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Perspective

A situational analysis of current antimicrobial governance, regulation, and utilization in South Africa



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ABSTRACT

The Global Action Plan on antimicrobial resistance calls for the use of antimicrobial medicines in human and animal health to be optimized, in tandem with a strengthening of the knowledge and evidence base through surveillance and research. However, there is a paucity of consumption data for African countries such as South Africa. Determining antimicrobial consumption data in low-resource settings remains a challenge. This article describes alternative mechanisms of assessing antimicrobial consumption data, such as the use of Intercontinental Marketing Services (IMS) data and contract data arising from tenders (an open Request for Proposal, RFP), as opposed to the international norms of daily defined doses per 100 patient-days or per 1000 population. Despite their limitations, these serve as indicators of antimicrobial exposure at the population level and represent an alternative method for ascertaining antimicrobial consumption in human health. Furthermore, South Africa has the largest antiretroviral treatment programme globally and carries a high burden of tuberculosis. This prompted the inclusion of antiretroviral and anti-tuberculosis antibiotic consumption data. Knowledge of antimicrobial utilization is imperative for meaningful future interventions. Baseline antimicrobial utilization data could guide future research initiatives that could provide a better understanding of the different measures of antibiotic use and the level of antibiotic resistance.

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Introduction

The provision of reliable antimicrobial consumption data is a prerequisite to understanding antimicrobial resistance (AMR), since selection pressure from antimicrobial use is one of the main

drivers of resistance (World Health Organization, 2015a). The Global Action Plan on AMR provides a 'One Health' blueprint for national action plan development across human, animal, and environmental health, and calls for the use of antimicrobial medicines in human and animal health to be optimized in tandem with a strengthening of the knowledge and evidence base through surveillance and research (World Health Organization, 2015a). However there is a paucity of consumption data worldwide, South Africa included (O'Neill, 2016; Laxminarayan et al., 2016). Obtaining reliable antimicrobial consumption data in South

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Africa's two-tiered human healthcare system has been especially challenging. The public sector caters for the majority of South Africans (approximately 84% of the population; 42 million people), while private healthcare is affordable only to a minority (approximately 16% of the population; 7 million people) (Minnie, 2015). Challenges include economic and prescribing difficulties. Although South Africa is classified as a middle-income country based on its income Gini coefficient, which ranges between 0.66 and 0.70, it is one of the most consistently unequal countries in the world (The World Bank, 2017).

A situational analysis of antibiotic use and resistance was conducted in 2011 as part of a collaboration between South African stakeholders and the Global Antibiotic Resistance Partnership, a Gates Foundation-funded project of the Centre for Disease Dynamics, Economics and Policy (Centre for Disease Dynamics, Economics and Policy, 2017; Global Antibiotic Resistance Partnership, 2011). It identified several constraints limiting the implementation of good infection control practices and antimicrobial stewardship programmes in humans and animals (Global Antibiotic Resistance Partnership, 2011). One such constraint was the availability of procurement data from Intercontinental Marketing Services (IMS), currently IMS Health, which was only forthcoming from the private sector and focused exclusively on antibiotics.

Infection represents the major burden of disease in South Africa, largely HIV and tuberculosis (TB), as well as high rates of community- and hospital-acquired infections (South African Medical Research Council, 2016). As of 2016, an estimated 7.03 million people were living with HIV in South Africa, giving an overall estimated HIV prevalence rate of 12.7% (Statistics South Africa, 2016). Hence, the data from IMS in the 2011 analysis fell considerably short of the real picture of antimicrobial consumption in South Africa. The collection of antimicrobial consumption data in the public sector was in its infancy, requiring manual computation from aggregate data methods to elucidate consumption in healthcare facilities. The acquisition of accurate consumption data from communities was precluded by fluid catchment populations. A lack of reliable data hampers antimicrobial stewardship efforts and the evaluation of stewardship interventions (Global Antibiotic Resistance Partnership, 2011; South African Antibiotic Stewardship Programme, 2017; National Department of Health, 2015a; National Department of Health, 2015b; Essack et al., 2011).

The last 6 years has seen major shifts in policy towards combating AMR in South Africa. In 2012, the South African Antibiotic Stewardship Programme (SAASP), a multidisciplinary group of experts across human and animal health, public and private health sectors, was formed to implement antibiotic stewardship programmes within hospitals and in primary care (South African Antibiotic Stewardship Programme, 2017). Consequently, there is a need to address this by looking to determine antimicrobial utilization across all sectors.

SAASP advocacy coupled with increasing global drivers of change, such as strengthened antimicrobial surveillance and efforts to ensure uninterrupted access to essential medicines of assured quality, has enhanced infection prevention and control efforts and the stimulation of new research and innovations (Leung et al., 2011; World Health Organization, 2014; World Health Organization, 2015b; Government of the Republic of South Africa, 2003). Similarly, momentum generated within the National Department of Health (NDOH) culminated in the publication of South Africa's Antimicrobial Resistance National Strategy Framework 2014–24 in October 2014, at a ministerial AMR summit (National Department of Health, 2015a).

