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- **Global Antibiotic Resistance Partnership**

  SITUATION ANALYSIS: Antibiotic use and resistance in South Africa

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The Global Antibiotic Resistance Partnership (GARP)

Antimicrobial resistance (AMR) is an important public health concern shared by developed and developing countries. In developing countries the burden of infectious diseases is greater and exacerbated by limited access to, and availability and affordability of, antimicrobials required to treat infections caused by AMR organisms. With drugs not listed on the essential drugs list (EDL), problems of increased morbidity, costs of extended hospitalisation and mortality are extremely serious. The problem of susceptibility to and spread of infections caused by multidrug-resistant (MDR) infectious agents is fuelled by factors such as limited access to clean water and sanitation to ensure personal hygiene, malnutrition, and the HIV/TB epidemic.

AMR is a consequence of complex interactions of many factors, including inappropriate use (clinical indication, choice, administration and dosing) and poor quality of antimicrobials, inadequate infection prevention and control, empirical treatment prescribed because of inadequate laboratory support, problems with the supply chain, increased mobility of people as a result of ease of travel and escape from conflict zones, patient non-compliance in taking antimicrobials, and the use of antimicrobials in agricultural and veterinarian animal settings. In contrast to most developed countries, there are scant data on the extent of the problem and trends of AMR in developing countries, including South Africa.

In South Africa, considerable AMR information can be found, or mined, from South African experts in the field and from public and private health sector data sources. 'Classic' community-acquired infections such as sexually transmitted infections (STIs), opportunistic HIV/AIDS-related infections (e.g. cryptococcosis), specific enteric infections, and those caused by respiratory and meningeal pathogens (with particular, but not exclusive, focus on pneumococcal disease) have been researched in depth. Considerable information is available on the AMR challenges posed by some of these infections. Health care-associated infections, particularly *Klebsiella pneumoniae* and *Staphylococcus aureus* from bloodstream isolates, are being monitored for their AMR profiles and trends.

National AMR surveillance activities in South Africa have focused predominantly on data available from the National Antibiotic Surveillance Forum (NSAF), superseded by the current South African Society for Clinical Microbiology (SASCM), in the public health care sector. The NSAF (SASCM) reports data from eight microbiology laboratories affiliated to academic centres nationwide. Although this approach provides useful data, it has several limitations, e.g. data are only collected from large academic centres. Since this does not profile AMR in the general population attending primary, secondary and non-academic tertiary health care facilities, it precludes the possibility of assessing the true extent of the problem of AMR countrywide. The private sector carries out surveillance of AMR in pathogens isolated from various sources. Access to these data, and their limitations, are highlighted in part V (Surveillance activities) of this AMR situational analysis issue of *SAMJ*.

No discussion on AMR is complete without considering the impact of antimicrobial use in the veterinary sector. Although the impact on the development and spread of resistance from use in animals is debated globally, it is generally accepted that it is prudent to reduce unnecessary use. Valuable work done in this regard is discussed in part VI (Antibiotic management and resistance in livestock production).

In order to slow the spread of AMR among our population, it is clear that interventions such as immunisation and infection prevention and control programmes should be given high priority at national, provincial and local levels. Limiting the unnecessary use of antimicrobials and introducing systems of checks and balances to monitor misuse or overuse of antimicrobials are crucial to limit the problem of AMR. In addition to those of doctors and nurses, the roles of the infection prevention control practitioner and the clinical pharmacist must be enhanced to assist prevention of transmission of MDR pathogens and to curb inappropriate/incorrect use of antimicrobials.

Ultimately, South Africa's contribution in investigating strategies and solutions to curb AMR does not end at national level. AMR is of global concern and some of the issues and solutions that we discover will undoubtedly be of interest and relevance in other countries. Thus we embrace our role as a founding country in an active and ongoing collaboration with the Global Antibiotic Resistance Partnership (GARP), whose mission, vision and proposed phases of work with regard to AMR are described in part I of this issue.

Finally, this is the first document to be published in South Africa that attempts to bring together all the initiatives, research and proposed future directions for dealing with AMR in our country. I thank all the contributing authors for the outstanding work that they have done, and will continue to pursue.

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Executive summary

Authors: **H Gelband, A G Duse**

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.

Part I. The Global Antibiotic Resistance Partnership (GARP)

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Keywords: antibiotic (antimicrobial) resistance

The global problem of antimicrobial resistance is particularly pressing in developing countries, where the infectious disease burden is high and cost constrains the replacement of ineffective antibiotics with newer, more expensive ones. Gastro-intestinal, respiratory, sexually transmitted and hospital-acquired infections are leading causes of disease and death in the developing world; their management is compromised by the appearance and spread of resistance. Actions taken now can slow the spread of resistance without impairing access to antibiotics when they are appropriate. These, as well as extending access where it is currently inadequate, are the ultimate aims of the Global Antibiotic Resistance Partnership (GARP).

Drug resistance is usually viewed as a medical problem, but the causes of resistance – at least the pace of escalation – are also cultural and economic. Patients, physicians, veterinarians and medicine retailers have little motivation to weigh up the negative impact of their use of antibiotics on others. This is especially the case where alternative treatments are few or non-existent and the consequences of inappropriate use are likely to occur in the future. Standard government responses, such as increasing surveillance and launching public information campaigns on the hazards of resistance, while a necessary part of an overall policy response, are unlikely to work on their own. To be effective, policy solutions must alter incentives for patients, physicians and others in the health care system to act in society's best interests. Evaluating policy solutions involves understanding the epidemiology of infectious diseases in populations and making sure that changes are beneficial, or at least not detrimental, immediately *and* in the longer term. Research evaluating focused, context-specific policy solutions is a first step. Translating these policy solutions to policy action is the second.

Antibiotic resistance does not top any list of national problems, and the strategies proposed should not drain resources from more pressing concerns. At its best, controlling antibiotic resistance should not involve extra cost. In the long run, and maybe even in the shorter term, it is likely to save money and save lives.

Country-specific goals

Drivers of antibiotic resistance are multifaceted and measures to address them must consider the specific conditions of a country, including the health care system, the socio-economics of the populace, the strength and reach of regulatory authorities, and even geography. GARP, funded through a grant from the Bill & Melinda Gates Foundation, aims to define policy solutions and opportunities by investigating the particular contexts of four target countries: India, South Africa, Kenya and Vietnam. In each country, national working groups, with support from the Center for Disease Dynamics, Economics & Policy (CDDEP), have developed a set of strategies tailored to local conditions, based on the information compiled and analysed in this report. The strategies encompass two basic approaches: first, to target the use of antibiotics in human health and livestock production better; and second, to reduce the demand for antibiotics by reducing the incidence of infections in the hospital and community, and on the farm. The strategies will be discussed and debated by a wide range of interested parties from government and civil society near the end of the process. A subsequent phase will involve implementation of the agreed-upon policy strategies in the four countries, and extension to other countries.

GARP inaugural meeting

GARP-South Africa was launched at the Spier Estate in Stellenbosch on 8 - 9 February 2010. Professor Adriano Duse, Chair of the GARP-SA Working Group and Director of the Department of Clinical Microbiology of the University of the Witwatersrand, led a gathering of 40 experts from the clinical, research, pharmaceutical, veterinary and policy spheres, all with an interest in preserving the effectiveness of antibiotics for the greater good. Professor Keith Klugman of Emory University, chair of the GARP International Advisory Group, outlined the scope of the problem of antibiotic resistance globally and in sub-Saharan Africa, while the remaining sessions focused on levels of antibiotic resistance at particular sites, national surveillance efforts, and interventions aimed at promoting rational antibiotic use.

Drs Adrian Brink and Colleen Bamford described strong initiatives aimed at curbing antibiotic resistance in both the public and private sectors. Dr Anne von Gottberg presented on surveillance for meningitis and respiratory pathogens, Dr Karen Keddy on enteric pathogens, and Professors Anwar Hoosen and David Lewis on antibiotic resistance in patients with sexually transmitted infections. Mr Andy Zoepke, from the South African medical device company, Smith & Nephew, took the meeting in a different direction, exploring the role of topical antibiotic preparations for wound care and burns. These products provide substitutes for systemic antibiotics, reducing exposure of commensals and thus the unnecessary spread of resistance elements. A national surveillance system, the fate of which is not yet known, was proposed and described by Dr Olga Perovic. Professor Sabiha Essack described her work documenting increasing levels of antibiotic resistance from district to regional to tertiary hospitals in KwaZulu-Natal. These findings are discussed in part IV of this report.

The importance of antibiotic use in animals in the development and spread of antibiotic resistance in humans is a perennial topic for debate. Dr James Oguttu reported relatively high levels of resistance to a range of antibiotics (including quinolones not used in poultry) in *Escherichia coli* organisms from the gastro-intestinal tracts of slaughtered broilers raised in factory farm conditions that included antibiotic use. Dr Maryke Henton expanded on antibiotic use in other farm animals (and provided evidence to dismiss aquaculture use as a problem), and Dr Jackie Picard ended the veterinary session with a look at 2 years of recent surveillance data, showing high levels of resistance to a variety of antibiotics of human significance. The data from this session are presented in part VI of the report.

Presenters also discussed the pharmaceutical industry and interventions to reduce bacterial disease and resistance. A window into the antibiotic market was opened by Mr Deon Benjamin from Sanofi-Aventis, the largest seller of these products in South Africa by sales value. Sales appear to be increasing for both patented and some generic antibiotics, with more detail promised to separate out effects of price and volume. Vaccines that prevent infectious diseases clearly save antibiotics, and the status of vaccines deployed, on the shelf and in development, was reviewed by Professor Anwar Hoosen. Dr Gary Kantor spoke about Best Care…Always! (BCA), a national campaign recently begun by Discovery Health, and its emphasis on infection-control practices and 'antibiotic stewardship' by hospital physicians as elements of the campaign. Completely voluntarily, 137 hospitals have signed on for at least one intervention. If successful, BCA can provide

a platform for extending work on reducing antibiotic resistance. Parts III and VII review information from these discussions.

Finally, the meeting reviewed the work of other GARP (India, Vietnam, Kenya) and sub-Saharan African (Ghana, Uganda) countries, as well as activities of the Alliance for the Prudent Use of Antibiotics (APUA) and ReAct, represented by Drs Anibal Sosa and Otto Cars, respectively. In most respects, South Africa has a head start, at least in information.

The meeting closed with a discussion on the next steps, concluding that the first priority was consolidating what is and is not known about antibiotic resistance. The importance of forming a GARP-SA Working Group was also highlighted. The product of these decisions is found in this report – a situation analysis on antibiotic use and resistance in South Africa, authored by the GARP-SA working group.

Global efforts

In addition to country-specific work, GARP is developing tools and conducting research in support of a global effort to understand, quantify and address antibiotic resistance. With collaborators, CDDEP is working on methodology to estimate the health and economic burden of disease, including mortality, attributable to antibiotic resistance. Surprisingly, the required methods do not yet exist. The aim is to develop an approach that can be used in all countries of the world with a minimal amount of information.

A second major thrust is developing a mathematical model of pneumococcal disease – 'PneuMOD' – that can be used to examine strategies for curbing the evolution and spread of antibiotic resistance and to compare modalities. At the heart of most ideas for controlling antibiotic resistance is the notion that the way antibiotics are used and their level of use in a population drive the development and spread of antibiotic-resistant organisms. Mathematical models play a useful role in highlighting policies that offer the greatest potential, even where information is insufficient to complete the analyses. At a minimum, the information needed can be identified and the necessary mechanisms set in motion.

Part II. Health and economic context

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Keywords: **health indicators; demographic indicators; economic indicators; health sector organisation; health services**

This overview of South Africa's demographic profile, economic development and health system provides the context in which to view the situation of antibiotic access and resistance. It presents information on national health policy and governance, infrastructure and human resources. The presence and utilisation of these features within the health system are discussed in relation to access to essential medicines, with a particular focus on antibiotics.

Demographics and economy

Demographic and social context

With an estimated population of 49.9 million, South Africa is a nation of diverse cultures, languages and religious beliefs.[1] Approximately 61% of the population live in urban areas (2008) compared with the regional urbanisation levels of 37%. The median age is a relatively young 24 years (2008), similar to that of other middle-income countries such as Mexico (26) and Brazil (29). Population growth has declined, dropping from 2.4% in 1994 to 1.06% in 2009. This reflects the decreasing total fertility rate in the country, which went from 6.7 births per woman in the late 1960s to about 2.4 in 2010, and was among the lowest total fertility rates reported for the whole of sub-Saharan Africa.

