Executive summary

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South Africa has faced many challenges over the past two decades, accomplishing profound positive changes in the social structure and government of the nation. This has not yet fully translated into better health for the population, however, particularly the poorest segment. In fact, the population has lost ground since the 1990s in virtually all important health indicators, leaving South Africa with a high burden of infectious disease.

Given current concerns, it would be foolhardy to place antibiotic resistance as an issue on a par with HIV/AIDS or other infectious diseases in South Africa. But it should take its place on the health agenda, nonetheless. In a country with as high a burden of infectious disease as South Africa, it is essential that first-line, affordable antibiotics remain effective for as long as possible. Fortunately, interventions to enable this can be fashioned to be low in cost, but these do not happen spontaneously. The goal of the Global Antibiotic Resistance Partnership (GARP) is to recognise the issues and recommend policy alternatives that are right for the time and place – South Africa in the second decade of the 21st century.

As with other shared resources, antibiotics consumed by an individual – whether the individual benefits from the antibiotic or not – 'use up' a bit of the effectiveness of that drug. As antibiotics become less and less effective, South African citizens will be forced to either pay more for newer drugs to replace the inexpensive standards or forgo treatment because it is too costly. That choice can be thrust upon the population sooner – years from now – or can be pushed into the future – decades from now, depending upon on our current stewardship of antibiotics now and in the near term. The growth in resistance can be curbed and even reversed, and the health of the public enhanced, by preventing many infections through vaccination and by better targeting antibiotic use for curable bacterial infections, eliminating much of the current inappropriate use for viral, fungal or parasitic illnesses – which are unresponsive to antibiotics.

GARP, co-ordinated by the Center for Disease Dynamics, Economics & Policy (CDDEP), aims to develop policy responses to manage antibiotic effectiveness through the actions and recommendations of national working groups of experts, such as the contributors to this situation analysis. They have begun by assembling what is known about the rates of antibiotic effectiveness, the ways in which antibiotics are used by people and in agriculture, and have considered the 'drivers' of antibiotic use, hence, resistance. The next step, begun here, is to fully analyse the interventions that will be feasible, affordable, and most effective in the South African context. Similar processes are under way in three other countries: India, Kenya and Vietnam.

Burden of infectious disease

All countries use antibiotics because bacterial infections occur everywhere. South Africa has a high burden of infectious diseases, including a large portion of bacterial origin, but that is not all. The country is said to face a quadruple burden of disease, involving the HIV/AIDS epidemic, other infectious diseases, injuries, and non-communicable diseases. About 29% of the population is infected with the virus and it accounts for 26% of deaths, the single most important cause that is five times greater than the next largest single cause of death.

In absolute terms, South Africa has the fourth-largest tuberculosis (TB)-infected population in the world (behind India, China and Indonesia) and bears 28% of the global burden of TB related to HIV. In young children, diarrhoea and pneumonia still cause 15% of deaths.

The consequences of antibiotic resistance on clinical outcomes, through either treatment failures or the development of more virulent infections, are largely unknown. Therefore, the full burden of antibiotic resistance on health in South Africa remains to be assessed. It is clear, however, that effective antibiotics must be available if the population is to maintain and improve its health.

Antibiotic resistance in South Africa

Antibiotic resistance is driven by many factors, many of which are associated with inappropriate antibiotic management and consumption. The regulatory environment, knowledge of health care workers and patient expectations all influence antibiotic use. Furthermore, misuse is exacerbated by the impoverished living conditions characterising the majority of patients suffering from common bacterial infections, including insufficient supply of antibiotics to the public sector, the use of degraded and expired medicines, and unreliable access to diagnostic facilities and clinicians.

High levels of antibiotic resistance already exist in South Africa. Paradoxically, despite poor health status, South Africa has had the most active surveillance for antibiotic resistance of any African country. The details of what is known, including the many mechanisms of resistance, are included in the separate sections of this situation analysis. Data from elsewhere in Africa are also included. The bullets below summarise what is known of the rates of resistance in South Africa.

