Our collective contribution matters: Pharmacists unite in tackling antibiotic resistance for South Africa

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The relentless misuse (including under dosing, inappropriate duration and incorrect indications) of antibiotics globally has over time hastened the natural process of antibiotic resistance which Sir Alexander Fleming warned us of in 1945. Many bacteria today have gained resistance mechanisms to combat antibiotics causing experts to caution that we are currently at the dawn of a post antibiotic era. As a result, the advancements in modern medicine including organ transplants, chemotherapy and joint replacement surgery could one day be a memory of the past since these procedures may be too risky to perform without effective antibiotic prophylaxis.

It is safe to say that antibiotic resistance is currently one of the biggest global public health threats. It is predicted to be the leading cause of mortality by 2050 (one person dying every 3 seconds) if the existing status quo continues[1]. In this overview, we describe the state of antibiotic resistance in South Africa and how pharmacists can work together to tackle antibiotic resistance.

Multi-drug resistant (MDR) bacteria, only sensitive to last line therapy or pan resistant are escalating at a distressing rate in South Africa. These organisms, particularly MDR Gram-negative pathogens, pose a specific threat to hospital environments necessitating the use of older, more toxic drugs such as colistin, as a final option to help treat severe infections[2, 3, 4].

An editorial entitled "Wake up, South Africa! The antibiotic horse has bolted" indicated that the rise in MDR Gram-negative bacteria including the carbapenem-resistant Enterobacteriaceae (CRE) was as a result of a home grown multifaceted problem including the abuse of all antibiotics[5].

A study by Kift et al. (2014) indicated that carbapenem susceptibility decreased by 18% over a four year period in South African public sector hospitals[6].

A local prevalence study conducted by Paruk et al. (2012), evaluated antibiotic prescription practices in the intensive care units (ICU) of both public and private sector hospitals in five provinces. This study found that unsuitable antibiotics were initiated in over 50% of patients reviewed and 72% of these patients received antibiotic therapy for an inappropriate duration[7].

Alarmingly, van Boeckel et al. (2014) noted that antibiotic consumption increased in proportionately to population growth during 2000-2010 in the BRICS countries, of which South Africa is one[8].

The problems experienced currently with drug-resistant tuberculosis and non-*albicans Candida* infections which are resistant to first line antifungal therapy further enhances the crisis South Africa is facing with MDR organisms[9].

Carbapenem resistance among the Gram-negative Entero-bacteriaceae can occur through various mechanisms; however, the most common is through the production of beta-lactamases, a bacterial enzyme which hydrolyses carbapenems and all other beta lactam antibiotics including penicillins and cephalosporins. These CRE's often contain additional mechanisms of resistance to the aminoglycosides and to some extent the fluoroquinolone class of antibiotics[10]. Risk factors for CRE organisms include previous antibiotic exposure, prolonged hospitalization, severe illness and surgery, to name a few[10].

Often, colistin is the last resort antibiotic used to combat severe CRE infections. Devastatingly, documented reports have emerged globally indicating instances of colistin-resistance within Gram-negative pathogens including: *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Acinetobacter baumannii*[5]. In such instances the consequences of MDR and pan-resistant organisms are dire and

are associated with an increased risk of patient mortality. Colistin, also known as Polymixin E, exerts bactericidal antibiotic properties with dangerous nephrotoxic and neurotoxic side effects. Colistin can be used both intravenously and by nebulisation depending on the nature of the infection[11]. In South Africa, colistin is available as a Section 21 medicine through special application and approval granted by the Medicines Control Council.

In South Africa, no local information of why and how colistin is prescribed is available and compliance to current dosing guidelines is unknown. Preliminary results from a study conducted across four South African hospitals evaluating current colistin prescribing practices revealed that colistin administration occurred mostly in the intensive care units (76.6%).

Therapy was regularly administered intravenously (IV) (90.6%) followed by nebulisation (7.8%). The mean duration of colistin therapy was 13.6 days. The compliance rate of administration of a loading dose (95.8%) and as combination therapy (98.3%) was high, although daily dosing regimens in million units (MU) of colistin varied considerably from 1MU, 1,5MU, 2MU and 3MU IV 8 hourly to 1,5, 2MU, 3MU, and 4.5 MU IV 12 hourly.

Colistin was prescribed as directed or definitive therapy in 73.4% of patients, with 26.6% of treatment being initiated empirically. Organisms justifying the need for colistin use include: *Klebsiella pneumoniae* (35.9%), *Pseudomonas aeruginosa* (26.6%) and *Acinetobacter baumannii* (15.6%). Outcomes measures reflected a 29.7% overall mortality rate and an average length of stay in hospital of 55.9 days.

The data suggests that several opportunities to improve appropriate colistin use exist particularly regarding the dose and duration of therapy – elements that fall directly within a pharmacist's scope of influence – and should be addressed urgently.

