Introduction

The development of antibiotics in the 1940's was a significant breakthrough in public health. Antibiotics transformed health care by dramatically reducing morbidity and mortality due to infectious diseases and have allowed for major advancements in medicine such as surgery and organ transplants to be made possible. On the contrary, the widespread use and overuse of these agents, has resulted in the development of resistant organisms. As early as 1945, Sir Alexander Fleming, the discoverer of penicillin, foresaw this phenomenon and famously cautioned that the rampant overuse of penicillin would cause an epidemic of drug resistant organisms:

"The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out … In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted."

Globally, antimicrobial resistance is now considered a major threat to public health and without urgent coordinated action by many stakeholders, the world is headed for a post-antibiotic era, in which common easily treatable infections can once again kill. This situation is compounded by the rapid decline in discovery and development of new antibiotics. Although the lull in drug discovery has been eased to some extent in recent years, new products are mostly targeting gram-positive organisms. However it is the emergence of resistant strains of gram-negatives which currently poses a greater threat to human life, with very few antibiotics that can combat them in the development pipe-line.

Mechanisms of antimicrobial resistance (AMR) landscape

Antimicrobials are agents that kill or inhibit the growth of microorganisms and encompass antibiotics, antifungals, and antivirals. Antimicrobial resistance (AMR) develops when microorganisms adapt and grow in the presence of antimicrobials, rendering treatment with an antimicrobial drug ineffective. The factors leading to AMR are complex and multifactorial. Essentially, resistance occurs due to a natural evolutionary process which equips the microorganisms with mechanisms with which to counteract the effects of the antimicrobials. Antimicrobial resistance can happen, for example, when a microorganism produces an enzyme that destroys the drug directly (e.g. β-lactamases which degrade β-lactam antimicrobials). It can also occur through a genetic mutation of the pathogen, resulting in alteration of bacterial enzymes (e.g. mutated DNA-gyrases that resist quinolone binding) or changes in membrane permeability to antimicrobials (caused by efflux pumps) or protection of the target by DNA-binding proteins (known as Qnr). Development of resistance in a single microorganism or location can unpredictably and rapidly spread through various mechanisms, for example, through the exchange of genetic material between resistant and susceptible microorganisms (horizontal gene transfer) or through transmission in human and animal populations via food, water and the environment.

Prevalence of AMR

One of the cornerstones of the management of infectious diseases, and the basics of public health, is surveillance of drug-resistant infections and antimicrobial consumption.
Worldwide, AMR is increasing in prevalence resulting in infections that are difficult and expensive to treat. Currently, a number of common infections such as urinary tract infections, diarrhoea, gonorrhoea, tuberculosis, and other respiratory diseases are becoming more difficult to treat. Subsequently, terms like ‘superbugs’, multi-drug resistant (MDR), extensively drug-resistant (XDR), methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), pan-resistant bacteria, New Delhi Metallo-beta-lactamase-1 (NDM-1), *Klebsiella pneumoniae* carbapenemase (KPC) and second-line therapy, feature increasingly and prominently in our medical diction.

In 2014 an estimated 450 000 new cases of tuberculosis (TB) were reported in South Africa, with 1.8% of new cases and 6.7% of previously treated cases estimated to have MDR-TB. Recent surveillance data from the Centre for Disease Dynamics, Economics and Policy’s (CDDEP) online interactive tool, ResistanceMap, paint an even more dire picture of the AMR landscape. In 2014 *Escherichia coli* resistance to fluoroquinolones was 28%, methicillin-resistant *Staphylococcus aureus* (MRSA) was 31% and *Klebsiella pneumoniae* resistance against carbapenems showed an increasing rate from 2% in 2013 to 4% in 2014.

Irrational antibiotic use is not only limited to human use but also in agriculture. An estimated 80% of all antibiotics used globally are used for the purpose of animal health, for growth promotion in feed animals, or for agriculture and aquaculture to prevent or treat infection. These practices are posing a significant public health threat, contributing to drug-resistant pathogens. Estimated antimicrobial consumption in livestock in 2010, is projected to rise by 67% by 2030, and nearly double in Brazil, Russia, India, China, and South Africa.