Decreasing fertility levels are also mirrored in the age profile of the population. Unlike most countries in the region, South Africa faces a high ageing index, defined as the number of people aged 65 and over per 100 youths under the age of 15. The index varies considerably, however, when disaggregated by population group: it is highest among whites, moderate among Indians and lowest among the black population.

South Africa instituted a 'no-fee' school system in the last decade. As a result, the percentage of adults without any schooling has dramatically fallen from 18% in 2001 to 7% in 2010. There remains, however, a high degree of inequality in access to education by region and racial group. Housing conditions vary as well. Although 83% of households are connected to electricity nationally, households relying on wood or paraffin remain high in Limpopo (54%) and the Eastern Cape (41%). Most households have access to piped water, with the national average at 89% in 2009. The Eastern Cape, however, lags with only 75% access.

Economic context

South Africa has achieved a high level of economic stability since the transition to a constitutional democracy in 1994. It has the largest economy in Africa, contributing 40% of the continent's gross domestic product (GDP) and exerting significant influence on trade and investment on the continent.[2] Per capita gross national income is relatively high at US$5 786 (2009) and the annual growth rate in GDP stood at 3% at the close of 2010.[3]

As in other African countries, however, poverty remains a major challenge. Income is very skewed, and nearly half the population lives in developing-country conditions, despite average GDP placing South Africa among the middle-income countries.[2] At 25%, unemployment is high, and the poor have limited access to economic opportunities.[4] Addressing poverty has been a priority of the government since the end of apartheid, and commitment to achieving the Millennium Development Goals (MDGs) and the country's own articulated goals is strong, although progress has been mixed.[5]

With the launch of the Accelerated and Shared Growth Initiative for South Africa (ASGISA) in 2006, the government adopted a comprehensive approach to meet economic challenges through a number of programmes that emphasise employment, land reform and agriculture revival.[6] Further, the government combines cash transfers with social wage packages that include clinic-based free primary health care for all; compulsory education for children aged 7 - 13 years; provision of subsidised housing, electricity, water, sanitation, trash removal and transportation; and transfer of township housing stock to those who have been resident in these properties for a set minimum period of time.[7]

Of these approaches, social grants have had the most impact on both health outcomes and poverty indicators. Old-age pensions (the older persons' grant) were shown to dramatically improve household food security, and child support grants resulted in better nutritional status of children than those in households not receiving the grants. Conversely, the grant system has also led to negative unintended consequences. Reports of patients with tuberculosis (TB) opting to remain infectious and sell their sputum to TB-negative individuals seeking disability grants are common. As a result, not only is the system abused, but sick people also go untreated and can spread the disease to others. Finally, given the ability of illness to absorb the value of social grants, other strategies to complement this approach have been proposed.

Absolute poverty

Economic growth in the post-apartheid period and investments in human development have enabled a measurable decline in income poverty.[4] The population living on less than US$1 per day was more than halved between 2000 and 2006, from 11% to 5%.[7] The first MDG of halving poverty was achieved. However, when the highest poverty line set by the MDGs is used, i.e. US$2.50 a day, the proportion of South Africans below the threshold is considerable, at 35% (2006).

Uncertainty about the progress on poverty reduction goals exists when the definition of poverty is expanded beyond income, as found in the 2009 United Nations 'Rethinking Poverty' report.[1] Using data from the World Bank, this report found that 21% of the population was living on less than US$1.25 per day, compared with 10% found in the 2010 South Africa MDG report. Additionally, there are substantial differences in national and official estimates of the baseline and progress towards poverty reduction targets, affecting interpretations of whether or not targets are likely to be achieved.

Income inequality

Despite the impressive economic performance, inequality has increased as measured by the 'Gini coefficient' (a value of 0 expressing total equality and a value of 1 maximal inequality).[4] From 1995 to 2008 inequality rose from 0.64 to 0.67. The Southern Africa Labour and Development Research Unit observed that the gap between the rich and poor within each racial group is widening in the country, and the Gini coefficient has risen in all groups.[5]

Of the black population, 93%, and only 3% of the white population, earned income in the lowest decile. In the top income decile, 73% of income goes to the white population and 17% to blacks.

Health system

Health indicators

South Africa is a paradox of high health expenditure and supportive policies coupled with persistently poor health outcomes. The country has four concurrent epidemics, a health profile found only in the Southern African Development Community region.[8] These include HIV/AIDS, violence and injuries, especially violence against women, poverty-related illnesses, and a growing burden of non-communicable diseases. Although the country is classified as 'middle-income' in terms of the economy, its health outcomes are often worse than those of some low-income states. Life expectancy is low at 53/55 (male/female) (2010) and the child mortality rate is 104 deaths per 1 000 live births (2007).[1] With a maternal mortality rate of 625 deaths per 100 000 live births (2007), South Africa was identified by the 'Countdown to 2015 Initiative' as one of the 10 countries with least progress towards achieving related MDGs.[1,9] By most estimates, South Africa's per capita health burden is the highest of any middle-income country in the world, the brunt of which is carried by the poorest families.[1,8]

Malnutrition, another important health indicator, has increased since 1994. According to the 2010 South African MDG report, 10% of children under the age of 5 years were underweight in 2005, compared with 9% in 1994.[1] Stunting (an indication of chronic malnutrition) afflicts 27% of young children. According to the Global Hunger Index, South Africa's nutritional situation was the same in 2010 as in 1990 and, compared with other countries in sub-Saharan Africa, is worse than expected for the country's income level.

The political and social history of South Africa has profoundly affected the country's health outcomes and current health policies.[8] In particular, the situation stems from a history of racial and gender discrimination, the migrant labour system, and vast income inequalities. In the late 20th century, low wages, overcrowding, inadequate sanitation, malnutrition and stress caused the health of the black population to deteriorate. These factors continue to be linked with the high burden of poverty-related diseases. Income inequalities have also influenced problems of crime and violence. Table I summarises the country indicators.

Table I. Economic development and health indicators

Population (2010)	49 991 470
Population growth rate (2009)	1.06%
Life expectancy (2009)	53 years (male), 55 years (female)
Gross national income per capita (2009)	US$5.79
Child (under 5 years) mortality rate (2007)	104/1 000
Maternal (15 - 49 years) mortality rate (2007)	625/100 000
Population living in poverty (<US$1 per day) (2006)	5%
Population with access to clean water (2009)	89%
Adult (15+) literacy rate (2007/8)	82.5%

Source: World Bank, Country Brief; South Africa. September 2010[4]

Current health policies

According to the *South African Health Review*, the current health leadership in the country is committed to a substantial overhaul of the public health sector to address the complex burden of disease, improve health outcomes and increase access to services.[10] As evidence of this commitment, Parliament tabled the National Health Act and the National Health Amendment and Medical Schemes Amendment Bill in 2008. However, both eventually lapsed when Parliament closed before a decision on the changes was made. Further, despite the enabling legal and fiscal environment that exists to facilitate government health goals, there is fragmentation and lack of co-ordination in the various policy initiatives, which have been poorly managed and lack transparency and public participation.

Several initiatives exist with potential to improve antibiotic management, from prescribing and access to surveillance for bacterial disease and resistance. These include the Health Sector Road-map, integrated support teams, and the establishment of a ministerial task team on national health insurance.

Health sector road-map

In 2008, the Health and Education Committee of the National Executive Council of the African National Congress (ANC) commissioned a 'Health Road-map'. This was in response to national concerns that South Africa, unlike most emerging economies, had witnessed profound health deterioration since the late 1990s. Several meetings of working groups were convened between August and September 2008, with teams producing background documents on the health status of the population and a final report with a '10-point plan'. The road-map was intended to guide government health policy and identify opportunities to improve access to quality health care.

A review of government strategic plans for 2009 - 2013 suggests that a number of the Road-map's recommendations have been adopted. It is unclear, however, what remains to be addressed or how these recommendations have improved access to medicines and services in practice.

Integrated support teams

The Ministry of Health established integrated support teams (ISTs) in 2009. They were intended to quantify the waste and overspending in provincial health departments that had allegedly contributed to a halt in antiretroviral treatment in the Free State. The ISTs made a number of recommendations on finance, service delivery, human resources, information management, medical supplies and technology, which were given to the Minister of Health and the National Health Council.

Progress on the recommendations is slow. While some reports indicate that a number of provinces have incorporated the recommendations into their annual performance plans, others express concerns that, without improving management systems, initiatives will not lead to expected results.

Advisory Committee on National Health Insurance (NHI)

In 2007, the ANC resolved to 'reaffirm the implementation of national health insurance'. By 2009, a broad outline of the NHI was available for debate and discussion, and an Advisory Committee on NHI was established to support the Minister in developing policy and legislation for the implementation of NHI.

Unfortunately, there has been little transparency in the functioning or outputs of the advisory team. Currently, South Africa is still without a detailed plan for NHI.

Organisation and distribution of services

At the end of the apartheid era, South Africa was not structured to serve the health needs of the entire population adequately. The health system inherited by the newly elected government was well resourced compared with other middle-income countries, with total health care expenditure at 8.5% of GDP.[8] However, half the financial and human

resources were allocated to the private sector. The vast majority of the public – blacks – could not access health services and the centralised nature of the health system resulted in a total absence of medical facilities and providers in the more rural regions. In addition to the geographical inequalities in the distribution of infrastructure, there were large inefficiencies in the distribution of resources, of which the majority went to hospitals. Academic and tertiary level hospitals alone accounted for 44% of total public sector health care spending. Only 11% of spending was devoted to non-hospital primary care services.

Structure of the South African health sector

1. The National Department of Health is responsible for national health policy.
2. Nine provincial departments of health are responsible for developing provincial policy within the framework of national policy and public health service delivery.
3. Three tiers of hospital: tertiary, regional, and district.
4. The primary health care system – a mainly nurse-driven service in clinics – includes district hospital and community health centres.
5. Local government is responsible for preventive and promotive services.
6. The private health system consists of general practitioners and private hospitals, with care in private hospitals mostly funded through medical insurance schemes. In 2008, 70% of private hospitals lay in 3 of the country's 9 provinces, with 38% located in Gauteng (Johannesburg and Pretoria) alone.

Source: Coovadia *et al.*[8]

Today, the health care system still comprises both public and private sectors, with a shift in emphasis to primary health care. Public sector health services are organised according to a hierarchy of clinics and hospitals with care provided through a referral system.[11] Primary health care clinics are the first point of contact and are usually staffed by nurses and community health workers. Basic primary services are freely available for maternal and child health needs. If medical needs exceed the capacity of a clinic, nurses refer patients to district hospitals, staffed by local medical doctors and nurses. Regional hospitals (the next level of the referral chain) employ specialists, and tertiary hospitals are tasked with more advanced surgical services. At the apex, national central hospitals provide highly specialised referral units. With primary health care concentrated in urban areas, however, substantial parts of the rural population lack access to clinics, and are therefore left without access to the hospital referral system. Many of South Africa's poor continue to rely on the country's approximately 300 000 traditional healers and traditional medicines.

Higher earners and foreigners working in the country access health services through the private sector, funded largely through medical insurance. The number of private hospitals has grown in the past years, topping 200 in 2005. For medical conditions not requiring hospitalisation, patients can visit the practices of family physicians (general practitioners).

Financing

In the past two decades, the government transformed a disparate homeland system into an integrated, comprehensive national system, driven by the need to redress inequities and provide critical services to disadvantaged areas.[8] Despite these improvements, however, the public sector remains under-resourced and inequities persist in health expenditure; 55 - 60% of total health spending occurs in the private sector by less than 15% of the country's population, mirroring apartheid-era patterns.[12] Government expenditure on health care for the uninsured has been stagnant for the past 6 years, despite the additional burden on public services from the HIV epidemic. Of the government's total budget, health care in the public sector consumes 11%, which is allocated and spent by the 9 provinces. How resources are then used and the standard of care delivered, varies by province. Inefficiencies in the distribution of state resources have resulted in notably higher quality care in the wealthier provinces of Western Cape and Gauteng, and have left many patients without necessary services.[11] Health spending as a percentage of the GDP stands at 8.6% – less than what is required to meet the Abuja Declaration target of 15%.[12]

The market for private health insurance (also referred to as medical schemes) has slowly grown and covers the majority of spending in the private sector.[11] Out-of-pocket spending, however, has increased in the form of co-payments and higher deductibles for consultations and medicine. Schemes often require up-front payments to providers, which are then claimed back by the patients through the insurance company. This short-term financial burden is frequently more than patients can afford. At present, there is no public sector national health insurance system, although plans are in place to introduce a payroll tax to bring more salaried workers into low-cost private schemes. Discussions about a universal health insurance are ongoing, though progress is unclear.