Six years on from the initial analysis, this article presents the current regulatory environment related to antimicrobial medicines in humans, and describes an alternative mechanism of assessing

antimicrobial consumption data to the international norms of defined daily dose (DDD and DID) per 100 patient-days or per 1000 population (World Health Organization, 2015c). The DDD is the assumed average maintenance dose per day for a medicine used for its main indication. The number of DDDs provides a measure of the extent of use; however for comparative purposes, these data are usually adjusted for population size or population group, depending on the medicines of interest and the level of data disaggregation that is possible. For most antimicrobials, the DDD/1000 inhabitants/day (DID) is calculated for the total population including all age and gender groups (World Health Organization, 2015c).

This article proposes the use of procurement data available for antibiotics, antiretrovirals, and TB treatment at a population level as an alternative method for ascertaining antimicrobial consumption in human health. However, it should be borne in mind that procurement data are based on what is purchased rather than what is actually consumed by the end user. Such data are dependent on standardized national coding (i.e. Anatomical Therapeutic Chemical (ATC) classification) (World Health Organization, 2015c) and the integration of information from varying sources such as healthcare facilities or medicines depots and warehouses. Consumption data for animals are scarce, come from variable sources, and are often measured in per kilogram consumption due to the high proportion of in-feed utilization. A national programme to monitor antimicrobial distribution in animals should be essential, but such a programme is currently not implemented in South Africa.

Antimicrobial regulation in human and animal health in South Africa

Antimicrobial prescribing in the public sector is guided by Standard Treatment Guidelines (STGs) and is driven by the inclusion and availability of the medicine on the Essential Medicines List (EML) (Perumal-Pillay and Suleman, 2017). These guidelines are now also available electronically. Prescribing in the private sector is largely unrestricted, with prescribers selecting whichever antimicrobial they feel is clinically most appropriate (Chunnilall et al., 2015). Prescribing restrictions in the private sector may occur on a financial level when a patient is a member of a private healthcare insurer and the patient may not be reimbursed for the medicine prescribed unless prescribing thereof is in compliance with a particular formulary or policy (Pharasi and Miot, 2013). Antimicrobials are mostly prescribed by medical practitioners registered with the Health Professionals Council for South Africa. However, provision is made in the legislation for prescribing and dispensing by the nurse practitioner directly to the patient (under Section 56(6) of the Nursing Act 33 of 2005), particularly in the setting of HIV and TB in public healthcare centres (PHC). Primary Care Drug Therapy licences issued by the NDOH allow pharmacists to diagnose and prescribe medicines, including antibiotics, for specified conditions listed in the STG, which include a wide variety of common illnesses (Act No. 53 of 1974). Both nurses and pharmacists are restricted to the STGs and EML at the primary care level.

Veterinary control of antimicrobials in South Africa involves two authorities, the NDOH and the Department of Agriculture, Forestry and Fisheries. The Stock Remedies Act 36 of 1947 was promulgated by the Minister of Agriculture to initially control the multitude of external and internal parasites that infested South African livestock. Over time, a limited number of antimicrobials were included to enable farmers in rural areas to access essential livestock products over the counter (Department of Agriculture, Forestry and Fisheries, 2016). These include antimicrobials for growth promotion. The Medicines and Related Substances Act 101

of 1965 (as amended) was promulgated by the Minister of Health to facilitate the registration of prescription-only products. The Act was amended in 1979 to include veterinary medicines in its definition of a 'medicine'. All scheduled substances, including antibiotics for use under veterinary oversight, are controlled by this Act.

Approval for the registration of antimicrobials under either of these Acts is based on the evaluation of efficacy, safety, and quality. Notwithstanding, the dual registration system has basic flaws and has led to concerns that antibiotics registered under [Act 36 of 1947](#) will exacerbate the emergence of bacterial resistance if the lack of appropriate control is allowed to continue. Regulatory veterinary structures in South Africa have recognized these concerns; the National Veterinary Strategy 2016–2026 emphasizes a move towards the tightening of veterinary drug control under a single Act, driven as part of the 'One Health' initiative between the animal and human health sectors.

The veterinary statutory body, namely the South African Veterinary Council (SAVC), also exerts an influence on veterinary drug control in South Africa, through the Rules of the [Veterinary and Para-veterinary Professions Act 19 of 1982](#). In 2016, the SAVC issued a directive to all registered veterinary and para-veterinary professionals that the use of the critically important antibiotic colistin may only be justified for use in animals if bacterial sensitivity testing indicates that colistin is the only available antibiotic for a particular infection. Veterinary and para-veterinary professionals who do not comply with this directive may be found guilty of unprofessional conduct with concomitant consequences. This effectively removed colistin from veterinary use and is an example of national stewardship of a last resort antibiotic for human health ([South African Veterinary Council, 2016](#)).

