Sir Alexander Fleming discovered penicillin in 1928, and as early as 1945 warned 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.”

In fact, resistant bacteria had been identified before the discovery of penicillin, yet until the first decade of the current century, scientists and clinicians were not up-to-the-minute about antimicrobial resistance (AMR). Antibiotic consumption increased disproportionally to population growth during 2000-2010 in the BRICS countries, of which South Africa is one. Global AMR has now reached a tipping point towards a post-antibiotic era, where common infections that were previously easily treated, now require antibiotics of last resort, or are untreatable.

AMR currently represents arguably the greatest public health threat globally and modelling suggests that the current 700 000 annual deaths due to drug-resistant infections will surpass 10 million per annum by 2050, with one person dying every 3 seconds, and a global estimated annual cost of 100 trillion US dollars, if the increase in resistance is not slowed. Despite implementation of antibiotic stewardship programmes, antibiotic resistance has continued to increase, reinforcing the urgency of all healthcare professionals to take ownership, and the importance of all countries to share and coordinate best antibiotic stewardship practices globally.

The 2014 Antimicrobial Resistance Global Report on Surveillance showed high resistance rates in bacterial pathogens in all six of the World Health Organization (WHO) regions (see Table 1). In Europe, 25 000 patients die each year from resistant bacterial infections and in South-East Asia, 1 child dies every 5 minutes from a resistant bacterial infection. The first WHO GLASS report for 2016-2017, identified that carbapenem resistance to Klebsiella pneumoniae has now spread to all regions of the world. Resistance of Escherichia coli (E. coli) to fluoroquinolones in the treatment of urinary tract infections has reached a point where treatment is ineffective in more than half of patients in many countries. Widespread resistance against the first-line treatment options for Staphylococcus aureus occurs worldwide and patients who contract resistant strains of S. aureus are estimated to be 64% more likely to die than people who contract a non-resistant strain. Resistance to last-resort treatment options has also been reported and includes third generation cephalosporins for treatment of gonorrhoea in at least 10 countries (including South Africa) and colistin for treatment of Carbapenem Resistant Enterobacteriaceae (CRE) in several countries and regions.
South African perspective

A systematic review on antimicrobial resistance in Africa revealed high levels of resistance to trimethoprim, amoxicillin and penicillin. The same review reported Klebsiella resistance of more than 50% to ceftriaxone and gentamicin; *Streptococcus pneumoniae* (*S. pneumoniae*) to co-trimoxazole; *S. aureus* to amoxicillin and oxacillin; and *E. coli* to amoxicillin, amoxicillin/clavulanic acid, ampicillin and co-trimoxazole in Southern Africa.6

The occurrence of resistance is also increasing in antibiotics of last-resort in South Africa.10 Carbapenems such as meropenem, imipenem, ertapenem and doripenem were antibiotics of last-resort for treatment of multi-drug resistant bacterial infections. However, resistance to these antimicrobials has necessitated a change to colistin and tigecycline as last-resort antibiotics.10

Analysis of carbapenem resistance-reporting publications between January 2000 and 20 May 2016 showed that an estimated 2315 carbapenem-resistant cases were reported (mostly in Gauteng followed by KwaZulu-Natal). Carbapenem-resistant organisms most frequently included *Klebsiella pneumoniae* (*n*=1138), *Acinetobacter baumannii* (*n*=332), *Enterobacter cloacae* (*n*=201) and *Serratia marcescens* (*n*=108).10

The most commonly reported carbapenemases include New Delhi Metallo-b-lactamase (NDM-1) (n=860) and OXA-48 (n=584) that were reported increasingly after 2012, following initial detection in 2011.10 The incidence of NDMs was estimated to be 34% in 2014, increasing to 59% in 2015.10 Most of these carbapenem-resistant cases had no travel history outside South Africa, suggesting that these strains were selected from increased carbapenem use within the country.10

The increased carbapenem resistance in South Africa has led to a rapid increase in the use of colistin and tigecycline.10 Resistance against both colistin and tigecycline has already been reported in 40 out of 45 carbapenem-resistant *Enterobacteriaceae* (CREs) and also in *K. pneumoniae*, *A. baumannii*, *S. marcescens* and *E. cloacae*.10 Carbapenemase-producing Enterobacteriaceae have spread throughout South Africa.6