Human resource challenges

Insufficient human resources are the major challenge facing the South African health system. A 2008 report by the South African Department of Labour concluded that 'it is clear that there is a shortage of doctors in South Africa in both absolute and relative terms', and recommended 'urgent measures to recruit doctors and other health professionals back to South Africa'.[13] The private sector, which pays higher salaries and provides more competitive benefits, employs 79% of the country's doctors and 66% of the nurses.[8] Talented medical personnel are often lured overseas, where pay and working conditions are superior.[11] A 2006 study by the Center for Global Development found that 21% of doctors trained in South Africa were working abroad. The falling nurse-to-population ratio, from 149 public sector registered nurses per 100 000 population in 1998 to 110 per 100 000 population in 2007, is the result of the closure of nursing colleges in the late 1990s, migration from public to private sector and to jobs abroad, and HIV/AIDS, which affects 16% of the nursing profession. The staffing crisis is especially critical at the district level and persists despite 60% of the health budget being spent on human resources.[8]

Regarding antibiotic management, the human resource situation is dire. In 2007, there were insufficient personnel to render adequate pharmaceutical services in South Africa, with 25.5 pharmacists per 100 000 inhabitants. This equates to about 10 000 pharmacists in the entire country, with only 11% employed by the public sector nationwide and 40% of all pharmacists concentrated in Gauteng's private sector. Although registered pharmacists had increased to 12 813 in 2010, this was barely enough to maintain the same pharmacist/population ratio as in 2007, when accounting for population growth. The shortage of qualified pharmaceutical personnel is worsened by a yearly loss of 30% of pharmacy graduates to other countries, undermining the delivery of pharmaceutical care and the monitoring of rational drug use.[14]

Access to essential medicines and health care services

Coverage of health services in South Africa could be described as relatively good, as the majority of health care funding occurs through prepayment mechanisms.[15] Out-of-pocket payments only account for 14% of total health care funding, of which over 60% is made by medical insurance members in the form of co-payments, deductibles, or the cost of a service not covered by the insurance provider. About 80% of the population has access to the essential package of interventions within an hour's travel distance of a health facility based on any mode of transport available.

Despite these figures, there is room for improvement. While there is an extensive breadth of coverage 'on paper', many South Africans in reality cannot access health services when needed. While primary health care services are free of charge at point of service, distances to facilities and inability to cover transport costs to reach facilities that are not within a reasonable walking distance are particular problems. Other access constraints include limited facility working hours, insufficient staff, lost income as a result of taking time off work to wait for long periods at clinics, lack of availability of medicines, and poor service quality.

Overall, most children in all provinces are dependent on the public sector, where 7 - 8% live more than 30 minutes' travel distance from a primary health care clinic.[16] In the public sector, there is 1 paediatrician for every 40 180 children, though this ratio ranges from 1:9 856 in Western Cape to 1:1.1 million in Mpumalanga.

Although most children visit their local primary health care clinic at least 3 times a year, this is below the target number of 5 well-child visits per annum during the first 5 years of life. The health promotion value of these visits is also questionable, as immunisation coverage hovers around 80% (except in Western Cape) and the measles drop-out rate is close to 20%.

For women, the coverage gap in maternal health services is low by developing-country standards, with only 8% of women not attending antenatal care and 9% not delivering with a skilled birth attendant.[17] However, detailed local studies found much higher rates of home births, of 21 - 64%, depending on location. Prevention of mother-to-child transmission (PMTCT) is available at 90% of facilities, with 66% uptake in 2007.

There is a significant quality gap in the provision of critical services. To address the issue of sub-standard care, the Department of Health developed a quality of care policy.[18] The statement emphasised that scarcity of resources in the public sector and overuse of resources in the private sector could undermine quality care. In 2005, the revised Health Charter for the Republic of South Africa conceded that for a number of years there had been concerns about the attitudes of health personnel towards patients and that the health care system must become more patient-centred.[19] Furthermore, it was noted that, although most health care personnel were trying to deliver the best possible services under suboptimal circumstances, it was just this lack of respect for human dignity and of patient needs by a minority that remained an obstacle to achieving quality health services. The Minister of Health, in the release of the charter, stressed that the statutory health councils should play a meaningful role in instilling a sense of discipline and pride in the professions for which they are responsible, so maintaining a set of standards.

Demand side-issues are another component of evaluating access to health care. Currently, there is limited information on community-level dynamics influencing utilisation of health care services.[15,17] In the report of the National Committee on Confidential Enquiries into Maternal Deaths, patient-related demand was identified in 46% of maternal deaths reported in 2005 - 2007. A separate study assessing utilisation of maternal health services in Western Cape, Eastern Cape and KwaZulu-Natal found that distances to facilities and lack of transport were the biggest problems, but lack of quality care and poor provider communication with patients were also factors of low utilisation.

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Part III. Antibiotic supply chain and management in human health

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Keywords: **drug supply chain; drug procurement; antibiotics; Essential Drugs List; Standard Treatment Guidelines; pharmaceutical industry; antibiotic prescribing; antibiotic pricing**

This section examines the regulatory environment and supply chain for antibiotics for both the public and private sectors, followed by a review of what is known about patterns of antibiotic consumption in South Africa. It provides information pertaining to national policy documents and their relationship with drug supply and distribution, the position of antibiotics in therapeutic guidelines and dispensing regulations, and the current status of pharmaceutical management.

Policy framework for antibiotic management

The South African drug regulatory system is conceptualised in the National Drug Policy (NDP), published in 1996. The National Department of Health (NDoH) aimed to address previous structured inequalities and inaccessibility to medicines with the implementation of the NDP, hoping to ensure '… 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'.[1] The NDP outlines specific health, economic and national development objectives, including the availability and accessibility of essential medicines, the safety and quality of medicines, good dispensing and prescribing practices, and individual responsibility for health and informed decision-making. Other policies have also expressed economic goals such as promoting cost-effective use of medicines and establishing advisory groups for pharmaco-economics.

The Medicines and Related Substances Control Act 101 of 1965 (as amended) makes provision for the registration and control of medicines, as well as the licensing of professionals to dispense and manufacture them.[2] Those permitted to prescribe and dispense medicines are registered by their Professional Councils as enacted by the Pharmacy Act 53 of 1974, the Health Professions Act 56 of 1974, the Veterinary and Para-Veterinary Professions Act 19 of 1982, the Allied Health Professions Act 63 of 1982 and the Nursing Act 33 of 2005.

Quality control and efficacy of medicines

Regulatory authorities

The NDP aim of ensuring 'that drugs reaching patients are safe, effective and meet the approved standards' relates to the core pharmaceutical aspects of medicine quality, safety and efficacy and falls under the mandate of the Medicines Control Council (MCC). The MCC is responsible for the registration and re-licensing (retention) of medicines, dossier-based medicine evaluations and laboratory-based testing of all medicines used in South Africa in compliance with criteria for medicine evaluation and good manufacturing practice (GMP). The MCC subscribes to the World Health Organization (WHO)'s *Certification Scheme for the Quality of Pharmaceuticals Moving in International Commerce,* the *Guidelines for Donated Drugs,* the *Model List of Items to be Included in a Clinical Trial Protocol* and the *Ethical Criteria for Medicinal Drug Promotion*. When necessary, the MCC may implement need-based prioritisation of medicine registration and expedite the registration of essential medicines. The MCC serves as an inspectorate of guideline compliance in government depots, hospital stores and private pharmacies and among dispensing health workers on a provincial level, while retaining the specialised functions of inspecting manufacturing facilities and wholesale premises at a national level.[1]

Quality assurance requirements

Pharmaceutical and analytical quality assurance requirements of the MCC encompass pharmaceutical and biological availability, details on the active pharmaceutical ingredient, formulation, specifications and control procedures for pharmaceutical ingredients, containers and packaging materials, manufacturing procedures, stability data of the finished pharmaceutical product, pharmaceutical development, and the expertise and premises used for the manufacture of a biological medicine.[3] The stability testing and required information endorsed by the MCC is based on the tripartite guideline developed by the Quality Expert working group of the International Conference on Harmonization and is aligned with the Food and Drug Administration and the European Medicines Agency.[4] The MCC also stipulates the conditions under which *in vivo* (clinical trial) and *in vitro* bio-availability information is acceptable, in addition to stipulating criteria for the design and conduct of studies for orally administered pharmaceutical products, and bio-equivalence requirements.[5]

Until an independent quality control laboratory is established, universities conduct quality control testing under contract with the MCC. The NDoH has in the past outsourced, on tender, the quality assurance role of the MCC and two institutions were awarded tenders. The Centre for Quality Assurance of Medicines (CENQAM), located on the Potchefstroom campus of North West University, was contracted to perform post-marketing quality control surveillance on pharmaceuticals, while the National Control Laboratory (NCL) at the University of the Free State undertook quality control testing for the batch release of biological medicines and vaccines.[6] The last CENQAM contract ended in 1999, and the MCC has since made use of CENQAM services on an *ad hoc* basis, submitting only samples suspected of being sub-standard for testing.

Counterfeits

Counterfeiting of pharmaceuticals in South Africa is highly problematic, with an estimated one in five medicines sold believed to be counterfeit.[7] The majority of counterfeit medicines are imported from India and Pakistan and reach pharmacies through illegal means. The NDoH has a small team investigating the issue, but there had only been one successful prosecution as at 2010.

Pharmacovigilance

In 1992, the National Adverse Drug Event Monitoring Centre created at the University of Cape Town in 1987 became the first National Pharmacovigilance Centre in Africa to become a full member of the WHO International Drug Monitoring Programme.[8] In 1998, guidelines for the reporting of adverse drug reactions (ADRs) were

developed for the pharmaceutical industry and have served as a reference for all persons conducting clinical trials and applicants who have statutory obligations to report safety information to the MCC. In addition, a pharmacovigilance committee was formed and continues to serve the MCC to date. The ADR system also includes the Adverse Event Following Immunization system, formalised by the Expanded Programme on Immunization (EPI) in 1997, for reporting of vaccine reactions and related safety concerns.[9]

Programmatic pharmacovigilance and awareness of pharmacovigilance in South Africa was boosted when the Operational Plan for Comprehensive HIV/AIDS Care was launched by Parliament in 2003 with the responsibility of implementation delegated to the MCC. The pharmacovigilance programme has experienced a high staff turnover and systems problems, and, although the MCC secretariat is responsible for ensuring the proper functioning of the key units, there is no formal relationship between the MCC and the University of Limpopo/Medunsa unit, or any system of peer review of the unit.[10] As a result, many provinces have developed their own pharmacovigilance programmes and non-governmental organisations such as the President's Emergency Plan for AIDS Relief, Management Sciences for Health and Wits Health Consortium have also developed pharmacovigilance programmes that do not feed into the national system (personal communication by Dr Ushma Mehta).

Essential Drugs List and Standard Treatment Guidelines

Antibiotic management encompasses restrictions on the use of antibiotics by type and application, especially those to which resistance emerges rapidly.[11] Limiting the choice of antibiotics through the use of formularies may not only reduce hospital flora to a wide spectrum of antibiotics, but can save costs to the patient, the facility and the government. The development of Essential Drugs Lists (EDLs) and Standard Treatment Guidelines (STGs) forms part of this strategy in the public sector. In the private sector, formularies are developed at the discretion of the facility management and, reportedly, there is little enforcement of their use in practice.