Quantifying population-level antimicrobial data in humans

The data sources presented for antimicrobial procurement differ between the public and private health sectors. Variations in presentation of antimicrobial data are largely based on the differences in patient management systems – mostly manual/paper-based in the public sector, compared to electronic record-keeping for the private sector.

Private sector data were obtained from IMS Health. Although IMS Health does not report in standard units of consumption, i.e. DDDs, their units do help to show trends over time. IMS Health collects data from a variety of sources of healthcare information, including sales, de-identified prescription data, medical claims, electronic medical records, and social media.

Conversely, public sector data were obtained from contract data arising from tenders from wholesalers (an open Request for Proposal, RFP) where the NDOH solicits bids from suppliers and publishes this on the NDOH website ([National Department of Health, 2017](#)). However these data reflect only what has been awarded on the basis of the tender (i.e., quantities forecasted for use), rather than what is actually used. Different tenders are awarded based on their descriptions and may be awarded for different time periods, although it does appear that most contracts currently awarded are for a 2-year time period (e.g., October 2015 to September 2017) in the current contracting process ([National Department of Health, 2017](#)).

Presenting surveillance data on antimicrobial use in these two sectors can identify and target practice areas for quality improvement. The DDD (the usual adult dose of an antimicrobial for treating one patient for one day) has been considered useful for measuring antimicrobial prescribing trends within a hospital, including the various denominators from hospital

activities, i.e. beds, admissions, and discharges. This type of surveillance data for antimicrobial usage is not routinely available in South Africa, although increasingly implemented as the AMR strategic framework is progressively rolled out.

Antimicrobial data include three major categories of antimicrobials as per the World Health Organization (WHO) ATC classification system ([World Health Organization, 2015c](#)):

- Antibacterials for systemic use (ATC group J01)
- Antiretrovirals for systemic use (ATC group J05)
- Anti-tuberculosis agents for systemic use (ATC group J01GB and J04)

The selection of antibiotics and antiretrovirals for this analysis was classified based on the WHO classification system and was cross-referenced to the NDOH tender data. The selection of anti-TB medicines was based on the South African treatment guidelines for TB ([National Department of Health, 2014](#); [National Department of Health, 2015c](#)), which include those recommended for multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB ([National Department of Health, 2015d](#)). Capreomycin is not currently in the Hospital Level (Adult) STG and EML for MDR-TB; however it is available on the Master Procurement Catalogue list as a non-EML item ([National Department of Health, 2015d](#)). Bedaquiline, originally only available through the Bedaquiline Clinical Access Programme, is now registered with the Medicines Control Council, although it is still subject to a pre-approval process and therefore utilization is tightly controlled ([National Department of Health, 2015d](#)). Delamanid is currently not registered in South Africa, hence access is limited for patients.

The following four quantitative indicators for reporting antimicrobial consumption were used for the public and private sectors:

- The total number of antimicrobial units (QTY units): the number of units (tablets, vials, capsules, etc.) was determined by taking into account the pack size (units per pack) and the quantity of packs awarded in the contract to arrive at the quantity per unit. This value does not reflect doses ordered, but allows for standardization of volumes. This is particularly required where multiple manufacturers are contracted for the same active ingredient but with different pack sizes or strengths.
- In this analysis, the total sum of the quantity of units per ATC class for all dose strengths was calculated. This is useful when comparing utilization across different products, clinical indications, or countries.
- Moving annual total (MAT) units, i.e. the total value of the sales figures for the product, over the course of the period displayed.
- To derive a comparable metric of antimicrobial consumption across time, the compound annual growth rate (CAGR) of total antimicrobial consumption was calculated using the following formula: $CAGR = (SUEnd/SUStart)^{(1/N)} - 1$, where SUEnd is the total number of standard units for the last reported year, SUStart is the total number of standard units for the first reported year, and N is the number of years between the first and last year of reporting.

The European Surveillance of Antimicrobial Consumption (ESAC) project developed quality indicators to measure appropriate outpatient antibiotic use in Europe ([Coenen et al., 2007](#)). Guidelines on the management of infections are available in South Africa (STGs) and could assist in future studies to describe, by definition, appropriate antibiotic use. However, for the purposes of this article a focused overview of antimicrobial utilization will be given as a first step towards developing quality indicators specific for the local setting.

Table 1
Antibiotics—private sector.

