ANTIMICROBIAL STEWARDSHIP: FROM THEORY TO PRACTICE

Antimicrobial resistance (AMR) has increased worldwide to the extent that it is now regarded as a global public health crisis. In this regard, the emergence and rapid spread of extensive drug-resistant (XDR), including carbapenemase-producing Gram-negative bacteria (GNB) in South Africa, is of particular concern. The State of the World's Antibiotics report in 2015 highlighted South Africa's increasing incidence of these 'superbugs' (3.2% of *Klebsiellia pneumoniae* were carbapenemase producers), and in so doing, underscored South Africa's increasing reliance on colistin as the last line of defence.[1] Colistin resistance effectively renders such increasingly common infections untreatable. To illustrate the urgent need for antibiotic preservation across all sectors in South Africa (i.e. the One Health approach), a countrywide surveillance programme of poultry operations recently revealed that colistin resistance in *Escherichia coli* strains increased substantially in 2015, particularly where colistin was used.[2] Concurrently, colistin resistance emerged amongst clinical strains of *E. coli*, particularly in patients with urinary tract infections presenting in primary care.[2]

To alleviate the crisis, antimicrobial stewardship (AMS) has emerged as a concept that embodies the appropriate use of antibiotics with the goal of optimising patient outcomes whilst reducing the emergence of resistant bacteria.[3] Interventions to reduce excessive antibiotic prescribing to patients have been shown to reduce resistance and improve microbiological and clinical outcomes.[4] However, recent reviews have concluded that data on the effectiveness of antimicrobial stewardship in resource limited settings is sparse.[4] In fact, a global survey of stewardship activities revealed that in Africa and Asia only 14% and 53% respectively of respondents had any form of AMS in place.[5] Historically, barriers to implementing AMS in South Africa have been a lack of infectious disease (ID) expertise and resources (i.e. ID physicians, clinical microbiologists, ID and clinical pharmacists) outside of tertiary academic centres. Nevertheless, there is very encouraging news from South Africa.

EVOLUTION OF ANTIMICROBIAL STEWARDSHIP IN SOUTH AFRICA

The success of South Africa's AMR strategy development is attributed to strong leadership from the Minister and Director General of Health, in partnership with the South African Antibiotic Stewardship Programme (SAASP). SAASP spans public and private, human and animal sectors, providing leadership, advocacy for, and strengthening of AMS since 2012.[6] It was a key player in developing the national AMR strategy framework and implementation policy.[7] Within the strategy framework, a multidisciplinary Ministerial Advisory Committee (MAC) on AMR was recently established to coordinate intersectorial efforts nationally as well as to monitor and evaluate the implementation of the strategy. Besides primary care, this includes the institutionalisation of effective systems of AMS at national, provincial and institutional level in both the public and private sectors using the "one health" approach.

To facilitate the selection of antimicrobial agents on the Essential Medicine List based on trends and patterns of antimicrobial resistance (AMR), it also includes national structured surveillance

and reporting systems for antimicrobial use and resistance in the human health and agriculture sectors. In this regard, sponsored by the Centre for Disease Dynamics, Economic and Politics, the first composite resistance map (combining both public and private sector surveillance data) and reflecting South African provincial differences, was recently published.[8,9] Similar to the United Kingdom and France, AMS stewardship and infection control activities are closely linked as combating antimicrobial resistance is seen as a key objective of the national antibiotic resistance strategic framework to control hospital-acquired infections.[7,10] Therefore, progress as regards compliance with the standards for AMS and infection control and prevention, defined in the National Core Standards for all health institutions, is a matter of priority.

ANTIMICROBIAL STEWARDSHIP IN HOSPITALS

First reports of successful implementation of AMS interventions emanated from different settings. Introduction of an antibiotic prescription chart and a weekly multi-disciplinary AMS ward round led by ID clinicians in an academic teaching hospital in Cape Town led to a sustainable reduction in antibiotic consumption (19.6%) without impacting on inpatient mortality or 30-day readmission rates during the control and intervention periods.[11] However, the need for alternative stewardship models in South Africa that use available organisational infrastructure and resources that is not necessarily dependant on or driven by ID specialities or clinical microbiology led to consideration of non-specialised pharmacists in promoting interdisciplinary engagement in stewardship programmes in local hospitals or across health systems.[12,13]