Numerous initiatives globally and nationally are orchestrating mechanisms in which to minimize the threat of MDR organisms primarily through the promotion of appropriate infection control programmes and advocating the judicious use of antimicrobial agents through to antimicrobial stewardship programmes. International organizations including Centre for Disease Control (CDC), and the European Society of Clinical Microbiology and Infectious Disease (ESCMID), as well as, locally the Federation of Infectious Diseases Society of South Africa (FIDSSA) and the South African Antibiotic Stewardship Programme (SAASP) recommend antibiotic stewardship programmes to manage organism resistance problems in both humans and animals.

Mendelson et al. (2012) advocated the "return to rational antibiotic prescribing through strong antibiotic stewardship" programmes[5]. This message is further enhanced by the 'Best Care Always' campaign; a South African collaborative initiative across public and private hospitals which promotes implementation of quality improvement methodologies to enhance best patient care including reducing healthcare associated infections and the provision of guidelines relating to the implementation of antimicrobial stewardship practices. These initiatives are to ensure the rational use of antibiotics and the most positive outcomes for patients in an attempt to decrease antimicrobial resistance.

Since infectious disease specialist clinicians are limited in South Africa, existing resources such as pharmacists and nurses are perfectly placed to develop, and execute antibiotic stewardship initiatives in healthcare settings[12]. The collective impact of hospital pharmacists and their critical role as part of a multi-disciplinary team in various antibiotic stewardship initiatives has been demonstrated recently across a private hospital network in South Africa (Table 1).

Additional interventions undertaken by pharmacists globally include, to name a few; antibiotic stewardship in the emergency department, therapeutic drug monitoring of numerous antibiotics,

Table 1: The hospital pharmacists impact in various antibiotic stewardship initiatives in South Africa

Antibiotic Stewardship Initiatives	Pharmacists Impact
The prompt administration of antibiotics to improve patient outcome[13]	With every hour in delay of antibiotic administration mortality can increase by 7.6% in patients with sepsis and septic shock[14]. Therefore, ensuring the timely administration of antimicrobials is critical in the management of patients with infections. Implementation of a pharmacist driven initiative to ensure the prompt administration of antibiotics within one hour following prescription (commonly known as antibiotic 'hang-time') initially in ICUs and then including other wards significantly increased compliance to a hang-time by 47%.
Implementation of "low – hanging fruit" stewardship interventions to decrease antibiotic consumption[15]	Pharmacists undertook a prospective audit and feedback method to implement and monitor five foundational stewardship interventions including: duration of antibiotics greater than 7 and 14 days; ensuring a culture is taken prior to the commencement of antibiotic therapy; inappropriate duplicate antibiotic cover and the co-administration of more than four antibiotics. An intervention was required for one in every 15 prescriptions and overall antibiotic consumption significantly decreased over the study period by 18%.
Improving compliance to surgical prophylaxis guidelines to decrease surgical site infections[16]	Appropriate peri-operative antibiotic prophylaxis (PAP) is critical in minimising the risk of surgical site infections (SSI) post-op. Pharmacists undertook to improve compliance to a bundle of four PAP measures including: appropriate agent, appropriate dose, appropriate time of administration and appropriate duration of prophylaxis based on recommended peer reviewed guidelines mainly for caesarean sections and orthopedic surgeries. There was a significant improvement in compliance with all process measures and overall bundle compliance significantly increased by 24.7%. This had a direct impact on the SSI rate which decreased by 19.7%.

pediatric stewardship, vaccination campaigns and antifungal stewardship.

As is evident through Table 1, the general pharmacist can help lead and make a difference in antibiotic stewardship initiatives which have a direct and positive impact on overall patient care. Although much of this work occurred in the private hospital sector, it is applicable and can be adapted for implementation in public hospitals too, with appropriate institutional support and allocated 'protected stewardship time', as these principles are universal and applicable to all settings where antibiotics are prescribed.

Boyles et al (2013) showed that the implementation of a dedicated antibiotic prescription chart and weekly antibiotic stewardship ward rounds reduced antibiotic consumption and cost without impacting readmission rates and patient mortality in a Western Cape public hospital[17]. If pharmacist resources are constrained in a particular healthcare setting, monitoring and evaluation of simple stewardship elements from within the pharmacy through the interpretation and evaluation of the prescription chart can include;

- Duration of therapy
- Inappropriate duplicate cover of antibiotics
- Ensuring the correct dose is prescribed and administered
- Review if an antibiotic is prescribed prophylactically, empirically or definitively
- Evaluating if a culture was sent prior to the initiation of antibiotic therapy

It is certainly the responsibility of all pharmacists to adhere to the abovementioned principles in order to preserve the efficacy of antibiotics for future generations. The role of the dispensing pharmacist in South Africa, as the safe keeper of all medicines, including antibiotics, in tackling antibiotic resistance cannot be under estimated. Their position and unique healthcare skill including the scope to interpret, evaluate and monitor the prescription of antibiotics coupled with beneficial relationships with prescribers is a powerful and critical contributor to this crisis.

Dispensing pharmacists should commit to undertake and review these fundamental stewardship interventions in community, primary care and institutional pharmacy settings. If all pharmacists stand together alongside other health professionals, the impact of the collective contribution to this cause would be ground breaking for our country.

I am an antibiotic steward, are you?

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