South Africa evidently is using a large amount of antibiotics in food-producing animals, including a number of antibiotics that have been banned for use in other countries. Evidence has shown that when required to treat or prevent infection, the practice of treating the entire herd instead of the infected animal, or administering antibiotics for extended periods of time using sub-therapeutic concentrations, is prevalent. This is further compounded by the use of antibiotics for growth promoters without veterinary prescriptions and the lack of controls in the sale of antibiotics to farmers by veterinarians.

**Consequences of AMR**

Antimicrobial resistance threatens to reverse the gains of antimicrobials in advancing modern medicine. While the real magnitude of the problem is unknown, and the methods for measuring economic impact of resistance are not well elucidated, the monetary cost of treating antibiotic resistant infections globally is estimated to be several billions of dollars per year. Worldwide, it is estimated that 10 million deaths per year, and 2% to 3.5% reduction in global gross domestic product by 2050, will be a direct result of the current trends in AMR.

In a clinical setting, infections caused by resistant microorganisms may require more toxic therapy that can lead to adverse outcomes. In addition, in-hospital mortality rates and extended hospital stays will increase as a result of AMR. This is coupled with an up to two-fold increase in hospital-acquired infections and costs for patients with resistant versus susceptible infection, due to infections which are more difficult and more expensive to treat.

The societal and economic impacts of AMR are myriad. For the patient, some drug resistant micro-organisms require physical isolation from society in order to minimise transmission which may result in loss of work and family time. Furthermore, the patient may incur costs for extra visits to the doctor and lengthened hospitalisation, possible second-line treatments, laboratory tests and other diagnostic costs.

Lastly, AMR has the potential to cause calamitous effects on international travel and trade resulting from the cross-border transmission of resistant infections.

**Strategies to combat antimicrobial resistance**

*Global action plan on antimicrobial resistance*

Several regional and global resolutions have called for action on specific health aspects related to AMR. In 2008, the Global Antibiotic Resistance Partnership (GARP) was established to help developing countries build capacity and establish policies to deal with the growing problem of AMR. Following a World Health Assembly resolution in 2015, a global action plan on AMR was developed for adoption by member states, to produce national strategic plans to combat AMR. The overall goal of the action plan is to ensure, for as long as possible, continuity of the ability to treat and prevent infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them. To achieve this overall goal, the following five main strategic objectives were set out:

- Improve awareness and understanding of antimicrobial resistance through effective communication, education and training
- Strengthen the knowledge and evidence base through surveillance and research
- Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures
- Optimise the use of antimicrobial medicines in human and animal health
- Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions
The global action plan provides the framework for national action plans to combat AMR. For each of the objectives, key actions are stipulated to combat AMR, which should be taken by the various actors involved, using an incremental approach over the next 5–10 years. Antibiotic resistance is covered in great detail, however, reference is made to existing action plans for viral, parasitic and bacterial diseases, including HIV/AIDS, malaria and tuberculosis. Special emphasis is placed on strengthening of already existing principles of antimicrobial stewardship.


In South Africa, GARP conducted a situation analysis of antibiotic use and resistance. This situational analysis highlighted the emergence of ‘super-bugs’ and the need for action to contain AMR. Subsequently, the South African Antibiotic Stewardship Programme (SAASP) was established under the auspices of the Federation of Infectious Diseases Societies of Southern Africa (FIDSSA), comprising of members from the private and public sector, to strengthen antibiotic stewardship and education in South Africa.

In 2014, the National Department of Health in South Africa, published the Antimicrobial Resistance (AMR) National Strategy Framework, 2014–2024, in response to the preceding WHO global strategy for containment of AMR and advocacy by SAASP. This strategy defines South Africa’s approach to manage AMR, limit further increases in resistant microbial infections, and improve patient outcomes. The vision is “to ensure the appropriate use of antimicrobials by healthcare professionals in all health establishments in South Africa to conserve the efficacy of antimicrobials for the optimal management of infections in human and animal health.” South Africa’s national AMR strategy framework consists of four building blocks with strategic objectives that are reinforced by four key enablers (Figure 1).