The STGs and EDL form part of the country's 'Essential Drugs Concept', and are viewed as critical aspects of national health policy. Compiled and periodically reviewed by expert committees under the auspices of the National Essential Drugs List Committee and implemented through the South African NDoH, these documents serve to address medicine availability and accessibility problems at primary care and hospital-level health facilities. In the case of antibiotics, they also provide standards for rational prescribing. Drugs on the EDL are generic, criterion-based and stratified by primary and hospital care, and further stratified by guidelines for adult and paediatric patients. Drugs excluded from the list may be requested in exceptional circumstances for specific patients according to a standardised process. Some drugs may be included in institution-specific supplementary EDLs formulated and periodically reviewed by the institution's Pharmacy and Therapeutics Committee (PTC).[1]

Resistance and antibiotic selection

Two of the most important factors influencing the inclusion of an antibiotic in the EDL should be microbial aetiology of the disease and the incidence of resistance. The latter, however, 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.[11]

Traditional medicine

The low costs of traditional medicines make them a popular choice for many South Africans, with the market estimated at around R3 billion (US$492 million).[7] Around 350 of the country's plants are commonly used for medicinal purposes, with 20 000 tons being consumed by at least 27 million patients annually. In 2008, the government published a draft policy on African traditional medicine with the aim of institutionalising it within the health care system. The policy sought to regulate the market through registration, intellectual property provisions, research, and formalisation of the traditional healer profession. The impact of this market on antibiotic use and resistance is unknown. One remedy, the root extract *umckaloabo*, has been patented by the German company ISO Arzneimittel to treat pneumonia, tuberculosis and other bacterial diseases. As an antibiotic substitute, the efficacy of this medicine is worth further exploration. However, the extent to which other traditional medicines are mixed with antibiotics and to what effect have not been investigated.[12]

Antibiotic supply chain

Pharmaceutical industry and manufacturers

The pharmaceutical industry in South Africa is relatively well developed and mostly focused on the production of generics, including manufacturing copy medicines under licence.[7] Several multinational companies have a presence through local subsidiaries and increasingly view the country as a stable base from which to penetrate sub-Saharan Africa. The public sector tendering process is highly competitive and provides huge opportunities to bid winners.

The market is currently fragmented, with no one player holding more than 15% market share. Domestic producers meet around one-third of the country's pharmaceutical demand, with the percentage higher in the generics sector. Key foreign companies are GSK, Sanofi-Aventis, BMS and Johnson & Johnson. US companies supply over one-fifth of the market, followed by German, British and Swiss firms. In June 2010, South Africa's Minister of Trade and Industry welcomed Indian pharmaceutical companies to establish manufacturing units in the country. The invitation came as part of the government's larger industrial policy framework.

Distribution

The government maintains a cost-conscious medicine procurement policy, which is biased towards local industry and generics. The process begins with the submission of orders and expected pharmaceutical needs from hospital PTCs to the NDoH, which manages a competitive tender process among suppliers. Once a tender is awarded and fulfilled, medicines are distributed through government warehouse depots housed in each province. Primary health clinics generally order from large hospitals in their areas or from the supply depots. The majority work on an EDL and have a set protocol of antibiotics they can use for treating specific conditions. Their demand is included in the quantities the government calls for in the tender. Although varied, and presumably increasing, hospital demand should form the basis of the tender amounts. A review of tenders over the past 4 years (2007 - 2011) shows little to no change in the quantity of antibiotics requested. The reason for this is unclear.

The private sector functions differently. Three large hospital networks constitute the bulk of demand, viz. Netcare, Medi-Clinic and Life Healthcare. Each network reportedly has a formulary on which they base the types of antibiotics to order. Because private hospitals are not restricted to following formularies in the manner

that public hospitals are bound to the EDL, the formulary is not necessarily followed by facilities in the pattern of antibiotics stocked. Private sector facilities can purchase medicines directly from wholesalers and pharmaceutical companies, all of which must be approved by the MCC. Three distribution companies – IHD, Kinesis and PHD – distribute the majority of originator medicines on the market (IMS background paper). These distributors handle stocking on behalf of their principals and undertake delivery to wholesalers, pharmacists, dispensing doctors, private hospitals and other private outlets.

Prescribing and dispensing

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 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.[1] By law, only licensed practitioners may prescribe and/or dispense antibiotics. A prescription or verbal instructions of an authorised prescriber known to the managing pharmacist are necessary to purchase antibiotics from a hospital or private pharmacy, and unregulated over-the-counter sales are not the major concern of national antibiotic stewardship.

Pharmacists

The government requires that pharmacies operate under a licence and the full-time management and supervision of a registered pharmacist. In addition to playing a central community education role advising patients on the correct use of medicines, pharmacists are also expected to assume a leadership role in the rational use of medicines in both the health care and community environments. In the hospital setting, the pharmacist participates in the hospital PTC that regulates antibiotic use and is expected to communicate with antibiotic stewardship committees to determine resistance patterns in the local setting. Pharmacies also house mandatory reference sources and have access to additional information from the central drug information system.[1]

Two sets of ethical and professional conduct codes issued by the South African Pharmacy Council serve to guide pharmacists and hold them accountable. The standards emphasise a practice philosophy, patient respect and the pharmacist's role within a multidisciplinary team, an integral part of the role served by a clinical pharmacist.[12]

It is important to note that pharmacists may sell a greater or lesser quantity of antibiotics than prescribed. However, the quantity dispensed cannot be over 5% more or less than that specified in the prescription. The extent to which pharmacists and patients use this allowance when dealing in antibiotics and the impact it has on appropriate dosing are unknown.[2]

Medical practitioners and nurses

The Health Professions Council of South Africa and the Allied Health Professions Council of South Africa register medical practitioners to prescribe, compound, dispense and possess medicines.[2] Professional Council regulations make explicit mention of the conflict between being licensed to prescribe medicines and pharmacy ownership or management. Whereas other countries allow prescribers to both practise medicine and own pharmacies, South Africa prohibits it and may thus reduce associated abuses. It is not known whether the restriction has an impact on the financial incentives of prescribers or the amount and types of antibiotics they prescribe.

Upon successful completion of a suitable training programme, nurses can apply for a licence to prescribe and dispense medicines, with prescribing at primary care level being competency-based as opposed to occupation-based. In situations where medical practitioners are not available, nurses are further permitted to diagnose patients if authorised by the provincial Director-General of Hospital Services, the medical officer of such local authority or the medical practitioner in charge of such an organisation in consultation with the South African Nursing Council.[13]

Education and training

The NDP prioritises the education and training of medical practitioners, nurses, pharmacists, pharmacy support staff, health service managers and pharmaceutical depot managers in the context of all relevant aspects of pharmaceutical management, commonly used STGs, the EDL and rational drug use. The availability of scientifically validated drug information for health care professionals and the community through Drug Information Centres (DICs) also aids in supporting the informed use of medicines. Relevant professional councils are tasked with oversight of mandatory continuing education and training and ensure that core curricula of all educational programmes include adequate inclusion of the concepts of rational drug use, patient counselling and communication. The pharmaceutical industry is required to provide the public with 'patient information leaflets' that describe the medicines and their proper use in common language. Facilitating drug surveillance is a further function of the DIC.[1]

Population-level antibiotic consumption

Pharmaceutical pricing

Pharmaceutical pricing and reimbursement is a contentious issue in South Africa.[7] In the past prices were virtually uncontrolled, with the government, manufacturers, wholesalers and retailers all denying responsibility for the resulting high costs to patients. Reform through the Regulation on the Pricing of Medicines and Related Substances legislation in 2002 sought to address the problem, but implementation proved difficult. Further, controversy surrounded the 'single exit price', a flat fee system for dispensers, which replaced the mark-up system. Under the law, dispensing fees for prescription drugs were set at a maximum 26% of the manufacturer's selling price. After repeated disputes, the government revealed a new pharmacy dispensing fee system in which there are a series of mark-up percentage ceilings within medicine price brackets. Under the new structure, pharmacies charge less for low-priced, high-volume medicines like antibiotics, but can increase their fees for higher-priced products. Although it is hoped that this progressive system will increase access among low-income patients, this may be at the expense of independent, small pharmacies that are unable to sustain falling profit margins.

Antibiotic spending in the public sector and the generics market

At present, government tender documents are the only source of information on antibiotic spending and demand in the public sector. However, the information has yet to be evaluated or assessed and is therefore not available for this report.

Generics

Pharmacists are required to inform patients if a generic version of a medicine is available and are bound by law to dispense the generic. Exceptions are made only if the patient expressly refuses the generic

Table I. Antibiotic utilisation in units, 2008 - 2011

Antibiotic	Sum of MAT units, 2008	Sum of MAT units, 2009	Sum of MAT units, 2010	Sum of MAT units, 2011	Count of antibiotics in each class
J1A0 Tetracyclines + combs	327 379	325 061	327 557	327 701	44
J1B0 Chloramphenicols + combs	6 964	6 114	4 527	2 483	8
J1C1 Broad-spect. penicill. oral	10 683 704	11 441 888	11 962 722	12 305 433	277
J1C2 Broad-spect. penicill. inj.	551 335	1 251 442	1 133 503	1 463 327	45
J1D1 Cephalosporins oral	1 797 546	1 813 314	1 934 859	1 874 156	95
J1D2 Cephalosporins inj.	1 674 479	1 758 407	1 663 164	1 697 551	116
J1E0 Trimethoprim combs	3 261 544	4 021 542	3 300 302	3 316 420	124
J1F0 Macrolides + similar type	2 039 968	2 293 495	2 530 404	2 596 281	96
J1G1 Oral fluoroquinolones	3 242 849	3 617 302	3 635 646	3 832 065	95
J1G2 Inj. fluoroquinolones	479 409	554 631	565 952	584 255	21
J1H1 Plain med.-/narrow-spect. penicillins	419 243	386 095	485 923	435 640	42
J1K0 Aminoglycosides	80 624	87 089	83 880	80 349	41
J1P1 Monobactams	4 843	4 674	7 584	5 679	1
J1P2 Penems and carbapenems	679 147	809 668	916 184	1 019 767	8
J1P3 Carbacephems	7 652	15 512	23 191	69 908	3
J1X1 Glycopeptide antibact.	122 156	134 738	162 038	158 674	20
J1X9 All other antibacterials	15 132	14 361	15 849	16 229	10
Grand total	25 393 974	28 535 333	28 753 285	29 785 918	1 046

Table II. Antibiotics 2009 and 2010: value, growth and market share, private sector

ATC4	Value MAT _2009	Value MAT_2010	Value +-10 v. 09	MAT_2010 MS
J1 Systemic antibacterials	1 919 130 854.00	2 043 292 502.00	6.47%	
J1A0 Tetracyclines + combs	37 678 764.00	39 469 834.00	4.75%	1.93%
J1B0 Chloramphenicols + combs	387 828.00	481 295.00	24.10%	0.02%
J1C1 Broad-spect. penicill. oral	351 521 272.00	373 493 223.00	6.25%	18.28%
J1C2 Broad-spect. penicill. inj.	105 987 274.00	102 798 822.00	-3.01%	5.03%
J1D1 Cephalosphorins oral	175 751 215.00	176 182 721.00	0.25%	8.62%
J1D2 Cephalosphorins inj.	172 847 459.00	160 530 717.00	-7.13%	7.86%
J1E0 Trimethoprim combs	38 382 515.00	40 390 387.00	5.23%	1.98%
J1F0 Macrolides + similar type	213 230 281.00	226 893 341.00	6.41%	11.10%
J1G1 Oral fluoroquinolones	189 289 835.00	199 226 177.00	5.25%	9.75%
J1G2 Inj. fluoroquinolones	120 639 553.00	129 209 765.00	7.10%	6.32%
J1H1 Plain med.-/narrow-spect. penicillins	17 274 577.00	16 992 430.00	-1.63%	0.83%
J1K0 Aminoglycosides	9 403 552.00	9 375 484.00	-0.30%	0.46%
J1P1 Monobactams	2 093 055.00	1 578 338.00	-24.59%	0.08%
J1P2 Penems and carbapenems	240 862 282.00	285 758 027.00	18.64%	13.99%
J1P3 Carbacephems	2 225 316.00	9 822 331.00	341.39%	0.48%
J1X1 Glycopeptide antibact.	192 006 421.00	202 986 537.00	5.72%	9.93%
J1X9 All other antibacterials	49 549 655.00	68 103 073.00	37.44%	3.33%

or if the prescribing doctor has forbidden the generic in a note on the script. Substitution can also be overruled if the generic costs more than the originator or if the government declared the generic non-suitable.[12]

Medicines remain a key contributor to rising health care costs.[14] However, encouraging growth in the use of generic medicines could result in significant cost savings. Originators still account for 59% of the pharmaceutical market in terms of value sales, but generic

Table III. Antibiotics 2009 and 2010: value, growth and market share of the top 20 systemic antibiotics, private sector

Product	Value MAT _2009	Value MAT_2010	Value +-10 v. 09	MAT_2010 MS
Targocid	172 985 950.00	187 369 971.00	8.32%	9.17%
Meronem	149 200 888.00	172 476 098.00	15.60%	8.44%
Augmentin GSK	102 961 138.00	114 753 766.00	11.45%	5.62%
Tavanic	79 849 592.00	83 986 563.00	5.18%	4.11%
Invanz	50 054 356.00	69 909 764.00	39.67%	3.42%
Avelon	77 201 738.00	66 287 963.00	-14.14%	3.24%
Maxipime	61 066 520.00	60 873 261.00	-0.32%	2.98%
Zyvoxid	48 157 895.00	54 027 725.00	12.19%	2.64%
Orelox	40 696 072.00	46 530 583.00	14.34%	2.28%
Tienam	41 607 038.00	43 372 165.00	4.24%	2.12%
Zithromax	41 004 371.00	42 763 990.00	4.29%	2.09%
Tazocin	34 659 156.00	37 581 185.00	8.43%	1.84%
Amoclan bid	32 402 469.00	37 476 613.00	15.66%	1.83%
Ciprobay	37 613 878.00	36 945 114.00	-1.78%	1.81%
Sandoz Co-Amoxyclav	42 376 167.00	36 837 032.00	-13.07%	1.80%
Purbac	30 752 051.00	33 747 848.00	9.74%	1.65%
Rocephin	32 152 781.00	33 298 107.00	3.56%	1.63%
Augmaxcil	28 068 919.00	32 702 773.00	16.51%	1.60%
Ketek	30 181 032.00	31 565 630.00	4.59%	1.54%
Klacid	31 594 810.00	31 025 241.00	-1.80%	1.52%

medicines dominate the market in terms of sales volume.[7] By 2014, the pharmaceutical industry predicts that the generics market will have grown by 13.3% in local currency terms. Generic efficiency, or the number of times a generic could be dispensed, also increased from 69% in 2007 to 72% in 2009.[14] The reasons for this growth include but are not limited to more generic alternatives being made available on the market, and their encouraged use by medical schemes and the government.