Respiratory and meningeal pathogens

- *Streptococcus pneumoniae*. Penicillin-resistant pneumococci have been reported with particularly high frequencies in South Africa since the mid-1970s and in other African countries since the 1980s. Penicillin resistance in South Africa remains mainly intermediate in level, with only a low prevalence of fully resistant isolates. Resistance levels have increased annually, but the levels are clearly dependent on the site of specimen collection, the age of the patient, and location within the country. The emergence of multidrug resistance was first reported in Soweto, South Africa, in 1977. Subsequently, multidrug resistance emerged globally. In South Africa in 2004, a third of pneumococcal isolates studied displayed multidrug resistance.
- *Haemophilus influenzae*. The increasing prevalence of resistance among *H. influenzae* isolates to commonly used antibiotics is of concern. Resistance to penicillin is high, with prevalence rates of >45% reported in some settings.
- *Neisseria meningitidis*. Resistant isolates from two patients were reported in 1987, but these strains were lost. National laboratory-based surveillance for invasive meningococcal disease began in 1999. In specimens collected from 2001 to 2005, a relatively low prevalence, 6% of isolates, was found to be intermediately resistant to penicillin. No isolates tested were fully resistant. In 2009, South Africa reported its first case of fluoroquinolone-resistant *N. meningitidis*.

Enteric pathogens

- Non-typhoidal *Salmonella*. From 2003 to 2010, resistance has *declined* among non-typhoidal *Salmonella* isolates: to ampicillin, from 64% to 16%; to chloramphenicol, from 47% to 14%; to

ceftriaxone, from 40% to 10%; and to nalidixic acid, from 38% to 10%.

- *Salmonella* Typhi. *S.* Typhi resistance to ampicillin has fluctuated from 10% of isolates in 2003 to 40% in 2006. At the end of 2010, the rate was back to 10%. Resistance to sulfamethoxazole has remained consistently around 30%. Resistance to chloramphenicol has more than doubled, from 5% in 2003 to 13% in 2010. In 2009, 20% of isolates tested were resistant to nalidixic acid, the highest level since 2003. Over this same 8-year period, the proportion of ciprofloxacin-resistant *S.* Typhi has been zero, except in 2009 when that proportion rose to 2%.
- *Shigella*. Resistance to older antibiotics has been constant from 2003 to 2010; 50% for ampicillin, 50% for tetracycline, 80% sulfamethoxazole and 40% for chloramphenicol. For what is now first-line treatment, resistance to nalidixic acid has been found in 1% of isolates, and for both ciprofloxacin and ceftriaxone the proportion of resistant *Shigella* isolates has been just below 1%.
- *Vibrio* spp. In an outbreak in 2008 - 2009, all isolates were resistant to co-trimoxazole, 48% to chloramphenicol, 100% to nalidixic acid, 3% to tetracycline and 39% to erythromycin. In a second outbreak in 2008, in a different area, isolates were resistant to ampicillin, amoxicillin-clavulanate, sulfamethoxazole, trimethoprim, chloramphenicol, nalidixic acid, kanamycin, streptomycin and tetracycline, which was initially the antimicrobial agent of choice in the treatment of cholera in Africa. The isolates were susceptible to ciprofloxacin and imipenem. Resistance to the third-generation cephalosporins ceftriaxone and ceftazidime was observed.
- *Escherichia coli*. Consistently less than 1% of all diarrhoeagenic *E. coli* isolates are resistant to tetracycline, ampicillin, amoxicillin-clavulanate, co-trimoxazole, trimethoprim, sulfamethoxazole and chloramphenicol.

Sexually transmitted infections (STIs)

Of the many bacteria that cause STIs, antibiotic resistance is an issue only for *Neisseria gonorrheae.*

- *N. gonorrhoeae*. Gonococci isolated in South Africa remained fully susceptible to ciprofloxacin, the former first-line therapy, until 2003 when quinolone-resistant *N. gonorrhoeae* was reported from an STI clinic in Durban. Resistance ranged from 0% in Pretoria to 24% in Durban, although all isolates tested appeared susceptible to cephalosporins. Further rises were reported from Durban (24% in 2004, 42% in 2005), Pretoria (0% in 2004, 7% in 2005), Cape Town (7% in 2004, 27% in 2007) and Johannesburg (11% in 2004, 32% in 2007). Revised national guidelines, issued in 2008, named new cephalosporins as first-line treatment.