The strategic framework emphasises a governance model which is supported by relevant laws in order to ensure success of each objective and enabler, and to allow for oversight, monitoring and evaluation. The antimicrobial governance model is enabled through a multidisciplinary inter-sectorial ministerial advisory committee comprising of key stakeholders on AMR. Prior to the promulgation of the strategic framework for the AMR national strategy and the corresponding implementation plan, there was no single national guideline to address antimicrobial resistance, although the objectives and enablers were promoted in one form or another in various documents. For example, the Essential Medicines List (EML) and Standard Treatment Guidelines (STGs) recommend principles for the use of antimicrobials at different levels of the South African healthcare system. The National Core Standards for health establishments in South Africa endorse AMS and infection control and prevention interventions at the different facility levels.

**Antimicrobial stewardship in South Africa**

Antimicrobial stewardship (AMS) is defined as a multidisciplinary, systematic approach to optimising the appropriate use of all antimicrobials to improve patient outcomes and limit the emergence of resistant pathogens whilst ensuring patient safety. Antimicrobial stewardship programmes in South Africa as well as other countries have shown to be successful in promoting rational antibiotic use, improve patient outcomes and reduce adverse consequences of antibiotic use, including antibiotic resistance, toxicity and unnecessary costs.

Despite not having an outright mandate from the National Department of Health, the South African Antibiotic Stewardship Programme (SAASP) provides leadership, advocacy, and strengthening of antibiotic stewardship, in the public and private sectors in South Africa. They have published treatment guidelines on antibiotic prescribing, offer courses and educational materials on antimicrobial stewardship and an antibiotic prescription chart is available for use on its website.

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**Figure 1. Strategic framework for the antimicrobial resistance national strategy**
The National Department of Health recently prepared a draft Practical Guide to Antimicrobial Stewardship in South Africa. This guide is intended to act as a blueprint for all healthcare professionals in the public and private sector, to enforce AMS in line with the Strategic Framework and Implementation Plan, at all levels of care. The document further aims to be a practical, step-by-step or ‘how to’ guide, addressing the four pillars of the Strategic Framework. With the practical approach taken in the guide, much broader AMR programme activities and interventions are specified, compared to what is stipulated for AMS in the National Core Standards. A useful monitoring and evaluation framework for AMS implementation is offered for each level of the health system.

Central to the theme of AMS is the need to develop a collaborative practice between clinicians, pharmacy staff, microbiologists, laboratorians and infection control specialists in order to provide the best outcome for the patient, reduce healthcare costs and curb the emergence of infections and drug-resistant organisms.

Pharmacists’ role in combatting antimicrobial resistance

One of the main drivers of AMR is the widespread and inappropriate use of antimicrobials. Pharmacists are the custodians of medicines and are mandated to meet the healthcare needs of the population through the supply of safe, effective and quality medicines and providing of pharmaceutical care by taking responsibility for the outcomes of therapy. They have an important role to play in the community in that they often serve either as the first point-of-call for the patient in the healthcare-seeking chain, as well as a last contact when medicines are dispensed. In this gateway function, pharmacists have opportunities to providing information to the general public as well as clinicians in judicious antibiotic use and thus preventing unnecessary antibiotic use, which is strongly associated with increased resistance.

Figure 2 illustrates the role the pharmacist can play in response to the inappropriate use of antibiotics specifically.

In 2008, the International Pharmaceutical Federation (FIP) published a pioneering statement of policy control of antimicrobial medicines resistance. Similarly, the South African Pharmacy Council’s Good Pharmacy Practice (GPP) aims to strive for quality pharmaceutical services for all the people of South Africa. Although not explicitly to be used in relation to antimicrobials, the rules in the GPP serve as minimum standards with which the pharmacist can fulfil their role in antimicrobial stewardship. Lately, there have also been updated recommendations released by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) to complement current antimicrobial stewardship strategies.