Antibiotic class ATC-Descriptor	MAT units ^a (2014)	MAT units ^a (2015)	MAT units ^a (2016)	CAGR ^b (2014–2016)	% Market share (2016)
J1A0 TETRACYCLINES + COMBS	307 170	296 428	282 220	−3%	1%
J1B0 CHLORAMPHENICOLS + COMBS	1124	983	1014	−3%	0%
J1C1 BROAD SPEC PENICILL ORAL	8 249 655	8 607 223	7 826 870	−2%	35%
J1C2 BROAD SPEC PENICILL INJ	520 470	533 780	572 498	3%	3%
J1D1 CEPHALOSPORINS ORAL	1 951 706	1 854 653	1 705 486	−4%	8%
J1D2 CEPHALOSPORINS INJ	2 053 062	2 036 180	2 015 283	−1%	9%
J1E0 TRIMETHOPRIM COMBS	1 466 062	1 491 648	1 437 019	−1%	6%
J1F0 MACROLIDES + SIMILAR TYPE	2 822 661	2 935 812	2 874 181	1%	13%
J1G1 ORAL FLUOROQUINOLONES	3 618 738	3 576 474	3 378 464	−2%	15%
J1G2 INJ FLUOROQUINOLONES	641 067	659 363	560 007	−4%	3%
J1H1 MED/NARRW SPECT PEN PLAI	280 172	292 893	145 960	−20%	1%
J1K0 AMINOGLYCOSIDES	79 908	87 101	89 754	4%	0%
J1P2 PENEMS AND CARBAPENEMS	1 141 501	1 276 979	1 093 413	−1%	5%
J1X1 GLYCOPEPTIDE ANTIBACT	179 134	182 071	190 314	2%	1%
J1X9 ALL OTHER ANTIBACTERIALS	21 378	25 991	33 037	16%	0%
Grand total	23 333 808	23 857 579	22 205 520	−2%	100%

^a MAT units: moving annual total, i.e., the total value of the sales figures for the product, over the course of the period displayed.

^b CAGR: compound annual growth rate; this was used, as it is a measure of market growth over multiple time periods for the two sectors.

Antibiotics

The IMS unit data showed a CAGR of −2% over the past 3 years within the private sector antibiotic market (Table 1). The majority of the classes showed a decrease, with a 20% reduction in the medium/narrow-spectrum penicillin (J1H1) class. The dominant class with a market share of 35% remained the broad-spectrum penicillin oral (J1C1) class; however, this too was found to be declining at 2%. Broad-spectrum penicillins are very popular as they have been manufactured by national companies for decades, are relatively low cost in private sector pharmacies, and are bactericidal and available in an oral dosage form. Of concern is that the class of ‘all other antibacterials’ (J1X9), comprising daptomycin, fusidic acid, linezolid, and tigecycline, grew at a rate of 16% during the same period. This increase may be due to inappropriate use as first-line therapies, lack of awareness of appropriate antimicrobial prescribing, or simply a desire to use newer more expensive therapies driven by availability or marketing by the pharmaceutical industry, as well as possible increases in resistance. Various factors could be contributing to these trends seen in antibiotic usage in the private sector and further investigation is required to obtain a thorough understanding of the mechanisms driving these changes in consumption.

In the public sector (Table 2), a CAGR of 11% was observed overall in the same period. Substantial increases were observed in four classes: ‘all other antibacterials’ (J1X9), injectable fluoroquinolones (J1G2), injectable cephalosporins (J1D2), and broad-spectrum penicillins oral (J1C1), which showed increases of 6876%, 287%, 169%, and 167%, respectively. Nearly 80% of the public market share was derived from trimethoprim combinations (J1E0) (37%), medium/narrow-spectrum penicillin (J1H1) (22%), and broad-spectrum penicillin oral (J1C1) (20%).

Antiretrovirals

Within the private sector, a steady decline was seen within most classes of antiretrovirals, except for those present in fixed-dose combinations (FDCs) (Table 3). The most popular of these is the triple FDC of tenofovir disoproxil fumarate 300 mg, emtricitabine 200 mg, and efavirenz 600 mg (TEE). This group of products showed a year-on-year increase – and this from a very large base. TEE is also the current first-line choice for most medical practitioners, in line with most of the guidelines (Meintjies et al., 2014). Private medical insurance fully endorses and reimburses this group of products if the individual product price is within the reference pricing (Maximum Medical Aid Price,

Table 2
Antibiotics—public sector.