Antibiotic spending in the private sector

Information on antibiotic consumption in the private sector comes primarily from IMS Health. Data are collected from wholesalers as well as from direct sales from manufacturers to pharmacies.

Annual medicine expenditure can be broken into two components – cost and volume. Table I shows antibiotic consumption in terms of units. Although IMS does not report in the commonly accepted unit for pharmaceutical consumption, daily defined doses, their units do help to show trends over time. In the case of South Africa, the trend is an increasing one. In particular, unit sales of broad-spectrum penicillins, fluoroquinolones, carbapenems and penems, carbacephems and glycopeptides have increased annually. Use of chloramphenicols has decreased, while cephalosporins, trimethoprim combinations, aminoglycosides and monobactams have fluctuated.[15]

From a value perspective, the top three classes of antibiotics used in the private sector are oral broad-spectrum penicillin with 18.3% of the market, penems and carbapenems with 14% of the market, and macrolides with 11.1% of the market. While penicillins and macrolides both exhibited growth rates over 6% from 2009, use of penems and carbapenems grew by 18.6%.[15] The value, growth and market share for antibiotic classes are shown in Table II.

The top 20 antibiotics contribute 61% towards the total systemic antibacterial market. Targocid is ranked first with a 9.2% market share and growth rate of 8.3% from the previous year. Meropenem, ranked second, has a market share of 8.4% and growth of 15.6%, and Augmentin GSK is ranked third with 5.6% of market share and growth of 11.5%.[15] The value, growth and market share of the top 20 antibiotic agents are shown in Table III.

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Part IV. Human infections and antibiotic resistance

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South Africa has a high burden of infectious diseases, including a large portion that are of bacterial origin. This section reviews the national burden of disease and levels of antibiotic resistance in common bacterial infections in the human population. The consequences of resistance on clinical outcomes, through either treatment failures or the development of more virulent infections, are largely unknown. The full impact of antibiotic resistance on health in South Africa therefore remains to be assessed.

National burden of disease

South Africa faces a quadruple burden of disease, as a result of the HIV/AIDS epidemic, other infectious diseases, injuries, and non-communicable diseases. Tables I and II show the top five causes of death for all ages and for children under the age of 5 (information from the Revised Burden of Disease Estimates for South Africa 2000[1] and the 2010 South African Health Review[2]).

The largest single cause of death for all ages is HIV/AIDS, accounting for 26% of deaths.[1] This is 5 times greater than the next largest single cause of death, ischaemic heart disease and stroke (7% each) followed by tuberculosis (TB) and interpersonal violence, each accounting for about 6%. While males have higher proportions of deaths owing to homicide/violence and TB than females, females have higher proportions of deaths due to HIV/AIDS, heart disease and stroke.

There is considerable uncertainty around estimates of child mortality in South Africa because of incomplete vital registration.[2] Existing numbers suggest that HIV/AIDS is the leading cause of death (46%), followed by neonatal causes dominated by preterm complications, asphyxia, and infection. Diarrhoea, pneumonia and injuries together account for 17% of mortality.

HIV/AIDS and TB

The most pressing health concern in South Africa is the HIV/AIDS epidemic, with around 29% of the population infected with the virus (2009). In addition to a high incidence of chronic illness and violence-related deaths, South Africa has the largest number of people living with HIV/AIDS in the world (over 5.5 million), and 1 000 people are estimated to die as a result of AIDS daily.[3] The Health Economics and HIV/AIDS Research Division predicts that HIV patients will soon account for around 60 - 70% of all hospital expenditures. HIV-related illnesses currently account for 50% of hospital admissions.

In absolute terms, South Africa has the fourth-largest TB population in the world (behind India, China and Indonesia) and bears 28% of the global burden of TB related to HIV. In 2007 data from the Global TB database, almost 1 000 per 100 000 of the population are infected with the disease annually. The emergence in South Africa of extremely drug-resistant tuberculosis (XDR-TB) that is considered virtually untreatable is of particular concern in a country with a high prevalence of HIV and a poor record of TB treatment.

Bacterial disease and antibiotic resistance

Our data are summarised from national surveillance efforts and site-specific case studies. The picture is incomplete because causes of illnesses and deaths are not well counted in South Africa, as is often the case in low-resource countries. Furthermore, separating bacterial from viral diseases requires a level of detail that, in most cases, does not exist. Nonetheless, the available information provides a basic idea of the current situation.

We present information on the burden of disease, current treatment options and antibiotic resistance for acute respiratory infections, diarrhoeal infections, sexually transmitted infections and nosocomial infections.

Acute respiratory and meningeal infections

As causes of severe respiratory tract, systemic and meningeal infections such as pneumonia, bacteraemia, and meningitis, the bacterial pathogens *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* are major contributors to morbidity and mortality worldwide.

Antimicrobial chemotherapy has substantially decreased morbidity and mortality from these infectious diseases. However, their control is threatened by the global increase in antimicrobial resistance (AMR), including multidrug resistance. Resistant infections may adversely affect mortality, treatment costs, disease spread and duration of illness, increasing pressure on the choice of appropriate antibiotics.

Table I. Leading causes of mortality in all ages

Age group	HIV/AIDS	Ischaemic heart disease	Stroke	Tuberculosis	Interpersonal violence and injuries
All ages	25.5%	6.6%	6.5%	5.5%	5.3%

Source: Revised Burden of Disease Estimates for South Africa 2000.[1]

Table II. Leading causes of mortality in young children

	HIV/AIDS	Age group	Diarrhoea	Pneumonia	Injuries
Children under 5	46%	29%	9%	6%	2%

Source: 2010 South African Health Review.[2]

In developing countries such as South Africa and sub-Saharan Africa, where respiratory and meningeal diseases are more frequent because of the high burden of HIV infections, limited access to health care, costly antibiotics and low vaccination coverage, lack of access to antimicrobials and resistance to those available may increase the morbidity and mortality of vaccine-preventable diseases.

Streptococcus pneumoniae

S. pneumoniae is a leading cause of bacterial infection worldwide.[4] The World Health Organization (WHO) estimates that 1.6 million people, including up to 1 million children aged <5 years, die annually of pneumococcal infection, with most deaths in developing countries.[5]

Treatment

Successful management of pneumococcal disease involves use of early antimicrobial therapy.[6] During the 1940s, clinical pneumococcal isolates exhibited complete susceptibility to antibiotics such as penicillin, the antibiotic of choice for the treatment of pneumococcal infections.[7] However, in Australia, intermediate penicillin resistance was observed for the first time in 1967.[8] In South Africa, fully penicillin-resistant *S. pneumoniae* strains were detected in 1977,[9] and in 1978 the occurrence of multidrug-resistant and highly resistant strains was reported.[10,11] Since then, the prevalence of *S. pneumoniae* antibiotic resistance has increased around the world, not only to penicillin but also to non-β-lactam drugs, such as the macrolides, tetracycline, chloramphenicol, the fluoroquinolones and co-trimoxazole. Resistance to non-β-lactam drugs is often associated with decreased susceptibility to penicillin, so the prevalence of multidrug-resistant strains is also increasing.[12]

Antibiotic resistance

The increasing prevalence of pneumococcal resistance to single and multiple antimicrobials in South Africa demonstrates the need for new strategies to combat the problem, especially in terms of preventing increased mortality and treatment failures in penicillin-resistant pneumococcal meningitis.[13,14] The clinical impact of antibiotic resistance has been reported as treatment failures for acute otitis media,[15] and for pneumococcal meningitis.[13,16] However, using the revised penicillin susceptibility breakpoints of 4 μg/ml for intermediate and ≥8 μg/ml for resistant strains, there is no evidence for a relationship between penicillin resistance and pneumococcal pneumonia treatment failures.[17,18]

Surveillance data reveal that rates of resistance to penicillin and other antibiotics among *S. pneumoniae* vary by geographical location. Penicillin-resistant pneumococci have been reported with particularly high frequencies in South Africa since the mid-1970s[19] and in other African countries since the 1980s.

A 1997 African multicountry study revealed that penicillin resistance levels among all isolates of *S. pneumoniae* ranged from 9% to 61%, and that an increase in resistance has been observed in four countries across Africa.[20] Resistance levels in North Africa are generally high, as reported by Algeria (35% of all isolates),[21] Egypt (49% of invasive isolates),[22] and Tunisia (41% of all isolates),[20] although in Morocco levels are much lower (9% of all isolates).[20] Penicillin resistance in West Africa varies from 62% in Senegal,[20] 31% in Ghana[23] and 22% in Ivory Coast[20] down to 7% of invasive isolates in The Gambia.[24] In East Africa, the prevalence in Ethiopia and Kenya has increased over the years to 29% of clinically significant isolates, and 48% of paediatric invasive isolates, respectively.[25-27] In Malawi, a 1997 study of paediatric nasopharyngeal isolates revealed penicillin resistance of 21%.[28] In Zambia, 14% of paediatric non-invasive isolates were penicillin-resistant in 1994[29] and in Mozambique, a prevalence of 14% of paediatric invasive isolates was reported.[30] No systemic studies have defined the reasons for the diversity in resistance rates reported.

South Africa has been the primary site of pneumococcal penicillin resistance surveillance and research in Africa, and has had one of the highest reported rates in the world.[31] Since the first reports of resistance in the 1970s, the prevalence of resistance in *S. pneumoniae* in South Africa has increased. Between 1979 and 1986, the prevalence of resistance to one or more antibiotics in pneumococcal cerebrospinal fluid and blood isolates increased from 4% to 14%.[32,33] A continuation of the same survey, between 1991 and 1998, reported that antibiotic resistance increased from 19% to 25% among all age groups, and in children from 32% to 38%.[34] Among all age groups during this period, penicillin resistance increased from 10% to 18%.[34] In 1992, 40% of isolates causing community-acquired meningitis or bacteraemia in children were penicillin-resistant.[31] A 1999 Alexander Project study of pneumococcal isolates from the private sector in Johannesburg revealed that 79% were penicillin-resistant.[31] Also in 1999, a study of nasopharyngeal isolates from private paediatric practices in Johannesburg found that antibiotic resistance was 69%, with 37% being multiply resistant.[35] In 2003, a report on isolates from private clinical laboratories in South Africa showed that the rate of penicillin resistance among all age groups was 76%.[36] Other studies in that year on invasive pneumococcal isolates from adults outside the private sector who were likely to have been exposed to less antibiotic prescribing revealed penicillin resistance levels of 13%,[37] and a study on non-invasive isolates from HIV-infected adults reported penicillin resistance at 15%.[38] A study conducted in Gauteng in 2006 on adults with bacteraemic pneumonia showed that 33% of isolates were penicillin-resistant, when using the historical meningitis susceptibility breakpoints.[39] Penicillin resistance in South Africa remains mainly intermediate in level, with a low prevalence of fully resistant isolates. Although, annually, resistance levels have increased overall, these are dependent on the site of specimen collection, age of the patients, and their location in the country.