The minimum roles of the pharmacist in encouraging judicious use of antimicrobials and minimising antimicrobial resistance in the different practice settings are cross-cutting across most sectors of pharmacy. Table 1 shows examples of the specific roles pharmacists can play in AMR in line with the building blocks of the national strategy framework for AMR in South Africa.

The goal of these efforts is always to improve health outcomes for the patient, i.e. reduced morbidity and mortality, minimise hospital-acquired infections, limit the emergence of drug-resistant organisms and lower healthcare costs.

Hospital pharmacist

In the clinical environment, pharmacists may play an oversight role amongst healthcare professionals by formulating and monitoring adherence to standard treatment guidelines, including rational antibiotic prescribing by clinicians. The pharmacist and the nurse can actively collaborate in AMS programmes in the ward, acute and outpatient setting, to optimise antimicrobial use and combat AMR. Ideally, doctors should be part of such an integrated team.

As a core member of a multi-disciplinary antibiotic stewardship committee, the pharmacist can also provide appropriate guidelines regarding empiric and prophylactic use of antibiotics through the use of evidence-based medicine principles. These include antibiotic cycling, de-escalation therapy, dose optimisation and/or parenteral to oral conversion when applicable. The hospital pharmacist through collaboration with the laboratory services, can ensure the availability of rapid diagnostic testing such as accurate point of care tests to guide clinicians on the most appropriate use of antibiotics.

The hospital setting is ideal for prospective audit and feedback after two or three days of treatment in order to ensure the right drug is prescribed at the right time for the right diagnosis. This is more so for targeted antibiotics such as those that treat emerging drug-resistant bacterial infections.

These activities require professional diligence through continuing education programmes of prescribers and dispensers as well as as prospective monitoring and evaluation to avoid irrational prescribing.

Community pharmacist

The community pharmacist has a vantage point in being able to directly initiate therapy. The pharmacist in this instance may recommend alternative treatment for minor infections and reassure patients of the inappropriateness of antibiotics for viral infections. The community pharmacist must exercise due diligence in upholding the law and not permit the over-the-counter sale of antibiotics. In instances when an antibiotic is indicated, the pharmacist can then advise the patient to complete the course and warn of possible side-effects or interactions in order to aid adherence. Technologies such as electronic measurement devices can be used to improve adherence to antibiotic therapy. The community pharmacist can teach community members to dispose of any unused medicines appropriately.

Academic pharmacist

Pharmacists in academia have a significant role to play in educating current and future pharmacists and other healthcare professionals in the appropriate use of antibiotics. They have an important role in research and continuing education programmes of prescribers and dispensers as well as prospective monitoring and evaluation to avoid irrational prescribing.
providers on the rational use of medicines and AMS. Although AMS training is included in the undergraduate pharmacy curriculum, a recent study amongst final year pharmacy students reported significant differences between the eight universities in the country, with 90% of students indicating that they would like more training on AMS. Central to their role in AMS, academic pharmacists can also develop curricula for continuing professional development in this field so as to improve current and future performance of all health practitioners as well as veterinarians. Academic pharmacists are in the ideal position to contribute towards collection and interpretation of surveillance data and conduct research, in collaboration with other members of the healthcare team.

**Industrial and wholesale pharmacist**

In their role in AMS, manufacturing pharmacists have an obligation to ensure the manufacture of safe, efficacious and good quality medicines. In addition, they should proactively seek to promote innovation and research on new antimicrobials as well as ensure the steady production of essential antimicrobials to meet supply. Pharmacists practising in a wholesale environment can ensure that only authorised channels of distribution are used to supply the medicines to hospital and community pharmacies in order to minimise the availability of counterfeit and substandard medicines, and the rerouting of essential antimicrobials to non-approved clients.