Antibiotic class ATC-Descriptor	Total QTY units ^a (2011)	Total QTY units ^a (2013)	Total QTY units ^a (2015)	CAGR ^b (2013–2018)	% Market share (2015)
J1A0 TETRACYCLINES + COMBS	226 993 000	114 988 400	168 296 842	21%	9%
J1B0 CHLORAMPHENICOLS + COMBS	121	109	93	−8%	0%
J1C1 BROAD SPEC PENICILL ORAL	530 513 290	54 045 080	385 061 012	167%	20%
J1C2 BROAD SPEC PENICILL INJ	49 241 030	34 687 670	54 987 307	26%	3%
J1D1 CEPHALOSPORINS ORAL	12 221 600	1 455 300	7 300 010	124%	0%
J1D2 CEPHALOSPORINS INJ	16 097 300	10 565 000	76 629 057	169%	4%
J1E0 TRIMETHOPRIM COMBS	966 535	783 509 493	700 365 086	−5%	37%
J1F0 MACROLIDES + SIMILAR TYPE	185 162 200	8 019 700	16 427 840	43%	1%
J1G1 ORAL FLUOROQUINOLONES	11 995 000	23 465 600	33 679 945	20%	2%
J1G2 INJ FLUOROQUINOLONES	58 481	144 100	2 158 000	287%	0%
J1H1 MED/NARRW SPECT PEN PLAI	626 304 600	515 183 440	424 833 433	−9%	22%
J1K0 AMINOGLYCOSIDES	6578 500	6 975 300	6 295 783	−5%	0%
J1P2 PENEMS AND CARBAPENEMS	1 991 900	460 000	809 878	33%	0%
J1X1 GLYCOPEPTIDE ANTIBACT	257 500	285 700	651 093	51%	0%
J1X9 ALL OTHER ANTIBACTERIALS	2 530 000	5 899	28 704 650	6876%	2%
Grand total	1 670 911 057	1 553 790 791	1 906 200 029	11%	100%

^a Total QTY units: total number of antimicrobial units. The number of units (tablets, vials, capsules, etc.) was determined by taking into account the pack size (units per pack) and the quantity of packs awarded in the contract to arrive at quantity per unit.

^b CAGR: compound annual growth rate; this was used, as it is a measure of market growth over multiple time periods for the two sectors.

Table 3
Antiretroviral data—private sector.

Antiretroviral class ATC-Descriptor	Total QTY units ^a (2013)	Total QTY units ^a (2015)	CAGR ^b (2013–2015)	% Market share (2015)
J05AE PROTEASE INHIBITORS	102 749	59 806	–24%	1.69%
J05AF NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS	256 537	202 173	–11%	5.71%
J05AG NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS	584 759	409 065	–16%	11.55%
J05AR ANTIVIRALS FOR TREATMENT OF HIV INFECTIONS, COMBINATIONS	2 415 447	2 855 217	9%	80.64%
J05AX OTHER ANTIVIRALS	8347	14 217	31%	0.40%
Grand total	3 367 839	3 540 478	3%	100%

^a Total QTY units: total number of antimicrobial units. The number of units (tablets, vials, capsules, etc.) was determined by taking into account the pack size (units per pack) and the quantity of packs awarded in the contract to arrive at quantity per unit.

^b CAGR: compound annual growth rate; this was used, as it is a measure of market growth over multiple time periods for the two sectors.

Table 4
Antiretroviral data—public sector.

Antiretroviral class ATC-Descriptor	Total QTY units ^a (2013)	Total QTY units ^a (2015)	CAGR ^b (2013–2015)	% Market share (2015)
J05AE PROTEASE INHIBITORS	1 528 000	3 395 000	49%	0.06%
J05AF NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS	2 672 240 000	554 208 000	–54%	10.21%
J05AG NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS	976 696 000	681 832 000	–16%	12.56%
J05AR ANTIVIRALS FOR TREATMENT OF HIV INFECTIONS, COMBINATIONS	1 187 336 000	4 188 540 000	88%	77.15%
J05AX OTHER ANTIVIRALS	36 000	1 170 000	470%	0.02%
Grand total	4 837 836 000	5 429 145 000	6%	100%

^a Total QTY units: total number of antimicrobial units. The number of units (tablets, vials, capsules, etc.) was determined by taking into account the pack size (units per pack) and the quantity of packs awarded in the contract to arrive at quantity per unit.

^b CAGR: compound annual growth rate; this was used, as it is a measure of market growth over multiple time periods for the two sectors.

Manufacturer's List Price, or own medical aid pricing structure). Reference pricing is part of the South African private sector market and one of the ways to manage cost containment.

National guidelines for the management of HIV infection use FDC as first-line therapy. The public sector has seen a three-fold increase in FDC utilization (Table 4). However, there has also been a significant increase in protease inhibitor use, which is almost certainly driven in the main by failure of first-line therapy. This is of concern, as second-line therapy is more expensive, with side effects. Similarly, the utilization of raltegravir (other antivirals, J05AX) was found to have increased in both sectors, albeit currently at a low level of less than 1% of the total market share. Raltegravir has been used in third-line salvage regimens in the public sector and in some managed care settings such as Aid for AIDS, part of the Medscheme group. It will be interesting to follow the consumption of integrase inhibitors once access to dolutegravir increases in South Africa, as this is likely to replace efavirenz-based first-line therapy in the near future.

Medicines used for tuberculosis

TB in South Africa is mainly treated in the public sector as part of the national Directly Observed Therapy, Short Course (DOTS)

programme. Hence, the utilization of anti-TB medicines in the public sector is considerably higher than that in the private sector (Tables 5 and 6).