Macrolide resistance. The increasing incidence of penicillin-resistant *S. pneumoniae* has been paralleled by an increase in resistance to other classes of antimicrobials, suggesting that penicillin resistance serves as a marker of resistance to other drugs.[40-43] Almost 25% of *S. pneumoniae* isolates from South Africa show full erythromycin resistance, with over 90% of these also resistant to clindamycin.[31] Additionally, 40 - 50% of penicillin-resistant isolates show cross-resistance to macrolides.[31] In 2001, a national multicentre study of private clinical laboratories in South Africa revealed that a high prevalence (61%) of non-invasive isolates were macrolide (clarithromycin and azithromycin) resistant,[36] whereas a national 2005 study showed that 14% of invasive pneumococcal isolates were resistant to macrolides.[44]

Co-trimoxazole resistance. The Alexander Project in Johannesburg in 1996 - 1997 revealed that 15 - 20% of isolates were resistant to co-trimoxazole,[31] while a 2001 study showed that co-trimoxazole resistance was as high as 72%.[36] Other South African studies have found that co-trimoxazole resistance is associated with multidrug resistance in pneumococcal isolates from childhood carriers in hospitals[11] and healthy children in the community.[45] In a 1986 study, 43% of penicillin-resistant strains among childhood carriers in South Africa were also resistant to co-trimoxazole.[46]

Fluoroquinolone resistance. A Canadian study showed that 1% of pneumococci have reduced susceptibility to fluoroquinolones.[47] An increase in the frequency and degree of resistance to fluoroquinolones among pneumococci occurred particularly in penicillin-resistant *S.*

pneumoniae, and in adults over 65 years.[47] In South Africa, 2008 study data suggest that the use of fluoroquinolones to treat multidrug-resistant TB in children has led to the emergence of invasive pneumococcal disease (IPD) caused by levofloxacin-non-susceptible *S. pneumoniae*,[48] although these strains remain rare outside those institutions.

Multidrug resistance. *S. pneumoniae* resistance to three or more different classes of antibiotics, defined as multidrug resistance, is a problem of increasing concern worldwide.[49] The emergence of multidrug resistance was first reported in Soweto, South Africa, in 1977.[11] Subsequently, multidrug resistance emerged globally.[20,41,50,51] In South Africa in 2004, a third of pneumococcal isolates studied displayed multidrug resistance.[49] Successful multidrug-resistant clones that are disseminated worldwide belong to only 10% of the 93 pneumococcal serotypes, including serotypes 3, 6A, 6B, 9N, 9V, 14, 19A, 19F and 23F.[52]

Neisseria meningitidis

N. meningitidis causing meningitis and other meningococcal diseases, such as meningococcaemia, is a major cause of morbidity and mortality in children worldwide, and of epidemics in Africa and Asia.

Antibiotic resistance

In Africa, limited data are available regarding antimicrobial non-susceptibility of *N. meningitidis*. Few studies have documented the existence of penicillin and other antimicrobial non-susceptibility in Africa other than South Africa. A study in Morocco reported an average rate of 4% for penicillin intermediately resistant invasive meningococcal isolates collected from 1992 to 2000.[53] All isolates tested were susceptible to cefotaxime, chloramphenicol and rifampicin. Laboratory-based surveillance in Egypt from 1998 to 2004 reported high rates (86%) of resistance to co-trimoxazole but low rates of resistance to penicillin (1%) and ampicillin (5%); 40% of isolates were intermediately resistant to either ampicillin (minimum inhibitory concentration (MIC) 0.25 - 1 μg/ml) or penicillin (MIC 0.12 - 0.25 μg/ml) and 34% were intermediately resistant to both penicillin and co-trimoxazole.[54] One isolate, with intermediate resistance to penicillin, tested positive for β-lactamase production.

A serogroup A meningitis outbreak in northern Ghana in 1998 showed no evidence of resistance to any of the drugs tested, with the exception of sulphadiazine.[55] No resistance to β-lactam agents or chloramphenicol was reported during surveillance of meningococcal meningitis in Cameroon during the 2007 and 2008 meningitis seasons. In Ethiopia, epidemic meningococcal isolates collected during 2002 - 2003 were compared with those from the 1988 - 1999 epidemic.[56] All 40 isolates were fully susceptible to the antibiotics tested, except for sulfamethoxazole (MIC >256 μg/ml). A study of the aetiology of bacterial meningitis in Nigeria was conducted between 1987 and 1992, and *N. meningitidis* was the most common pathogen isolated.[57] Antimicrobial susceptibility testing by disc diffusion of 118 meningococci demonstrated 39% and 67% non-susceptibility to penicillin and co-trimoxazole, respectively; 5 were resistant to both penicillin and chloramphenicol but were susceptible to ciprofloxacin. Non-susceptibility to penicillin increased progressively over the period analysed, seemingly caused by the abuse of penicillin, which is readily purchased over the counter.

In South Africa, β-lactamase-producing penicillin-resistant (MIC >256 μg/ml) meningococcal isolates from two patients were reported in 1987, but the mechanism of resistance was not confirmed genotypically and the strains were lost.[58] National laboratory-based surveillance for invasive meningococcal disease in South Africa was initiated during 1999. A study that genotypically characterised invasive meningococci collected from 2001 to 2005 reported a relatively low prevalence of penicillin non-susceptibility.[59] During this period 6% of isolates were intermediately resistant to penicillin, with MICs ranging from 0.094 μg/ml to 0.25 μg/ml. No isolates tested were fully resistant or tested positive for β-lactamase production and all were susceptible to other drugs tested, with the exception of rifampin (0.3%). In 2009, South Africa reported its first case of fluoroquinolone-resistant *N. meningitidis*.[60] MICs for ciprofloxacin and levofloxacin were 0.125 μg/ml, and 0.25 μg/ml for ofloxacin. Resistance appeared to be mediated by a single amino acid substitution in the DNA gyrase enzyme. The isolate was susceptible to other drugs tested but was resistant to nalidixic acid (12 μg/ml). No subsequent cases of fluoroquinolone-resistant meningococci have been reported.

Haemophilus influenzae

H. influenzae is an important cause of acute otitis media, sinusitis, chronic bronchitis, community-acquired pneumonia and meningitis.[61] Before the introduction of *H. influenzae* type b (Hib) conjugate vaccines, globally Hib was estimated to be responsible for approximately 3 million serious illnesses and 386 000 deaths annually;[62] 95% of these cases and 98% of all deaths occurred in patients from developing countries, mainly in children <5 years.[63] In sub-Saharan African children, Hib is responsible for 20% of all radiologically confirmed pneumonia cases and 40% of all meningitis cases.[64,65]

Treatment

Antimicrobial treatment is pivotal in the management of *H. influenzae* disease. Until the early 1970s, when *H. influenzae* resistance to ampicillin was first reported,[66] ampicillin was the cornerstone of therapy.[67,68] In sub-Saharan Africa, chloramphenicol and penicillin are the first-line antibiotics to treat meningitis and severe pneumonia, while mild pneumonia is treated with co-trimoxazole, ampicillin or amoxicillin.[69,70] In South Africa, β-lactams such as penicillin, ampicillin or amoxicillin are still recommended as empirical first-line therapy for the treatment of respiratory tract infections in patients <65 years old and without co-morbid illness.[71,72] Alternative agents recommended for treating patients >65 years old, or who have co-morbid illness, include amoxycillin-clavulanate or selected oral cephalosporins (cefuroxime axetil or cefpodoxime).[71,72]

Antibiotic resistance

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.[69,70,73,74] Resistance to ampicillin and other β-lactams is almost exclusively due to β-lactamase production. Isolates expressing this mechanism remain susceptible to β-lactamase-inhibitor combinations such as amoxicillin-clavulanic acid. A second non-β-lactamase-mediated resistance mechanism is conferred by mutations in the *ftsI* gene, encoding the transpeptidase region of penicillin-binding protein 3 (PBP3), which results in decreased affinities of the PBP3 for β-lactams.[75] Such strains are termed β-lactamase-negative ampicillin-resistant (BLNAR). Worldwide, BLNAR strains continue to be isolated at very low frequencies.[75-78] However, their prevalence has recently increased in countries such as Japan,[79,80] Spain[76,79] and Korea.[81]

In Africa, data for *H. influenzae* AMR, especially regarding trends, are sparse.[69,70,82,83] Increasing rates of chloramphenicol and co-trimoxazole resistance have been reported in Africa.[70,82,84] In Cameroon, chloramphenicol resistance levels of up to 84% have been reported,[84] while high prevalence of co-trimoxazole resistance have been reported in Mozambique (46%)[82] and Kenya (66%).[70]

Beta-lactamase production is by far the most common mechanism of ampicillin resistance in South African isolates of *H. influenzae*.[75] From 2003 to 2008, 2 177 cases of invasive *H. influenzae* were reported to the national laboratory-based surveillance system, of which 54% had viable isolates available for antimicrobial susceptibility testing. Of the viable isolates, 2% and 15% were found to be intermediately resistant and resistant to ampicillin, respectively. Of the 190 ampicillin non-susceptible isolates, 99% were β-lactamase producing and 1% were phenotypically β-lactamase-negative ampicillin resistant (BLNAR) and were characterised as low-level BLNAR (MIC 2 µg/ml). In addition, a β-lactamase-positive amoxicillin-clavulanate-resistant (BLPACR) strain was identified (MIC 8 µg/ml).

In the only previous report of South African BLNAR strains (ampicillin MIC 2 µg/ml),[85] a BLNAR prevalence of 6% among isolates collected from various sources, including respiratory secretions and blood, was reported during a SENTRY worldwide surveillance programme in the Asia-Pacific region.

Diarrhoeal infections

Non-typhoidal *Salmonella*

Salmonellosis due to non-typhoidal *Salmonella enterica* spp. accounts for a large burden of disease worldwide. Illness is usually self-limiting and antimicrobial therapy is not required, but in cases of invasive disease antimicrobial therapy is important for a successful clinical outcome. Over the period 2003 - 2010, the Enteric Diseases Research Unit (EDRU) at the National Institute for Communicable Diseases (NICD) has documented 16 435 records of laboratory-confirmed cases of non-typhoidal *Salmonella enterica* isolates from human and non-human sources for South Africa. Isolates received from non-human sources (*N*=224) include samples of water, food and animal specimens processed at the EDRU for study purposes, or as a service by special request and not as part of their routine surveillance activities. These isolates were therefore not screened for antimicrobial susceptibility. Of the 16 211 human isolates, 13 702 were viable and were screened using antimicrobial agents.

Treatment

The treatment of choice for such infections are third-generation cephalosporins and fluoroquinolones, as resistance to ampicillin, chloramphenicol and co-trimoxazole has been present worldwide for many years.[86] Failure to respond to treatment with the fluoroquinolones, as isolates have displayed decreased susceptibility to ciprofloxacin, has recently been reported. AMR to nalidixic acid has been used as a proxy to identify isolates that may not respond to treatment with ciprofloxacin.

Antibiotic resistance

Resistance to quinolones usually occurs as a result of alterations in the target enzymes (DNA gyrase and topoisomerase IV) and as a result of changes in drug entry and drug efflux.[87] Resistance to quinolones can also be mediated by plasmids that carry genes coding for Qnr proteins, which protect the quinolone targets from inhibition. Plasmid-mediated quinolone resistance among South African strains of non-typhoidal *Salmonella* has been previously reported, as well as the detection of mutations in the DNA gyrase enzyme of clinical non-typhoidal *Salmonella*.[88]

In the period 2003 - 2010 there has been a decrease in the proportion of non-typhoidal *Salmonella* isolates showing resistance to ampicillin from 64% to 16%, chloramphenicol from 47% to 14%, ceftriaxone from 40% to 10%, and nalidixic acid from 38% in 2003 to 10% in 2010. Although the overall proportion of non-typhoidal *Salmonella* isolates showing resistance to nalidixic acid has decreased over time, when comparing non-typhoidal *Salmonella* isolates causing invasive disease with non-typhoidal *Salmonella* isolates causing non-invasive disease, isolates causing invasive disease account for the greater proportion of isolates showing resistance to nalidixic acid. There has been no increase in the proportion of non-typhoidal *Salmonella* isolates exhibiting resistance to ciprofloxacin. In 2004, the greatest proportion of non-typhoidal *Salmonella* isolates, just less than 2% (26/1 597), showed resistance to ciprofloxacin. Overall, just less than 1% of all non-typhoidal *Salmonella* isolates exhibited resistance to ciprofloxacin from 2003 to 2010. Over this same period the proportion of non-typhoidal *Salmonella* isolates exhibiting resistance to sulfamethoxazole has fluctuated from 40% of isolates in 2003, to a high of 78% of isolates for 2004 and 2005, to 48% of isolates in 2010, but overall there has been a general decrease in resistance to sulfamethoxazole since the highs of 2004/2005.