Hospital-acquired infections (HAIs)

Various groups currently collect data on antibiotic resistance in HAIs. These include the South African Society for Clinical Microbiology, private sector antimicrobial resistance (AMR) data collaborators, the Antimicrobial Resistance Reference Unit (AMRRU) of the National Institute of Communicable Diseases (NICD), Best Care...Always!, and the Division of Hospital Epidemiology and Infection Control of the National Health Laboratory Service (NHLS) (Central Region).

In both public and private sector hospitals, rates of resistance among the most common Gram-negative bacteria are very high. Gram-negative resistance to the carbapenems is common in hospitals with major intensive care units. The extent of the problem of HAIs in all categories of South African health care facilities remains to be determined. Furthermore, information about the clinical impact of AMR in patients infected with HAI-associated pathogens is urgently needed. HAIs represent a global crisis, but fortunately one for which interventions exist and are beginning to be implemented in South Africa, at least in some hospitals.

Surveillance for antibiotic resistance

South Africa has the most active antibiotic surveillance of any country in Africa. In the public sector two main groups, with contributions from other parties, have been active during the past decade: the Group for Enteric Respiratory and Meningeal disease Surveillance in South Africa (GERMS-SA) and the National Antibiotic Surveillance Forum (NASF)/South African Society for Clinical Microbiology (SASCM). The STI Reference Centre, in collaboration with the National Department of Health (NDoH), also conducts surveillance. NASF/SASCM collects data on selected invasive pathogens isolated from blood and cerebrospinal fluid specimens at academic hospitals. The participating laboratories, which participate voluntarily, have been principally those serving academic tertiary care hospitals.

The NASF/SASCM system has its strengths, but is limited by lack of clinical information on cases, variability in analytics, the inability to differentiate between community- and hospital-acquired infections, the limits on population coverage, differences in methods, etc. These are, however, being addressed by initiatives identified at a September 2010 workshop.

Private sector AMR data are generated through a collaborative effort involving private pathology (microbiology) laboratories that use a common laboratory system, Meditech, that enables all participants to use a standardised and reproducible means of data extraction for the generation of AMR reports. As for the NASF/SASCM system, there are both advantages and disadvantages to this approach.

AMRRU of the NICD introduced, in July 2010, a laboratory-based AMR surveillance (LARS) system to elucidate the epidemiology of AMR HAI-associated *Staphylococcus aureus* and *Klebsiella pneumoniae* isolates collected from patients at designated sentinel sites throughout South Africa. Furthermore, full characterisation of the resistance mechanisms of these isolates, as well as their molecular epidemiology, will be determined.

GERMS-SA collects data in three areas: AIDS-related opportunistic infections, epidemic-prone diseases and vaccine-preventable diseases. GERMS-SA regularly audits participating laboratories for quality and completeness. The stored isolates form can be accessed for special studies that are conducted periodically. Germs-SA produces an annual report, as well as a quarterly surveillance bulletin and numerous publications, maintaining an extensive database on antibiotic resistance.

The Enteric Diseases Reference United (EDRU) collects data on patients presenting throughout South Africa with both invasive and non-invasive diarrhoea-causing bacteria. EDRU collates patient and isolate information under a single record, compiled from 2003 onward. EDRU attempts to represent the entire country by offering free serogrouping, serotyping and antibiotic susceptibility testing to all diagnostic laboratories throughout the country.

Since it was started in 2003, the STI Reference Centre has tested *N. gonorrhoeae* isolates for antibiotic susceptibility, collected from 270 sites across the country. It has played a leading role in the development of the Gonococcal Antimicrobial Surveillance Programme (GASP) in Africa, a global programme co-ordinated by the World Health Organization (WHO). It has supported isolate collection and laboratories in Namibia, Zimbabwe, Madagascar and Tanzania, providing technical assistance and training.