The following resistance patterns and trends have thus far been identified in South Africa:12

- Vancomycin-resistant *S. aureus* and *Enterococcus faecium*12 (sensitivity in private sector of *E. faecium* to vancomycin varied between 33-100% depending on geographical location)8
- Penicillin-resistant *S. pneumoniae*12
- Methicillin-resistant *S. aureus* (MRSA)12 (about 75% of all *S. aureus* infections in one tertiary level paediatric hospital were MRSA)8
- Third-generation cephalosporin-resistant *E. coli* and *K. pneumoniae*12
- Carbapenem-resistant *Klebsiella pneumoniae*, *Enterobacter* spp. and *Pseudomonas aeruginosa*12
- Glycopeptide-resistant *Enterococcus*12
- Multi-drug resistant *Mycobacterium tuberculosis*, *A. baumannii*, *E. coli* and *P. aeruginosa*12

Although drug-resistant bacteria initially appeared in hospitals, resistant bacteria have also become a serious problem in the community, in particular the appearance of ampicillin-resistant *Haemophilus influenzae* and *N. gonorrhoeae*.12

There is an escalating prevalence of resistance to antimicrobials, including antibiotics of last resort in South Africa. It is particularly concerning that these data are not representative of the whole burden of resistance in South Africa. Due to the persistent and largely under-detected nature of resistant strains, specifically carbapenem-resistant strains in many South African hospitals, the possibility of outbreaks, interhospital and intrahospital circulation, and transmission via hospital staff and patients to homes and communities is very high.10

The WHO identified the need for coordinated action9 and issued the Global Strategy for Containment of AMR in 2001.7 This was followed by the establishment of the Global Antibiotic Resistance Partnership to help developing countries build capacity and establish policies to deal with the growing problem of AMR. A Global Action Plan on Antimicrobial Resistance was approved in May 2015 to produce national strategic plans to combat AMR. The goal of this action plan is “to ensure, for as long as possible, continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them.”1 The plan sets out the following five strategic objectives:5

- 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

In South Africa, The Global Antibiotic Resistance Partnership (GARP-SA) published a situational analysis of AMR in humans and animals in 2011. This was followed by the establishment of the South African Antibiotic Stewardship Programme (SAASP) in 2012 with the objective of promoting
appropriate antibiotic prescribing, education and engagement with the support of the National Department of Health. The SAASP has published guidelines on antibiotic prescribing as well as an antibiotic prescribing chart and also offers courses and educational material on antimicrobial stewardship. The National Department of Health published a South African Antimicrobial Resistance National Strategy Framework and implementation plan in 2014 based on antimicrobial resistance governance, enhanced surveillance, antimicrobial stewardship and infection prevention and control.

### Strategies to reduce antimicrobial resistance

#### Awareness and training

Multisite surveys of South African medical and pharmacist students’ perceptions and knowledge of antibiotic resistance and appropriate prescribing, demonstrated that final year students are inadequately prepared for the challenges presented by AMR and reported that students need more education on appropriate antibiotic use.

Less than two-thirds of final year medical students reported being familiar with the term “antibiotic stewardship” and only one-third felt confident to prescribe antibiotics. 92% agreed that antibiotics are overused and 87% agreed that resistance is a significant problem. However, less students thought that overuse (63%) and resistance (61%) were problems in the hospitals where they had worked.

Perceptions that antibiotic resistance is less of a problem in their local setting may contribute to inappropriate prescribing behaviours. Prescribing confidence was higher in students using prescribing guidelines, those familiar with antibiotic stewardship and those with more frequent contact with infectious disease specialists.

Formal lectures were amongst the least popular suggested methods to improve preparedness for antibiotic prescription, suggesting that other, more interactive, educational approaches, are required to complement traditional passive training. These approaches, which may include clinical case discussions and interactive e-learning, are generally considered to be more effective for influencing prescribing behaviours.