Extended-spectrum β-lactamase (ESBL)-producing non-typhoidal *Salmonella* isolates have been identified by the EDRU since 2003. In 2003, 28% (452/1 597) of all non-typhoidal *Salmonella* isolates were found to be ESBL producing. The proportion of all non-typhoidal *Salmonella* isolates found to be ESBL producing has decreased to 8% in 2010. ESBL production in non-typhoidal *Salmonella* in South Africa is usually associated with nosocomial isolates of non-typhoidal *Salmonella*.[89,90] Govinden *et al.*[91] have suggested that among a selection of clinically isolated strains of non-typhoidal *Salmonella* there is co-expression of quinolone and ESBL.

Salmonella enterica serotype Typhi

S. Typhi bacterium causes typhoid fever and is transmitted via food or water contaminated with human faeces. It is of clinical importance, as humans are the only recognised reservoir of *S.* Typhi. Typhoid fever is a major contributor of illness and death in humans, particularly in developing countries. In 2000 it was estimated that typhoid fever caused approximately 22 million illnesses and 220 000 deaths globally.[92]

Treatment

Antibiotics are vital in the management of typhoid fever. Various fluoroquinolones such as ciprofloxacin have become the treatment of choice for infection with *S.* Typhi.[93] However, as with the non-typhoidal *Salmonella*, increased resistance to the quinolone nalidixic acid and reduced susceptibility to the fluoroquinolone ciprofloxacin have been reported.[86]

Antibiotic resistance

South Africa, with an estimated typhoid fever burden of disease of 100/100 000 of the population, has not been spared nalidixic-acid-resistant *S.* Typhi.[92] Smith *et al.*[87] reported on 27 nalidixic-acid-resistant isolates collected between 2003 and 2007 that exhibited mutations in both gyrase and topisomerase genes and an active efflux of antibiotic as mechanisms of quinolone resistance. Keddy *et al.*[94] subsequently reported on the first locally isolated strain of fluoroquinolone-resistant *S.* Typhi. The associated mechanism of resistance was the presence of a single amino-acid mutation in the gyrase A gene along with a QnrS protein and active efflux of antibiotic. They concluded that the strain was possibly imported through contact with a traveller from the Asian sub-continent.[94]

In the period 2003 - 2010, the EDRU received 706 viable *S.* Typhi isolates that have been screened using antimicrobial agents. Of these 706 viable *S.* Typhi isolates 595 caused invasive disease. The proportion of *S.* Typhi isolates resistant to the older antibiotic ampicillin has fluctuated over this period from 10% in 2003 to a high of 40% in 2006, and 10% at the end of 2010. The proportion of

S. Typhi isolates resistant to sulfamethoxazole remained consistently around 30%. In terms of chloramphenicol, the proportion of *S.* Typhi isolates identified by the EDRU as resistant has more than doubled from 5% in 2003 to 13% in 2010. The proportion of *S.* Typhi isolates causing invasive disease resistant to chloramphenicol for the year 2010 was 15%. In 2009, 20% (*N*=60) of all *S.* Typhi were resistant to the quinolone nalidixic acid. This proportion of quinolone-resistant *S.* Typhi isolates has been the highest identified through laboratory surveillance by the EDRU since 2003. In 2003, the proportion of quinolone-resistant *S.* Typhi was 10%, which decreased to 5% in 2006 and increased to 15% at the end of 2010. Over this same 8-year period, the proportion of ciprofloxacin-resistant *S.* Typhi was zero, except in 2009 when that proportion rose to 2% with the isolation of the fluoroquinolone-resistant *S.* Typhi mentioned earlier. Although there have been reports of ESBL-producing *S.* Typhi, none has been isolated in South Africa to date.[95]

Shigella

Shigellosis is caused by the enteric bacteria *Shigella* species. The disease is a worldwide problem, particularly in areas with poor access to clean water and sanitation, causing an estimated 600 000 deaths annually. As a result *Shigella* is a pathogen associated with water or food contamination as it can easily be spread by the faecal-oral route. The only reservoirs of significance, except for primate colonies, are humans. *Shigella dysenteriae* type 1 is probably the most important *Shigella* variant because it is epidemic-prone and the production of Shiga toxin by this variant of *Shigella* results in severe illness.[96] *S. sonnei* has been associated with food- and water-borne outbreaks.

Treatment

Shigella isolates that are multidrug-resistant to ampicillin, trimethoprim, sulfamethoxazole and tetracycline have become prevalent. As a result, reliance on antibiotic treatment has shifted toward fluoroquinolones such as ciprofloxacin as first-line treatment. Although optimal treatment is to replace fluid and electrolytes, the use of antibiotics to shorten the duration and severity of disease and to decrease the period of pathogen excretion is important.[97]

Antibiotic resistance

From 2003 to 2010, the EDRU received 9 538 viable *Shigella* isolates. Of the 9 538 *Shigella* isolates only 337 caused invasive disease. Antimicrobial screening shows that the proportion of *Shigella* isolates resistant to older antibiotics over the 8-year period has been consistent: 50% for ampicillin, 50% for tetracycline, 80% for sulfamethoxazole and 40% for chloramphenicol. In terms of what has now become first-line treatment, consistently from 2003 to 2010 the proportion of *Shigella* isolates resistant to nalidixic acid has been 1% and for both ciprofloxacin and ceftriaxone the proportion of resistant *Shigella* isolates has been just below 1%. The proportion of *Shigella* isolates exhibiting ESBL production has also consistently been less than 1%. Despite the consistent low levels of resistance to both quinolones and fluoroquinolones, there is concern that the numbers may increase over time.

Vibrio species

Vibrio spp. are commonly found in aquatic environments and infection occurs as a result of poor access to clean water and sanitation. Of more than 30 species of *Vibrio*, 12 have been associated with illness in humans,[98] of which the most important are *V. cholerae* subgroups O1 and O139, the causative agent of epidemic cholera.[99] Although infection occurs with non-O1 *V. cholerae* the clinical manifestation is milder because this subgroup of *V. cholerae* lacks the cholera-toxin-producing gene. Pandemics of the devastating diarrhoeal disease caused by *V. cholerae* have been documented since 1817.[98] Most epidemics occur in developing countries where it is endemic. The debilitating disease caused by *V. cholerae* is the result of an enterotoxin known as choleragen. *V. cholerae* O1 occurs in 3 serotypes (Ogawa, Inaba and Hikojima), and is further characterised into two biotypes – El Tor and classic.[98,99]

Treatment

Although antimicrobials are prescribed for the management of severe cases, to shorten the duration of illness and reduce the volume of rehydration solution required, *V. cholerae* strains are resistant to a number of antimicrobials including tetracycline, co-trimoxazole, trimethoprim and sulfamethoxazole. Knowledge of the AMR profile of local strains is important for the management of complicated cases, but adequate and timely rehydration therapy remains the gold-standard treatment for cholera.[99]

Antibiotic resistance

In 2008, an outbreak of cholera started in South Africa and continued into 2009. This was linked to cholera in Zimbabwe, with patients crossing the border to seek health care in South Africa. During 2009, the EDRU processed 570 *V. cholerae* O1 isolates associated with the outbreak. Further laboratory characterisation showed that 98% of the isolates were serotype Ogawa and 2% were serotype Inaba; all were biotype El Tor and 99.5% of the isolates were positive for the cholera toxin. The 2008/2009 outbreak isolates showed 100% resistance to co-trimoxazole, 48% resistance to chloramphenicol, 100% resistance to nalidixic acid, 3% resistance to tetracycline and 39% resistance to erythromycin. Although there was 100% resistance to nalidixic acid, none of the isolates associated with this outbreak was resistant to ciprofloxacin.[100]

In a second outbreak in 2008, reported from Shebagold Mine in the Ehlanzeni district of Mpumalanga, 31 isolates were submitted for analysis to the EDRU. All were biotype El Tor and displayed resistance to ampicillin, amoxycillin-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. Although the isolates exhibited resistance to nalidixic acid they were susceptible to ciprofloxacin and imipenem. Further resistance to third-generation cephalosporins ceftriaxone and ceftazidime was observed, indicative of ESBL activity.[101]

The EDRU routinely conducts antimicrobial screening on all *V. cholerae* O1 isolates and has data available from 2007. Since 2007, the EDRU has received 899 viable *V. cholerae* O1 isolates. In 2007, 13 of the 30 isolates received were resistant to sulfamethoxazole. The summary of these recent outbreaks is the most accurate description of the current situation of AMR among *V. cholerae* isolates in South Africa.

Diarrhoeagenic *Escherichia coli*

E. coli is commonly found in the normal flora of the colon and is used as an indicator of faecal contamination of water. Although a commensal organism, *E. coli* is an important human pathogen that has been associated with several gastro-intestinal syndromes. There are 6 major categories of diarrhoeagenic *E. coli*; enterotoxigenic (ETEC), entero-invasive (EIEC), enteropathogenic (EPEC), enterohaemorrhagic (EHEC), diffusely adherent (DAEC) and entero-aggregative (EAggEC). The most clinically important is EHEC. The strain *E. coli* O157:H7 has been associated with outbreaks and clinical presentation of haemorrhagic diarrhoea, colitis and haemolytic

uraemic syndrome.[102, 103] *E. coli* O157:H7 produces two cytotoxins, one a verotoxin and the other a toxin identical to the Shiga toxin produced by *Shigella dysenteriae* type 1. These Shiga-toxin-producing *E. coli* are referred to as STEC. STECs are not limited to the *E. coli* O157:H7 serotype, as any of the non-O157:H7 serotypes may present as EHEC or STEC.

Treatment

Fluid replacement is recommended as treatment for gastro-enteritis caused by *E. coli* O157:H7 or non-O157:H7 STEC infection, as it believed (although evidence is lacking) that antimicrobial therapy is of no benefit and may increase the risk of haemolytic uraemic syndrome.[103]

Antibiotic resistance

As part of the EDRU's surveillance activities, a screening multiplex polymerase chain reaction (M-PCR) analysis is conducted on all *E. coli* isolates submitted to the unit to categorise the isolate into one of the aforementioned diarrhoeagenic *E. coli* categories. This is done because antimicrobial screening is conducted only on isolates that are EHEC or STEC. Over the years 2003 - 2010, the EDRU received 3 109 viable *E. coli* isolates, of which 17 were found to be STEC and 21 to be EHEC by M-PCR. Antimicrobial screening of these isolates shows that consistently less than 1% of all STEC or EHEC isolates are resistant to tetracycline, ampicillin, amoxycillin-clavulanate, co-trimoxazole, trimethoprim, sulfamethoxazole and chloramphenicol. The proportion of *E. coli* isolates showing ESBL activity for the same period was also consistently lower than 1%.

A recent study of clinical isolates of ESBL-producing *E. coli* isolates screened for ESBL enzymes found that 16 of the 22 isolates were resistant to ciprofloxacin as a result of the presence of *aac (6_)-Ib-cr*, a variant of an aminoglycoside modifying enzyme.[104] Nothing from the EDRU surveillance data suggests that there may be *E. coli* resistant to the fluoroquinolones, as none was found to be resistant to ciprofloxacin, but these findings should be taken into consideration.

Sexually transmitted infections

Bacterial sexually transmitted infections (STIs) cause significant morbidity in South Africa and may rarely cause death, for example from ruptured ectopic pregnancy secondary to tubal damage from *Neisseria gonorrhoeae* and *Chlamydia trachomatis* or fetal death from congenital syphilis. They account for 87% of male urethritis syndrome (MUS) cases, 30% of vaginal discharge syndrome (VDS) cases and 10% of genital ulcer syndrome (GUS) cases. Importantly, both ulcerative and genital discharge syndromes are key co-factors for augmenting HIV infectiousness and susceptibility and increase transmission risk by 2 - 5 times in prospective studies.[105]

Patients with bacterial STIs may present with MUS, VDS, scrotal swelling syndrome (SSW, i.e. epididymo-orchitis), lower abdominal pain syndrome (LAP, i.e. pelvic inflammatory disease), GUS or buboes. As the syndromic management approach does not utilise laboratory testing, it is not possible to determine the national burden of bacterial STIs by individual STI pathogen. The bacterial burden also differs according to STI syndrome; recent aetiological surveillance data from South Africa showed that bacteria account for 87% of cases of MUS, 30% of cases of VDS and only 10% of GUS cases (Table III).