Despite a seemingly high CAGR of 25% in the private sector, the actual consumption increase in real terms in the total market was found to be low. The increase in the private sector was largely driven by an escalation in isoniazid (J04AC) consumption. This is possibly because of the increasing utilization of isoniazid preventive therapy (IPT), particularly in pregnancy, young children, and HIV-infected patients, which is now recommended in the treatment guidelines (National Department of Health, 2014; Churchyard et al., 2014). The use of high-dose isoniazid to overcome resistance caused by mutations in the *inhA* promoter region may also have played a minor role in the increasing consumption. In the public sector, the order quantities of ethionamide (J04AD), a drug commonly used for MDR-TB, increased by more than 30%.

The IMS data reflect all clinical indications for a particular medicine and it was therefore not possible to determine which products were used specifically for TB treatment and which were used for other clinical indications. For example, linezolid, levofloxacin, and moxifloxacin are used in the treatment of drug-resistant TB and for other bacterial infections. However, the

Table 5
Anti-tuberculosis agents—private sector.

Anti-tuberculosis class ATC-Descriptor	MAT units ^a (2014)	MAT units ^a (2015)	MAT units ^a (2016)	CAGR ^b (2014–2016)	% Market share (2016)
J01GB OTHER AMINOGLYCOSIDES	984	1109	2056	45%	1%
J04AA AMINOSALICYLIC ACID AND DERIVATIVES	15	0	0	–100%	0%
J04AB ANTIBIOTICS	54 743	54 882	47 878	–6%	23%
J04AC HYDRAZIDES	6535	12 735	91 811	275%	43%
J04AD THIOCARBAMIDE DERIVATIVES	289	272	233	–10%	0%
J04AK OTHER DRUGS FOR TREATMENT OF TUBERCULOSIS	4142	5583	4089	–1%	2%
J04AM COMBINATIONS OF DRUGS FOR TREATMENT OF TUBERCULOSIS	68 118	69 850	65 615	–2%	31%
Grand total	134 826	144 431	211 682	25%	100%

^a MAT units: moving annual total, i.e., the total value of the sales figures for the product, over the course of the period displayed.

^b CAGR: compound annual growth rate; this was used, as it is a measure of market growth over multiple time periods for the two sectors.

Table 6
Anti-tuberculosis agents—public sector.

Anti-tuberculosis class ATC-Descriptor	Total QTY units ^a (2013)	Total QTY units ^a (2015)	CAGR ^b (2012–2018)	% Market share (2015)
J01GB OTHER AMINOGLYCOSIDES	1 787 300	1 929 660	3.9%	0.24%
J01MA FLUOROQUINOLONES	16 224 100	16 412 360	0.6%	2.01%
J04AA AMINOSALICYLIC ACID AND DERIVATIVES	3 822 000	2 317 350	–22.1%	0.28%
J04AB ANTIBIOTICS	2 894 000	4 951 023	30.8%	0.61%
J04AC HYDRAZIDES	182 831 200	262 522 736	19.8%	3.20%
J04AD THIOCARBAMIDE DERIVATIVES	25 292 800	45 104 424	33.5%	5.53%
J04AK OTHER DRUGS FOR TREATMENT OF TUBERCULOSIS	106 219 760	97 459 630	–4.2%	11.96%
J04AM COMBINATIONS OF DRUGS FOR TREATMENT OF TUBERCULOSIS	438 736 000	384 481 900	–6.4%	47.17%
Grand total	777 807 160	815 179 083	2.4%	100%

^a Total QTY units: total number of antimicrobial units. The number of units (tablets, vials, capsules, etc.) was determined by taking into account the pack size (units per pack) and the quantity of packs awarded in the contract to arrive at quantity per unit.

^b CAGR: compound annual growth rate; this was used, as it is a measure of market growth over multiple time periods for the two sectors.

dataset created from the contract awards allowed these medicines to be identified specifically as treatment for TB.

Limitations

The analysis presented in this article is subject to limitations, one of the most important being the absence of true patient-level consumption data, measured using the DDD (introduced by the WHO). The DDD is generally preferred over standard units because it allows for a comparison between different antimicrobials and across different healthcare environments. However, antimicrobial data collected for a developing country such as South Africa, using IMS Health and tender data, could potentially be regarded as a good source of information when surveillance networks are either missing or weak. It might also be relevant to other low and middle-income countries that cannot at this stage provide DDD consumption data.