Targeted educational content is probably the most important in resource-limited settings. Several online educational tools and documents are available and Table 2 provides a list of documents available online in South Africa. The demand for education about antimicrobial use is evident from the fact that individuals from more than 124 countries accessed two online training courses on antimicrobial stewardship from Stanford University. Free educational resources are available from [https://med.stanford.edu/cme/learning-opportunities/antimicrobialstewardship.html](https://med.stanford.edu/cme/learning-opportunities/antimicrobialstewardship.html).

**Table 2: Documents, courses and websites providing South African training material on antimicrobial use**

<table>
<thead>
<tr>
<th>RESOURCES</th>
<th>TYPE OF EDUCATIONAL TOOL</th>
<th>WEBSITE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best Care Always Antibiotic Stewardship</td>
<td>Website with useful links</td>
<td><a href="http://www.bestcare.org.za/Antibiotic%20Stewardship">http://www.bestcare.org.za/Antibiotic%20Stewardship</a></td>
</tr>
<tr>
<td>FIDSSA (Federation of Infectious Diseases Societies of Southern Africa)</td>
<td>South African Antibiotic Stewardship Programme - Website with useful links</td>
<td><a href="https://www.fidssa.co.za/SAASP">https://www.fidssa.co.za/SAASP</a></td>
</tr>
</tbody>
</table>
As part of surveillance and research to improve understanding of AMR, the 2014 Antimicrobial Resistance Global Report on Surveillanceshowed high resistance rates in bacterial pathogens in all WHO regions (see Table 1). Development of the Global Antimicrobial Resistance Surveillance System (GLASS) Report was based on the Antimicrobial Resistance Global Report on Surveillance and was launched in 2015 as an effort to standardise and improve poor data surveillance. The GLASS-system requires reporting of AMR on the following eight organisms from blood, urine and stool samples as well as urethral and cervical swabs:

**Blood**
- Acinetobacter baumannii
- Klebsiella pneumoniae
- Staphylococcus aureus
- Escherichia coli
- Streptococcus pneumoniae

**Urine**
- Escherichia coli
- Klebsiella pneumoniae

**Faeces**
- Salmonella spp.
- Shigella spp.

**Urethral and cervical swabs**
- Neisseria gonorrhoeae

Diagnostic testing

Most antibiotics (75-80%) for systemic use in children and adults are prescribed in the community for acute respiratory tract infections (ARTIs) such as bronchitis, pharyngitis and sinusitis. Although most ARTIs are of viral origin with no indication for antibiotics, they still account for most of the antibiotics prescribed in primary healthcare with almost 60% of patients estimated to have received an unnecessary antibiotic. The overlapping clinical features of viral and bacterial infections dramatically reduce the ability of the prescriber to distinguish which patients would benefit from an antibiotic, underlining the need for tools to reduce diagnostic uncertainty at the point of care.

The lack of availability of sensitive, specific and cost-effective tests to distinguish between viral and bacterial infections is especially problematic at community practice level. The mere presence of bacteria at the suspected site of infection is not necessarily an indication for the administration of an antimicrobial. This is because the presence of bacteria in the absence of inflammation may be caused by bacterial colonisation or contamination and not necessarily be an ‘infection’. This implies that good clinical history and examination alone may not be sufficient and the judicious use of biomarkers such as point-of-care testing for C-reactive protein (CRP) may aid in diagnosis and reduce antibiotic prescriptions.

Fear of missing a bacterial infection is a strong motivator for prescribing antibiotics, whereas having access to point-of-care testing (POCT) to help differentiate the cause of fever, increases appropriate antibiotic use and decreases the time to initiation of appropriate antibiotic.

A Cochrane review concluded that POCT for biomarkers (e.g. CRP) to guide antibiotic treatment of ARTIs in primary care can reduce antibiotic use and be used as an adjunct to a doctor’s clinical examination without having a negative impact on patient-reported outcomes including recovery from, and duration of, illness. The practical implications for considering POCT and CRP in South Africa that will need more attention include:

- Validation of the POCT CRP assay to confirm performance specifications
- Costs of acquiring and maintaining desktop analysers including calibration and external quality control
- Training on daily operation of equipment
- Instrument storage specifications

One study in a rural public hospital in KwaZulu-Natal reported underutilisation of diagnostic laboratory services. Although access is not limited, the use of this service is impractical in this setting owing to the distance to the facility and the analysis itself. Typically, getting a microbiological laboratory report with a sensitivity profile takes 5-7 days from the date of receipt of the sample. The average duration of treatment for inpatients of seven days, showed that empirical treatment was successful in treating infections without the need for diagnostic testing. Although culture results in this instance was not shown to be beneficial for specific patients from whom samples were taken, microbiological analysis has a crucial public health benefit in terms of antimicrobial resistance surveillance and shaping of local infection control programmes.