In the first of these, a non-specialised pharmacist-driven intervention was implemented to improve the timely administration of intravenous antimicrobials in participating Netcare hospitals.[12] In this quality improvement (QI) initiative, the tools of healthcare improvement spread methodology were used to shorten the time from prescription to administration of antibiotics (within one hour) in 33 hospitals. The change in improvement of "hang-time" compliance following implementation of the hang-time process improvement protocol was 41.2% pre-intervention in week one to 78.4% post-intervention in week 60 ($p < 0.0001$).[12]

In the second of these, successful implementation of a prospective audit and feedback AMS programme in the same hospital group but in 47 urban and rural hospitals took place, directed towards reducing excessive antibiotic prescribing, led by pharmacists and involving similar change management principles including behaviour change techniques (BCTs).[13] The model, a Netcare adaption of the "Institute for Healthcare Improvement (IHI) Model" and the "Breakthrough Series Collaborative", included a stepwise implementation phase in the five-year study directed towards auditing five basic targets designated as "low-hanging fruit".[14,15] These included excessive antibiotic duration (> 7 or > 14 days) or prescription of antibiotics with overlapping or duplicate spectra. In order to later facilitate de-escalation, it also included as process measure, compliance with cultures obtained prior to administration of antibiotics. The AMS model had a significant impact on antibiotic consumption with a reduction in mean antibiotic defined daily doses (DDD)/100 patient days from 101.4 to 83.0 in the pre-and post-implementation phases respectively, representing an 18.1% reduction in overall consumption ($p < 0{\cdot}001$).[13] Subsequently another antibiotic intervention was reported, in this instance the outcome of a peri-operative antibiotic prophylaxis audit and feedback model in 34 hospitals involving 24 206 surgical cases.[16] There was a significant improvement in compliance with all the process measures (such as choice, dose and duration of prophylaxis) from 66.8% (95% CI 64.8–68.7) to 83.3% (95% CI 80.8–85.8), representing a 24.7% increase ($p < 0.0001$). Concurrently, the surgical site infection rate decreased by 19.7% from a mean group rate of 2.46 (95% CI 2.18–2.73) pre-intervention to 1.97 post-intervention (95% CI 1.79–2.15) ($p = 0.0029$).

Experiences such as these are instructive and thus suggest that stewardship for institutionalised patients in settings without adequate ID resources should be approached by means of stepwise

implementation of process improvement initiatives and principles targeted to institutional needs. It confirms that, firstly AMS can be implemented in a variety of geographical and socio-economic settings by health-care workers without ID training and secondly, that skills beyond ID are critical in initiating and maintaining AMS.[13,17] These include an understanding of how to implement change, how to use BCTs effectively and how to measure improvement. [4,13,18] Thirdly, by selecting the most obtainable targets in low resource settings, one can have a significant impact on outcome with less effort, whilst embedding AMS practices within existing resource structures and systems. Key to the success of the AMS model was engagement with clinicians, nurses and infection control practitioners and their support of the process of change. In this scenario, the role of the non-ID pharmacist in promoting interdisciplinary engagement in stewardship programmes in hospitals or across health systems cannot be underestimated.

ANTIMICROBIAL STEWARDSHIP IN PRIMARY CARE

There is no doubt that the main objectives of various AMS programmes to limit further development of resistance and improve patient outcomes, would be easier to achieve if hospitals were to implement multidisciplinary team-based AMS. How clinicians implement AMS in the community is a challenging question. In this regard, a targeted application of AMS principles to the ambulatory setting has the potential to affect the most common indications for systemic antibiotic use in that the majority (80%) of antibiotic use occurs in the community, with acute respiratory tract infections (ARTI) being the most common indication.[3,19] Inappropriate antimicrobial prescribing is a significant problem, with approximately 50% of antimicrobial usage suboptimal in outpatients and often unnecessary and unlikely to benefit patients.[3,19]

However, the reasons driving the excessive prescription of antibiotics in the community are complex. They include the overlapping clinical features of viral and bacterial infections that dramatically reduce the ability of general practitioners (GPs) to distinguish which patients would benefit from an antibiotic or not (diagnostic uncertainty), constraints on consultation time, lack of appreciation of the impact on resistance, lack of antibiotic governance and accountability and perhaps most importantly, patient and parental pressures.[3] Therefore, it is clear that a single AMS strategy for primary care antibiotic use is unlikely to lead to changes in consumption and hence a multi-modal strategic approach for antibiotic use in the community may be required, as depicted in Table 1. Regarding these, several initiatives and pilot interventions in primary care are currently underway.

