	CRAB	Backbone for treatment of CRAB together with other agents	High
Aztreonam and aztreonam-avibactam	MBLs and ESBL	Phase 3 trials completed awaiting registration by FDA	High
Cefiderocol	CRE: MBL, CRAB	Only registered by FDA for >18 years, needs paediatric/ neonatal research	High
Colistin	CRE, CRAB	Dosing and renal toxicity concerns	High
Imipenem-relebactam	KPC	KPC-producing CRE organisms, not active against OXA-48	Medium
Meropenem-vaborbactam	KPC	KPC producing CRE organisms, not active against OXA-48	Medium

CRAB = carbapenem-resistant *Acinetobacter baumannii*; MBL = metalobetalactamase; ESBL = extended-spectrum betalactamase-producing *Enterobacterales*; CRE = carbapenem resistant *Enterobacterales*; FDA = US Food and Drug administration; KPC = *Klebsiella pneumoniae* carbapenemase; OXA-48 = oxacillinase-48.

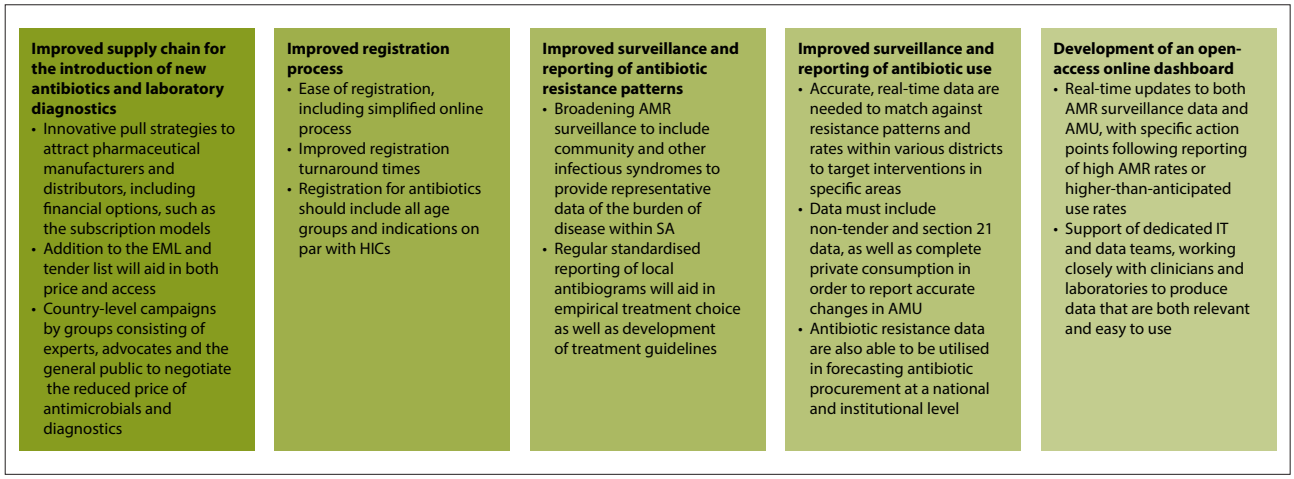

Fig. 1. Administrative recommendations for the introduction of new antibiotics into South Africa. (EML = essential medicines list; HIC = high-income country; SA = South Africa; AMR = antimicrobial resistance; AMU = antimicrobial use; IT = information technology.)

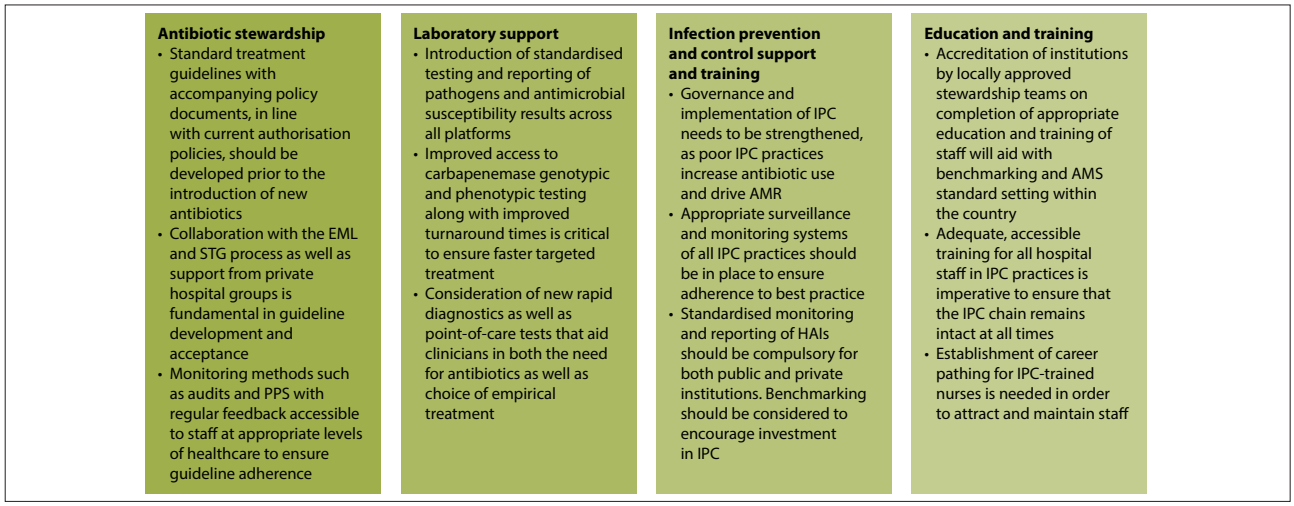

Fig. 2. Clinical recomendations for the introduction of new antibiotics into South Africa. (EML = essential medicines list; STG = standard treatment guidelines; PPS = point prevalence study; IPC = infection prevention and control; AMR = antimicrobial resistance; HAI = hospital-acquired infection; AMU = antimicrobial use.)

2024, which should be implemented in both the private and public healthcare sectors.

Conclusion

Antimicrobial resistance is increasing in SA, shifting AMU towards broader-spectrum watch antibiotics. Reserve antibiotic use is still low owing to lack of equitable access across the country, but use is increasing, and major gaps exist in the SA antibiotic armoury. Newer reserve antibiotics appropriate to the evolving AMR landscape need to be introduced urgently, in a responsible manner, in order to provide appropriate and effective treatment options while retaining effectiveness in the future.

Data availability. N/a.

Declaration. None.

Acknowledgements. None.

Author contributions. HF came up with the concept and outline. HF wrote the initial draft, WL drafted the AMR section, and all authors contributed to the manuscript, reviewed and agreed with the final recommendations.

Funding. Unrestricted funding was received from the Drugs for Neglected Diseases initiative (DNDi)/Global Antibiotic Research and Development Partnership (GARDP) Southern Africa as a GARDP network member, but GARDP had no input into final content of the document.

Conflicts of interest. VC, PJ, SJ, TM, TN, JN, AP, PS,VU and AW declare no conflicts of interest related to this work. WL has received honoraria for speaker fees from Pfizer and Merck Sharp and Dohme (MSD). HF does consultant work for GARDP.

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Received 24 June 2024; accepted 10 July 2024.