**Reduce the incidence of infection**

The mainstay of AMR containment is infection control and prevention. Some simple measures that can be implemented include hand washing, adequate ventilation, improved sanitation and access to clean water. The judicious use of vaccines also prevents infections and reduces the need to use antimicrobials.

Bacterial vaccines directly reduce the need for antibiotics by providing direct protection against bacterial diseases from both antimicrobial-resistant and non-resistant organisms. Vaccines also provide indirect protection by reducing acquisition and sometimes colonisation and transmission rates that in turn lead to reduced spread of infectious diseases in the community.

Introduction of the pneumococcal conjugate vaccine (PCV7) in children in South Africa, achieved an 89% reduction in the incidence of invasive pneumococcal disease due to the PCV7 serotypes within 4 years following introduction (direct protection). In addition, there was also a 57% reduction of invasive pneumococcal disease in unvaccinated adults.
Impact of antibiotic stewardship in South Africa

In South Africa, the main barriers to implementation of antimicrobial stewardship programmes have been inadequate infectious disease expertise and resources and the rural geographical location of several hospitals in South Africa. A study in 47 private hospitals in South Africa across a diverse group of urban and rural hospitals assessed the reduction of overall antibiotic consumption through implementation of an antimicrobial stewardship strategy using existing resources. Strategies focused on interventions that addressed excessive consumption of antibiotics, including prolonged duration, multiple concurrent antibiotics and redundant coverage. Implementation was pharmacist-driven in consultation with doctors, nursing managers, hospital managers and clinical staff, including infection prevention practitioners. The study showed a sustained reduction of 18.1% in antibiotic consumption over a period of 5 years (1 Oct 2009 to 1 Oct 2014).

Another study performed in a South African public sector hospital also achieved a sustained reduction of around 18% in antibiotic use, mainly intravenous antibiotic use, over 4 years. Savings due to direct antibiotic use, which is strongly associated with increased resistance. Savings due to direct antibiotic use, which is strongly associated with increased resistance. Savings due to direct antibiotic use, which is strongly associated with increased resistance. Savings due to direct antibiotic use, which is strongly associated with increased resistance.

Who is responsible then?

In low- and middle-income countries such as South Africa, with limited human resources and where infectious disease specialists are not available at every hospital, a study has shown that antimicrobial stewardship can be implemented successfully by utilising non-infection specialists.

The guidelines on the implementation of the antimicrobial strategy in South Africa, the so-called “One Health Approach” calls for an integrative effort from multiple disciplines, including government sectors and partners working locally, nationally and globally to attain optimal health for people, animals and the environment. The implementation study in South Africa has shown that antibiotic stewardship initiatives can be driven by any member of the team provided the programme is sustainable and is supported by policymakers and stakeholders.
Nurses

Nurses are a potential cadre of healthcare professionals with a proven track record in antimicrobial prescribing in South Africa. Primary care nurses are at the frontline of antibiotic prescribing for management of common conditions in primary care and safely initiate and re-prescribe antiretroviral therapy without detrimental effect. Appropriate antibiotic use is written into the Practical Approach to Care Kit (PACK) and the Standard Treatment Guidelines and Essential Medicines List at different levels of the South African healthcare system.

Intensive care units (ICUs) have the highest proportion of patients vulnerable to infection and use the most antibiotics in the hospital setting. Research into the prevalence of infections in the private ICU sector found that an inappropriate antibiotic was prescribed in 60.8% of patients, the duration of antibiotic administration was inappropriate in 81.7% of patients and de-escalation was used in only 19.7% of patients. AMS has developed a proactive healthcare initiative to promote appropriate use of antimicrobial therapy and infection control in the ICU. The ICU nurse plays an important clinical role in infection control, monitoring patients to identify early signs of infection and the correct administration of antimicrobials.