TABLE 1. A MULTI-MODAL STRATEGY-BASED APPROACH FOR ANTIMICROBIAL STEWARDSHIP (AMS) IN THE COMMUNITY

STRATEGY	COMPONENTS
Treat bacterial infection only	• Optimise clinical diagnosis and severity assessment • The use of C-reactive protein and other biomarkers in community practice incl. point-of-care testing • Need for tools to reduce diagnostic uncertainty
Judicious antibiotic prescribing principles	• Target maximum eradication of bacterial pathogens • Utilise pharmacokinetic/pharmacodynamics (PK/PD) to choose the most effective agents and appropriate dosage • Optimise duration of therapy • “Know your bugs”: local antibiograms • Prescribing antibiotics that are associated with less selection of resistant strains

Prescription strategies	• Immediate prescription • Delayed prescription • No prescription
Raise the public's "antibiotic threshold"	• Community awareness of AMR • Patient empowerment vs. patient satisfaction
Vaccination as a key AMS strategy	• Bacterial • Viral
Covering more territory" to fight resistance in the community	• Pharmacists • Nurses
An antibiotic "licence" to prescribe?	• Educational intervention • Educational support
AMS governance in primary care	• Leadership commitment • Accountability

NEXT STEPS IN SOUTH AFRICA TO ADVANCE AMS

Despite the current progress and success in reaching some of the short term targets contained in the National AMR strategy framework, considerable efforts are still required. Regarding the goals of the AMR framework, several other initiatives and pilot interventions are currently under way which include the following:

- As the pharmacist-driven AMS model referred to were undertaken in the private sector in South Africa it is required to ascertain whether implementation would work in the public sector where the majority of the population in South Africa receives healthcare. As part of this, a SAASP training QI initiative of implementing a pharmacist-driven prospective audit and feedback AMS study of eight process and outcome measures relating to compliance with the South African community-acquired pneumonia guideline across all health sectors, is being planned.
- Furthermore, mandated by the MAC, core curricula on AMR for health and veterinary professionals are being established.
- A knowledge, attitude and perception (KAP) antibiotic survey of public and primary care physicians is currently in progress to facilitate a national community advocacy, awareness and education campaign to reduce inappropriate use of antimicrobials amongst ambulatory patients.
- In this regard, a diagnostic stewardship clinical guideline to reduce diagnostic uncertainty in ARTIs in non-hospitalised patients which includes the use of point-of-care testing for C-reactive protein was recently published.[3]
- Besides current annual SAASP AMS educational and training workshops, one aimed at front-line prescribers, one at pharmacists and other healthcare workers, and one at GPs, other educational activities extend to a free online-AMS course for clinicians with the ultimate aim of a statutory "licence to prescribe".[20] The pilot course is available on the official SAASP YouTube channel.[21]
- In addition, a free SAASP residential 'Train the Trainer' course to up-skill key prescribers nationally at two sites commenced (for the first time) in June 2016.

- Regarding pharmacists, in 2010, the South African Society of Clinical Pharmacy (SASOCP) was formed in response to the resurgent interest in clinical pharmacy from a stewardship point of view.[22] Thus, while training has been instituted in several pharmacy schools, their role in advancing AMS, and the potential benefits to the country, is eagerly awaited.
- Finally, similar to this fifth edition of the Ampath guidelines to antimicrobial therapy and the laboratory diagnosis of infectious diseases, a concise SAASP pocket guide for antibiotic prescribing for adults in South Africa, including an SAASP App, was recently published and is currently been updated http://www.fidssa.co.za/Content/ Documents/SAASP_Antibiotic_Guidelines_2015.pdf [23] (Last accessed 2 March 2017).

In conclusion, key factors for current progress and success in South Africa have been strong leadership and the National Department of Health's commitment to AMS, mentoring programmes, improvement models and education through SAASP and SASOCP. AMS requires a collaborative effort on the part of policymakers, healthcare insurance companies, clinicians and pharmacists including diagnostic laboratories, other healthcare care providers and patients. However, future success will depend to a large degree on the barriers to change, not only amongst healthcare providers but also the public and agricultural sectors. Tailored interventions to overcome identified barriers to change might be needed to effect change. In any event, the potential for pharmacist- and nurse-led models of stewardship to complement that of clinicians affords an exciting opportunity for SA to offer an integrated range of AMS models to serve the whole population.

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