Several important studies have also been conducted in the private sector. Currently, the Federation of Infectious Diseases Societies of Southern Africa (FIDSA) conducts surveillance for various pathogens, reported on their website.

The regulatory environment and drug supply

The South African National Drug Policy (NDP) was developed as a framework to remedy the disparities that existed in 1990, to ensure an 'adequate and reliable supply of safe, cost-effective drugs of acceptable quality to all citizens of South Africa and the rational use of drugs by prescribers, dispensers and consumers'. The inequities were vast, however, and will be dealt with for many years before the vision of the NDP becomes reality. The players include the Medicines Control Council (MCC), which is responsible for registering and relicensing medicines and for ensuring that domestic drugs are produced following good manufacturing practices (GMP).

Quality testing is conducted by universities under contract with the MCC because no government laboratories exist for this purpose. As for counterfeits, an estimated 1 in 5 medicines, most imported from India and Pakistan, are thought to be fakes. A small team is charged with investigating this issue, but only one successful prosecution had been completed by 2010.

The government has issued an essential drugs list (EDL) and standard treatment guidelines (STGs), which directly address the use of antibiotics in the public sector. In the private sector, formularies play this role, but reportedly their use is not enforced and they lack influence. The STGs and EDL form part of the country's 'essential drugs concept', and are viewed as critical aspects of national health policy. However, the prevalence of resistance has not played a role in the development of the South African STGs or EDL. When the expert committees compiled the documents, they did so without the benefit of surveillance studies or even sentinel-site data. Given the high burden of bacterial infections in the public health system as a result of the HIV/AIDS epidemic, researchers recommended that surveillance data be collected and utilised to inform amendments to the present STGs.

The NDP aim of developing 'human resources to promote the concepts of rational drug use' is enabled by pharmaceutical support staff appointed to ensure an optimal distribution chain. Multidisciplinary hospital pharmacy and therapeutic committees (PTCs) are recommended in the public and private sector to ensure efficient and cost-effective medicine supply and use by compilation of a hospital formulary and good supply-chain management. By law, only licensed practitioners may prescribe and/or dispense antibiotics. By and large, and unlike the situation in many other developing countries, antibiotics are available only on prescription and generally cannot be purchased over the counter at pharmacies and shops.

Antibiotic use in animals

Antibiotics for use in animals are regulated by the Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act (Act 36 of 1947), administered by the Department of Agriculture, Forestry and Fisheries, and the Medicines and Related Substances Control Act (Act 101 of 1965), administered by the NDoH. The older law lists antibiotics that can be purchased by the public – 'stock remedies'– without the assistance of a veterinarian and the newer one covers all other veterinary medicines (though some antibiotics may fall under both statutes).

As in many countries, it is very difficult to obtain an accurate estimate of the amount of antibiotics used in livestock production in South Africa. A recent study reports that the greatest volume of antibiotics are used in intensively farmed poultry (including broilers for meat and layers for eggs) and pigs, followed by feedlot cattle and dairy cows.

The most frequent uses of antibiotics by weight (as measured by sales) were for treating and preventing diseases in poultry and pigs, and as growth promoters generally. Tylosin, one of four growth promoters banned in Europe, was the most extensively sold antibiotic in South Africa, according to the recent survey. It is primarily administered through animal feed at sub-therapeutic levels and is available over the counter as a stock remedy. The survey found that about two-thirds of the antibiotics used were administered in feed.

Only a few relatively recent surveys and reports on antibiotic resistance in isolates from animals in South Africa have been carried out. The studies are small and clustered in the Johannesburg and Pretoria area. They vary in choices of antibiotics tested and many other parameters, and in their results.

A surveillance system for antibiotic use in animals is currently operating, based on an Office International des Épizooties (OIE) call to member countries, made in 2001 by the OIE Regional Commission for Africa. The South African National Veterinary Surveillance and Monitoring Programme for Resistance to Antimicrobial Drugs (SANVAD) released a report in 2007 demonstrating rates of resistance that were generally higher than those reported for Europe for *E. coli* and *Enterococcus*.