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**Figure 2. Inappropriate antibiotic use and the role of the pharmacist**

- **Prescribers**
  - Optimise antibiotic prescribing
    - Confirm **indication** for antibiotic use
    - Use **drug** (antibiotic) with narrowest spectrum
    - Correct **dose** according to renal and/or hepatic function
    - Dose **frequency** – therapeutic drug monitoring if required
    - **Duration** – should be evidence-based
    - **Route** – depends on site and severity of infection, absorption and whether an orally active antibiotic is available
    - De-escalation – convert from parenteral to oral use as soon as possible
  - Reinforce delayed prescription where appropriate
  - Use ‘high-dose short-course’ strategy
  - Use tools for clinical diagnosis

- **Pharmacist**
  - **Collaboration & cooperation**
  - **Communication and education**

- **Patient**
  - Prevent infection – hand hygiene
  - Reduce risk of infections – promote vaccination
  - Advice on self-limiting infections against bacterial and viral disease
    - Duration of symptoms
    - Symptoms which require medical attention
    - Self-care
  - Counselling and advice
    - Do not ask for antibiotics
    - Use antibiotics exactly as prescribed
    - Do not share antibiotics
    - Never save antibiotics for later
    - Do not buy antibiotics over the counter
  - Tell friends and family about antibiotic resistance
  - Provide information leaflets
  - Delay filling of prescription for uncomplicated respiratory tract infections

- **Public**
  - Use of antibiotics when not indicated e.g. treating minor infections or viral infections
  - Over reliance on empirical therapy when treating infections without laboratory confirmation
  - Indiscriminate use of broad-spectrum antibiotics to treat very susceptible bacteria
  - Unnecessarily prolonged use of antibiotics when no longer needed
  - Antibiotics given at the wrong dosages (under/over dosed)
  - Use of a wrong antibiotic to treat an infection
  - Patient and parental beliefs, fears and expectations
  - Counterfeit or sub-standard antibiotics
  - Ease of access to antibiotics by the general public without a prescription

- **Antibiotic resistance**
  - ↑ Health care costs
  - ↑ Drug-resistant organisms
  - ↑ Morbidity and mortality
# Table I. The role of the pharmacist in containing antimicrobial resistance