In addition, the ICU nurse also plays an important organisational role in documentation and monitoring of patient records, including antimicrobial treatment, laboratory results, antibiograms and noting changes in doctors' instructions. This documentation and monitoring forms an integral part of the AMS programme. Nursing and non-nursing staff in the ICU setting felt strongly that the patients should be administered the correct antimicrobial treatment for an infection and that they had the responsibility to promote the interest of the patient by reminding specialists of the duration of treatment to facilitate de-escalation. Infection control nurses are also in the ideal position to play a collaborative role through constant contact with the patient and effective communication during their interactions with the doctor, pharmacist and microbiologist.

Nurses should be an important part of AMS, and monitoring of antimicrobial use should be done by hospital pharmacists, microbiologists, doctors and nurses.

Future strategies

Cellular hysteresis

Cellular hysteresis is a persistent change in bacterial physiology, reminiscent of cellular memory, which is induced by one antibiotic and enhances susceptibility towards another antibiotic. A recent study demonstrated that high level cellular hysteresis constrains evolving bacteria by:

- Increasing extinction frequencies
- Reducing adaptation rates
- Limiting emergence of multidrug resistance

The study used *P. aeruginosa* as a model and investigated three clinically relevant bactericidal antibiotics with distinct cellular targets: ciprofloxacin, gentamycin and carbenicillin. Cellular hysteresis was found to be most effective when antibiotics were changed within 12 to 24 hours, imposing specific selective pressure on bacteria that disfavors resistance mutations. Fast changes between antibiotics are key, because they create the continuously high selection conditions that are difficult for bacteria to counter. Pre-exposure to gentamycin, which is known to cause translational stress, protected cells from killing by carbenicillin, while pre-exposure to carbenicillin, which causes cell envelope stress, increased bactericidal activity of gentamycin. This emphasizes the importance of drug order for the design of effective treatment protocols. Further exploration of inducible physiological effects may help to find new ways of improving antibiotic therapy, using the available drugs in a rational and redefined way.

Nanotechnology

Nanotechnology can be used in different ways for the management of antimicrobial resistance:

- Nanoparticles can be coupled with existing antimicrobial agents for enhancements of their physiochemical behaviour against drug-resistant microbes. Nanoparticles target the bacterial cell wall. For example, silver nanoparticles can be coupled with the relevant antibiotics to enhance their antibacterial action through synergy.
- Colloidal forms of zinc, silver, copper and titanium are nanoparticles that can be used as antimicrobial. Nanoparticles affect the bacterial respiratory system and generate reactive oxygen species that ultimately leads to bacterial cell death.
Antimicrobial peptides (AMPs) are emerging antimicrobial agents. AMPs have been found in animals, microorganisms and plants and have a broad spectrum of antimicrobial activity, being particularly active against bacteria, fungi and protozoans. These potential antimicrobials work by interaction and insertion of AMPs into the cell wall and cellular membranes of microbes. Although they usually cause damage to cellular membranes, AMPs can also target other proteins, DNA, RNA and regulatory enzymes and seem to be a promising substitute for classical antibiotics. However, development of resistance is expected as soon as their use is implemented in clinical practice and it is therefore essential to better understand their mechanisms of action and resistance patterns before using AMPs as alternatives to conventional antibiotics.

### Conclusion

Microorganisms underwent Darwinian selection to develop some stringent mechanisms to escape the lethal effects of antimicrobial substances. Although antimicrobial resistance occurs naturally over time, usually through genetic changes, the misuse and overuse of antimicrobials is accelerating this process. The global burden of AMR has no signs of receding and although the eradication of AMR is not attainable, progression may be decelerated. Global antibiotic stewardship starts with individual stewards with a global perspective, reaching out and collaborating to share experiences, education and resources. Antibiotic stewardship models need to involve cadres of healthcare professionals including pharmacists, nurses and community health workers and this calls for each individual prescribing or issuing antibiotics to understand the societal burden of sub-optimal antibiotic use, take ownership and become an antibiotic steward.