Efforts to address antibiotic resistance in the human population

A number of intervention strategies exist in South Africa to address the problem of antibiotic resistance in South Africa. These can be broadly divided into three categories: (*i*) those that monitor the extent of the problem and trends of AMR with the aim of informing key policy makers and opinion leaders on how to spare the currently fragile antimicrobial armamentarium – i.e. *surveillance* activities; (*ii*) those designed to reduce the burden of infectious diseases in susceptible populations and, where appropriate, reducing the demand and potential overuse or misuse of antibiotics – i.e. *vaccination* strategies; and (*iii*) those aimed at containing AMR, thus preventing spread of resistance – i.e. *infection prevention and control* activities.

Surveillance

Current AMR surveillance activities have been briefly mentioned in this executive summary. South Africa has a good start on antibiotic resistance surveillance. However, AMR needs to be urgently profiled in regional (non-academic) facilities providing all levels of health care. The information acquired from this research must be used to inform, and be incorporated into, STGs and EDLs as this is currently not being done.

Vaccination

Vaccination reduces the demand for antibiotic treatment of certain vaccine-preventable bacterial infections and significantly reduces morbidity and mortality in susceptible at-risk populations. Furthermore, some viral diseases, e.g. rotavirus diarrhoea, are vaccine preventable, and inappropriate use of antibiotics for such clinical conditions again results in decreased appropriate use of antibiotics.

The current South African Expanded Programme on Immunization (EPI) includes vaccines against the six vaccine-preventable diseases, hepatitis B, *H. influenzae* type b (Hib), pneumococcal disease (currently a 7-valent conjugate vaccine), and rotavirus (Rotarix). Both the Hib (introduced in 1999 as part of the EPI) and pneumococcal vaccines have significantly decreased rates of invasive infections in children.

The Respiratory and Meningeal Pathogens Research Unit situated at Chris Hani Baragwanath Academic Hospital has focused closely in recent years on vaccine-preventable diseases other than pneumococcal, and the unit has evolved to include a vaccine-preventable diseases

research portfolio. Much work has focused on the differences in vaccine responses between HIV-infected and uninfected children to pneumococcal conjugate vaccine, *H. influenzae* type b conjugate vaccine, rotavirus vaccine, and parainfluenza virus type 3 live-attenuated vaccine. Vaccination strategies in adults have also been explored in studies conducted by the unit. Influenza vaccination studies in pregnant women are in progress, and plans are under way to conduct a *Streptococcus agalactiae* vaccination study in pregnant women attending antenatal clinics in Soweto in the near future.

Infection prevention and control

Infection prevention and control (IPC) is listed among the top four health priorities identified by the NDoH that are of critical importance for South Africans. Overcrowding in and understaffing of health care facilities are important factors that fuel HAI outbreaks. Although in many health care facilities a nurse is identified as having to provide IPC support he/she is often burdened with numerous other nursing activities precluding him/her from giving this important discipline the attention it deserves. In an attempt to meet the training needs of IPC practitioners, several training institutions in both the private and public sector offer basic, certification, diploma and postgraduate courses in IPC.

Data on local and national prevalence or incidence of HAIs are either limited/inadequate or lacking. For IPC to receive the priority that it deserves it is imperative that research to determine the extent and cost of HAIs is conducted urgently. Implementation and evaluation of appropriate intervention strategies to minimise HAIs and prevent the spread of AMR pathogens will obviously follow.

Finally, antibiotic stewardship is one of five interventions prioritised by the Best Care…Always! Campaign (BCA) launched in 2009, which has become a focused, national patient safety and quality improvement campaign active in both the private and public sectors and endorsed by professional societies as well as by provincial and national government. BCA's major focus, the reduction of preventable health care-associated infections (central line-associated bloodstream infection, ventilator-associated pneumonia, catheter-associated urinary tract infection and surgical site infection) reduces the need for antibiotic treatment, thus alleviating selective pressure leading to AMR, and is therefore synergistic with antibiotic stewardship.