Recommendations

This situational analysis aimed to provide a baseline scientific basis for future investigations and interventions to improve the use of antimicrobials in South Africa. This was achieved by providing all of the available information and highlighting the current regulatory and policy frameworks. Further to this, based on the current findings and the urgent call by the Global Action Plan, the following are recommendations for future interventions:

- The development and implementation of a national strategic surveillance plan and reporting structure.
- The use of a set standard of coding (e.g. ATC classification) for antimicrobial use throughout all healthcare settings across South Africa. The WHO Collaborating Centre for Drug Statistics Methodology (World Health Organization, 2015c) describes a unit called the ‘defined daily dose’ (DDD) according to the ATC classification system. To make comparisons between geographical areas possible, the number of DDDs per 1000 inhabitants per day (DID) may be calculated. If this is not attainable in all hospitals across the country, procurement data as used in this article are a useful alternative to describe trends in antimicrobial use (not consumption). However, set standards for measurement should be used, e.g. CAGR, MAT units, and total number of antimicrobial units (QTY units), obtained from either IMS Health (where possible) or tender data.
- The collection and quantification of data on antibiotic consumption in animals and use in the environment.
- Two quality indicators for future implementation include tailoring empirical antibiotic therapy according to national antibiotic guidelines and assessing antibiotics prescribed against recommended national antibiotic guidelines.

Concluding remarks

Determining antimicrobial consumption data in low-resource settings remains a challenge. An alternative methodology is described herein, which with all of its limitations serves as an indicator of antimicrobial exposure at the population level. South Africa is well placed to contribute to the growing knowledge base on antimicrobial use and represents a platform on which to increase collaboration and initiate regular documentation and measurement of robust data on antimicrobial consumption.

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Conflict of interest

None.

References

- Chunnillal D, Peer A, Naidoo A, Essack [50_TD\$DIFF]S. An evaluation of antibiotic prescribing patterns in adult intensive care units in a private hospital in KwaZulu-Natal. *S Afr J Infect Dis* 2015;30(1):17–22. doi:<http://dx.doi.org/10.1080/23120053.2015.1103956> [Accessed August 19, 2017].
- Churchyard GJ, Mamejja LD, Mvusi L, et al. Tuberculosis control in South Africa: successes, challenges and recommendations. *S Afr Med J* 2014;104(3 Suppl 1):244–8. doi:<http://dx.doi.org/10.7196/SAMJ.7689>.
- Coenen S, Ferech M, Haaijer-Ruskamp FM, et al. European Surveillance of Antimicrobial Consumption (ESAC): quality indicators for outpatient antibiotic use in Europe. *Qual Saf Health Care* 2007;16:440–5 <http://qualitysafety.bmj.com/content/16/6/440.short>. [Accessed August 19, 2017].
- Department of Agriculture, Forestry and Fisheries (DAFF). South African Veterinary Strategy document (2016–2026). March 2016. <http://www.nda.agric.za/docs/media/Vet%20strategy%20final%20signed.pdf>. [Accessed February 15, 2017].
- Essack S, Schellack N, Pople T, et al. Part III. Antibiotic supply chain and management in human health. *S Afr Med J* 2011;101(8):562–6.
- Global Antibiotic Resistance Partnership (GARP). Situation analysis: antibiotic use and resistance in South Africa. *S Afr Med J* 2011;101(8):549–96 https://www.cddep.org/sites/default/files/garp/sitan/pdf/sa_full_8.pdf. [Accessed Feb 15, 2017].
- Government of the Republic of South Africa. Norms and standards regulations applicable to different categories of health establishments. Under Section 90 (1A) of the National Health Act, 2003 (Act No. 61 of 2003). Pretoria, Government Printer. 4 January 2017. http://www.gov.za/sites/www.gov.za/files/40539_gon10.pdf. [Accessed February 15, 2017].
- Laxminarayan R, Matsuoka P, Pant S, Brower [51_TD\$DIFF][52_TD\$DIFF]C, Røttingen JA, Klugman K, et al. Access to effective antimicrobials: a worldwide challenge. *Lancet* 2016;387:168–75.
- Leung E, Weil DE, Raviglione M, Nakatani H, on behalf of the World Health Organization World Health Day Antimicrobial Resistance Technical Working Group. The WHO policy package to combat antimicrobial resistance. *Bull World Health Organ* 2011;89:390–2. doi:<http://dx.doi.org/10.2471/BLT.11.088435>.
- Meintjies G, Black J, Conradie F, et al. Adult antiretroviral therapy guidelines 2014. *South Afr J HIV Med* 2014;15(4):121–43. doi:<http://dx.doi.org/10.4102/saj-hivmed.v15i4.330>.
- Minnie T. A review of the South African Pharmaceutical landscape. Prepared for UTI South Africa, November 2015. 2015. [Accessed February 15, 2017] <http://www.uti.org.za>