<table>
<thead>
<tr>
<th>Hospital pharmacist</th>
<th>Community pharmacist</th>
<th>Academic pharmacist</th>
<th>Industrial pharmacist</th>
<th>Regulators / health systems</th>
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<tr>
<td><strong>Enhanced surveillance</strong></td>
<td><strong>Antimicrobial stewardship</strong></td>
<td><strong>Infection prevention and control</strong></td>
<td><strong>Antimicrobial stewardship</strong></td>
<td><strong>Regulators / health systems</strong></td>
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<tr>
<td>• Monitor patient outcomes and provide information about incidence and prevalence of AMR</td>
<td>• Establish and enforce the prescribing on antibiotic prescription charts</td>
<td>• Key member of the hospital infection prevention and control committee</td>
<td>• Formulate and implement antimicrobial prescription charts for use at all health levels in the public and private sector</td>
<td>• Setup and implement national surveillance framework and development of indicators for AMR</td>
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<td>• Identify patients at risk of AMR</td>
<td>• Ward rounds to ensure dose optimisation based on patient characteristics and antibiotic susceptibility testing</td>
<td>• Ensure availability of cleaning agents and personal protective equipment for hospital staff</td>
<td>• Participate in expert committees formulating national EML and STGs</td>
<td>• Collate national antibiotic consumption data at all healthcare levels (private and public)</td>
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<td>• Post-prescribing audits to monitor antimicrobial consumption</td>
<td>• Monitoring of antibiotics use: surgical prophylaxis duration; de-escalation and reassessment of treatment need, hang time</td>
<td>• Encourage the use of single-dose packages of sterile drug products rather than multiple-dose containers</td>
<td>• Support continuous professional development in infection prevention and control and vaccination e.g. by developing online training materials on infection prevention and control and vaccination</td>
<td>• Overseeing role on medicines and diagnostics to ensure good quality medicines and diagnostic assays</td>
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<td>• Clinical pharmacists to conduct therapeutic drug monitoring (TDM) in collaboration with laboratory services in order to minimise adverse drug reactions</td>
<td>• Ensure access to EML, STGs and national antibiotic prescribing guidelines</td>
<td>• Enhance and encourage hand hygiene in the hospital setting in order to minimise transmission of hospital-acquired infections</td>
<td>• Strengthen pharmacovigilance systems and adverse drug reaction reporting</td>
<td>• Minimise pharmacy stock-outs to ensure that patient treatment is not interrupted</td>
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<td>• Minimise pharmacy stock-outs to ensure that patient treatment is not interrupted</td>
<td>• Develop hospital formulary with limited number of antibiotics in order to restrict the number and type of antimicrobials used</td>
<td>• Offer continuous training on hand hygiene</td>
<td>• Prospective monitoring and evaluation of prescribing habits and compliance to EML, STGs and antibiotic prescribing guidelines</td>
<td>• Conduct nationwide health awareness campaigns that promote the appropriate use of antimicrobials and the growing threat of AMR</td>
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<tr>
<td>• Prospective monitoring and evaluation of prescribing habits and compliance to EML, STGs and antibiotic prescribing guidelines</td>
<td>• Pre-authorisation for certain antibiotics, to ensure necessary oversight for appropriate use</td>
<td>• Educate and promote vaccination against viral and bacterial diseases</td>
<td>• Computerised clinical decision support</td>
<td>• Monitoring of antibiotics use: surgical prophylaxis duration; de-escalation and reassessment of treatment need, hang time</td>
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<td>• Timeous feedback and interventions to modify irrational prescribing</td>
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<td>• Support continuous professional development</td>
<td>• Minimise substandard and counterfeit antimicrobials in order to ensure good quality medicines</td>
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<td></td>
<td>• Promote use of algorithms to guide prescribers based on clinical signs and symptoms</td>
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<td>• Regulating contacts with pharmaceutical representatives to limit undue influence on prescribers</td>
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<td>• Develop tools to assist with clinical diagnoses in out-patient setting</td>
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<td>• Multi-disciplinary collaboration to develop and implement educational and behavioural interventions for appropriate prescribing</td>
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<td>• Active and passive surveillance for hospital-acquired infections, outbreaks and control</td>
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<td>• Programmes to ensure environmental safety i.e. clean water, sanitation, hygiene issues</td>
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18,22,23,25,27-35
Regulatory and health system pharmacist

Pharmacists can participate in the development of national policy, laws and guidelines which will promote appropriate use of antimicrobials and the implementation of such policies where they exist. In particular, they can collaborate with health-professional societies and associations to develop and facilitate the implementation of educational and behavioural interventions that will assist in rational antimicrobial use.

Furthermore, they can ensure legislation, which prevents dispensing without prescription, is enforced and that the antibiotics registered for use are safe, efficacious and of a good quality. Moreover, such pharmacists can enable an environment that ensures that there is minimum influence on prescribing and dispensing by the pharmaceutical industry.

Conclusion

Antimicrobial resistance is a major threat to public health. A post-antibiotic era is fast approaching, calling for an urgent and coordinated action by all stakeholders. South Africa’s AMR strategy framework with its four building blocks (AMR governance, enhanced surveillance, AMS, infection prevention and control) and strategic enablers, aims to ensure the appropriate use of antimicrobials by all healthcare professionals and in all health establishments. The framework provides an opportunity for pharmacists across all practice settings to get involved, collaborate and play a role in this important endeavour. Antimicrobial stewardship specifically has the potential of combating the threat of dwindling antibiotic resources while advancing pharmaceutical care. Pharmacists from all sectors of practice should proactively uphold the principles of rational antimicrobial use and participate in AMS programmes, within the multi-disciplinary healthcare team, and at all levels of care. It is in the interest of public health that change, collaboration and cooperation start with all of us.

References