- utipharma.co.za/documents/198965/199128/UTI+November+2015+-+South+Africa+V1.pdf/c9c979e4-41ce-4d2c-94dc-e24f5d8c1b43.
- National Department of Health, South Africa. Antimicrobial resistance. National Strategy Framework 2014–2024. 2015. . [Accessed February 15, 2017] <http://www.health.gov.za/index.php/antimicrobial-resistance>.
- National Department of Health, South Africa. Essential Drugs Programme (EDP). Medicine list. 2017. . [Accessed February 15, 2017] <http://www.health.gov.za/index.php/medicine>.
- National Department of Health, South Africa. Hospital level (adults) standard treatment guidelines and essential medicines list. 4th Edition Pretoria: Directorate: Affordable Medicines, Essential Drugs Programme; 2015.
- National Department of Health, South Africa. Implementation plan for the antimicrobial resistance strategy framework in South Africa 2014–2019. September 2015b. <http://www.health.gov.za/index.php/antimicrobial-resistance?...plan-for...south-africa>. [Accessed February 15, 2017].
- National Department of Health, South Africa. Introduction of new drugs and drug regimens for the management of drug resistant tuberculosis in South Africa: Policy Framework 2015. 2015 Pretoria; June.
- National Department of Health, South Africa. National tuberculosis management guidelines. TB DOTS strategy co-ordination. 2014.
- O'Neill J. Tackling drug-resistant infections globally: Final report and recommendations. The review on antimicrobial resistance. May 2016. <https://amr-review.org/>. [Accessed February 15, 2017].
- Perumal-Pillay V, Suleman F. Selection of essential medicines for South Africa – an analysis of in-depth interviews with national essential medicines list committee members. *BMC Health Serv Res* 2017;17:17. doi:<http://dx.doi.org/10.1186/s12913-016-1946-9> [Accessed August 19, 2017].
- Pharasi B, Miot J. Medicines selection and procurement in South Africa. In: Padarath A, English R, editors. *South African Health Review 2012/13*. Durban: Health Systems Trust; 2013. . [Accessed Feb 15, 2017] <http://www.hst.org.za/publications/south-african-health-review-2012/13>.
- Republic of South Africa. Fertilizers, farm feeds, agricultural remedies and stock remedies act, 1947 (Act No. 36 of 1947). http://www.nda.agric.za/doaDev/sideMenu/ActNo36_1947/act36.htm. [Accessed February 16, 2017].
- Republic of South Africa. Medicines and related substances act, 1965 (Act No. 101 of 1965, as amended). http://www.hpcs.co.za/Uploads/editor/UserFiles/downloads/legislations/acts/medicines_and_related_sub_act_101_of_1965.pdf. [Accessed February 15, 2017].
- Republic of South Africa. Nursing Act, 2005 (Act No. 33 of 2005, as amended). <http://www.gov.za/documents/nursing-act>. [Accessed February 15, 2017].
- Republic of South Africa. Pharmacy Act, 1974 (Act No. 53 of 1974, as amended). <http://www.gov.za/documents/pharmacy-act-16-oct-1974-0000>. [Accessed February 15, 2017].
- Republic of South Africa. Veterinary and Para-veterinary Professions Act, 1982 (Act No. 19 of 1982, as amended). http://www.savc.org.za/pdf_docs/act_19_of_1982.pdf. [Accessed Feb 15, 2017].
- South African Antibiotic Stewardship Programme (SAASP). <http://www.fidssa.co.za/SAASP>. [Accessed Feb 15, 2017].
- South African Medical Research Council (SAMRC). Burden of Health & Disease in South Africa: Medical Research Council briefing. Meeting Report. 15 March 2016. <https://pmg.org.za/committee-meeting/22198/>. [Accessed February 15, 2017].
- South African Veterinary Council (SAVC). Colistin use by veterinarians. 14 November 2016. http://www.fidssa.co.za/newsletter_FIDSSA/RSA_Use_of_Colistin_SAVC_and_MCC.pdf. [Accessed February 15, 2017].
- Statistics South Africa. Mid-year population estimates 2016. Statistical release P0302. <http://www.statssa.gov.za/publications/P0302/P03022016.pdf>. [Accessed February 15, 2017].
- The Centre for Disease Dynamics, Economics & Policy (CDDEP). Global Antibiotic Resistance Partnership. <http://www.cddep.org/garp/home>. [Accessed February 15, 2017].
- The World Bank. Overview of the South African Context, 2017. <http://www.worldbank.org/en/country/southafrica/overview>. [Accessed August 21, 2017].
- WHO Collaborating Centre for Drug Statistics Methodology, ATC classification index with DDDs, 2016. Oslo, Norway; 2015c. https://www.whocc.no/atc_ddd_index_and_guidelines/atc_ddd_index/. [Accessed Mar 12, 2017].
- WHO. Antimicrobial resistance: global report on surveillance 2014. Geneva: World Health Organization; 2014. . [Accessed February 15, 2017] <http://www.who.int/drugresistance/documents/surveillance-report/en/>.
- WHO. Global Action Plan on Antimicrobial Resistance. Geneva: World Health Organization; 2015. . [Accessed February 15, 2017] http://www.wpro.who.int/entity/drug_resistance/resources/global_action_plan_eng.pdf.
- WHO. Global Worldwide country situation analysis: response to antimicrobial resistance. April 2015. World Health Organization, Geneva; 2015b. http://apps.who.int/iris/bitstream/10665/163468/1/9789241564946_eng.pdf. [Accessed February 15, 2017].