Between April 2004 and March 2005, 1 654 776 new STI episodes were treated in primary health care (PHC) clinics throughout South Africa. Incidence rates of new STI syndrome episodes, calculated per 1 000 population aged 15 - 49 years, demonstrated a national incidence rate of 63 per 1 000 population. The highest incidence rates were recorded in Limpopo (90 per 1 000), KwaZulu-Natal (87 per 1 000) and the Eastern Cape (73 per 1 000); the lowest incidence rate was recorded in the Western Cape (38 per 1 000). During the same time period, a total of 145 818 new STI syndrome episodes (46 222 in males, 99 596 in females, 8.8% of the national total) were reported among 126 656 patients in the sentinel survey, with a peak in the 20 - 24-year-old age group. In men with STIs, the most frequent syndromes were MUS and GUS, whereas for women they were VDS and LAP (Fig. 1). The relative prevalence and incidence of MUS, the most reliable indicator syndrome for 'true' STIs, seen at the sentinel sites during 2004 - 2005, is shown by province in Table IV.

Neisseria gonorrhoeae

At present in South Africa, AMR is solely an issue for *N. gonorrhoeae* infection. It is very important to have effective microbiological

Table III. Bacteria causing the most prevalent STI syndromes in South Africa

Category	Male urethritis syndrome (MUS) (*N* (%))	Vaginal discharge syndrome (VDS) (*N* (%))	Genital ulcer syndrome (GUS) (*N* (%))
No. of enrolled cases	1 593 (100)	1 462 (100)	597 (100)
No. of bacterial cases	1 378 (87)	423 (30)	60 (10)
Bacterial aetiologies for MUS/VDS			
Neisseria gonorrhoeae	1 155 (73)	180 (12)	NA
Chlamydia trachomatis	287 (18)	203 (14)	NA
Mycoplasma genitalium	134 (8)	144 (100)	NA
Bacterial aetiologies for GUS			
Treponema pallidum	NA	NA	44 (7)
Haemophilus ducreyi	NA	NA	5 (1)
Chlamydia trachomatis L1-L3	NA	NA	6 (1)
Klebsiella granulomatis	NA	NA	-

Courtesy of DA Lewis, STIRC, National Institute for Communicable Diseases, National Health Laboratory Service, South Africa. Combined data from 8 surveys undertaken by the STI Reference Centre: Northern Cape (2006), Gauteng (2007, 2008, 2009, 2010), Western Cape (2007), Free State (2008), Eastern Cape (2010). NA = not applicable.

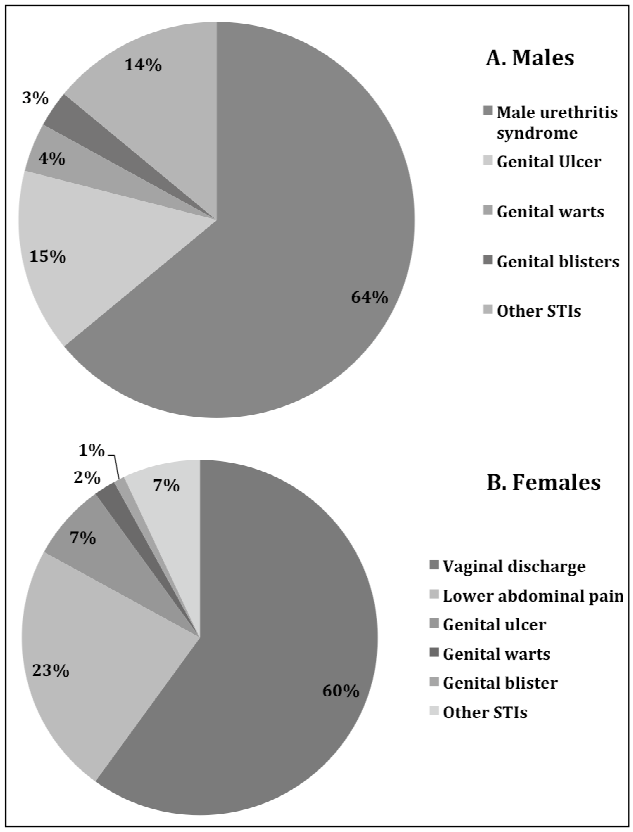

Fig. 1. Relative prevalence of STI syndromes in males (A) and females (B) presenting to primary health care facilities, South African national sentinel survey of STI syndromes (2004 - 2005). Courtesy of D A Lewis: STIRC, National Institute for Communicable Diseases, National Health Laboratory Service, South Africa.

surveillance systems in place in South Africa and its neighbouring countries to facilitate early detection of such strains. There is mounting public health concern that gonorrhoea may become untreatable in years to come, which would have an extremely deleterious effect on HIV transmission in South Africa, where the prevalence of both diseases is high. Accordingly, efforts must be made locally to reduce the burden of gonorrhoea and for the international community to invest in the search for a new class of antimicrobial agents active against *N. gonorrhoeae.*

Treatment

In South Africa, STIs have been treated using the syndromic management approach since the late 1990s. This approach is to manage symptomatic STIs and has the advantage of providing same-day treatment according to treatment flow charts, which can easily be adhered to by nursing staff at every PHC entry point across the country. Laboratory testing of STI patients is not required for case management, although the WHO recommended that periodic aetiological and AMR surveys are carried out in all countries using the approach. Lack of clinical samples has deskilled laboratory staff in terms of ability to culture and test gonococci for antimicrobial susceptibility. The syndromic approach generally works better for male-associated compared with female-associated STI syndromes. The poor specificity of syndromes such as VDS and LAP to predict the presence of STIs leads to overdiagnosis of STIs, unnecessary stigmatisation and potential relationship difficulties. Importantly, it results in substantial overprescribing of antimicrobial agents that may influence the development of AMR among sexually transmitted and non-sexually transmitted bacteria.[106] Mathematical modelling has shown that syndromic management is the cheapest programmatic approach to the management of STIs, although there remains debate as to whether it is the most cost-effective.[107,108]

Owing to the rapid emergence of quinolone-resistant gonococci in 2003, and their subsequent spread throughout the country, revised national guidelines were published in 2008. Gonorrhoea should now be treated with oral cefixime or intramuscular ceftriaxone. Gonococci exhibiting clinical resistance to oral cephalosporins have emerged in the Western Pacific region and have now spread to Europe. No such isolates have been found in Africa to date, but their emergence is likely in the near future. Other key changes include use of acyclovir in the GUS treatment algorithm and the replacement of erythromycin with amoxicillin for the treatment of presumptive chlamydial infection in pregnant women with VDS.

At least half of STI care episodes are estimated to be managed by the private sector, where the National Department of Health (NDoH) has less influence on prescribing practice.[109] An interview-based study conducted among general practitioners (GPs) in Gauteng over a decade ago highlighted poor knowledge of STI syndromic

Table IV. Male urethritis syndrome (MUS) indicators by province, primary health care

Province	New episodes (*N*)	Relative prevalence of MUS (%)	Incidence rate per 1 000 population aged 15 - 49 (95% CI)
Eastern Cape	60 147	25.6	40.8 (39.8 - 41.8)
Free State	20 533	25.1	28.6 (28.2 - 29.0)
Gauteng	61 139	23.7	19.4 (18.9 - 19.9)
KwaZulu-Natal	121 972	26.7	50.2 (49.3 - 51.0)
Limpopo	59 409	24.6	50.1 (48.9 - 51.4)
Mpumalanga	40 227	39.5	47.9 (47.4 - 48.3)
North West	36 394	24.1	33.5 (32.4 - 34.5)
Northern Cape	7 364	32.7	33.7 (33.0 - 34.5)
Western Cape	32 062	30.1	23.5 (22.7 - 24.3)
National	439 247	26.5	35.2 (34.2 - 36.3)

Note: The denominator for the relative prevalence of MUS includes males and females.
Source: Report on the National Clinical Sentinel Surveillance of Sexually Transmitted Infections at Public Sector Primary Health Care Facilities (2005), prepared by the STI Reference Centre (NICD/NHLS) for the National Department of Health.

management, and less than half of prescriptions overall were judged to be effective.[110] In addition, for most STI syndromes, uninsured patients were offered significantly cheaper and less convenient antibiotic regimens. Prescribing correct drug treatment for STIs by GPs has been associated with male gender and recent graduation of the GP, as well as the patient having medical aid.[111] A study of knowledge, beliefs and attitudes of GPs and public-sector nurses in Gauteng, conducted several months after the publication of the revised 2008 national STI guidelines, found that only a quarter of the GPs, as opposed to two-thirds of nurses, were aware that cefixime should now be used to treat gonorrhoea (D A Lewis, unpublished data). Within South Africa, there appears to be a lack of an effective pathway to disseminate revised NDoH guidelines to GPs, and this remains a key challenge for quality private-sector health care delivery. To make matters worse, at the time that the national STI guidelines were changed, the NDoH had to purchase cefixime directly from Merck in Germany, and it was only made available at PHCs. This led to an inequality in the health care system, where cefixime was available to patients with presumptive gonorrhoea attending public clinics whereas similar patients attending tertiary-level hospital or GP facilities could only be treated with ceftriaxone. Cefixime was finally made accessible to all practitioners for the treatment of gonorrhoea at the start of 2011.

Antibiotic resistance

The need for periodic aetiological and AMR surveillance, which is an integral part of syndromic management, has been largely ignored by most African countries. With the exception of South Africa, where good laboratory infrastructure and funding exist to support surveillance, Africa has minimal AMR data available for bacterial STI pathogens. Gonorrhoea is the only bacterial STI for which AMR surveys are currently undertaken in South Africa. Despite reports concerning AMR in chlamydial strains collected from patients failing treatment, it remains controversial whether documented stable homotypic drug resistance to antibiotics exists and AMR studies are not routinely performed for this STI pathogen anywhere in the world.[112,113] Although a high prevalence of tetracycline resistance has been documented among *Mycoplasma genitalium* isolates, susceptibility testing for this relatively new bacterial STI pathogen is performed in few specialist laboratories worldwide.[114,115] Screening for resistance in *Treponema pallidum* remains a challenge because of inability to culture this organism *in vitro*. Although resistance of *T. pallidum* to penicillin has not been described to date, a molecular assay for the macrolide resistance-associated A2058G mutation in 23S rRNA does exist.[116] The STI Reference Centre has failed to detect this A2058G mutation in *T. pallidum*-positive DNA extracts from genital ulcer swabs recently collected in South Africa (D A Lewis and E E Müller, unpublished data). Chancroid is now a rare cause of GUS, and it is no longer feasible to culture isolates to determine AMR. Chancroid was the most frequent cause of GUS in the 1990s and surveys performed at that time reported that most strains were resistant to penicillin, co-trimoxazole and tetracyclines but susceptible to amoxicillin-clavulanate, macrolides, quinolones and extended-spectrum cephalosporins.[117]

Gonococci isolated in South Africa remained fully susceptible to ciprofloxacin, the former first-line therapy used to treat gonorrhoea, until 2003 when researchers from the University of KwaZulu-Natal reported the abrupt emergence of quinolone-resistant *N. gonorrhoeae* (QRNG) among MUS patients attending an STI clinic in Durban.[118] Subsequently, the NDoH requested that the STI Reference Centre co-ordinate a gonococcal resistance survey in several South African cities, which included Cape Town, Durban, Johannesburg, Pietermaritzburg, Pretoria and Mthatha. The data revealed varying prevalence of QRNG, from 0% in Pretoria to 24% in Durban, although all isolates tested appeared susceptible to cephalosporins.[119] Despite the widespread problem with QRNG, revised national guidelines were not published until 2008, at which point ciprofloxacin was replaced by either cefixime or ceftriaxone as first-line therapy for presumptive gonococcal infection.[120] During this 4-year period, further rises in QRNG prevalence was 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).[118,121,122] The STI Reference Centre has conducted additional surveys in Kimberley (2006), Bloemfontein (2008), East London (2010), Rustenburg (2011) and Polokwane (2011), and observed a QRNG prevalence of 53%, 16%, 41%, 15% and 40% respectively (D A Lewis, unpublished data).

There is substantial public health concern about the global spread of gonococci with decreased susceptibility to oral cephalosporins which have resulted in gonorrhoea treatment failures in several countries, including Japan, China, Australia, Norway and the UK.[123-126] Japan, China and Australia therefore now use intramuscular ceftriaxone to treat gonorrhoea.[127] To date there has been no confirmed case of clinical failure with oral cephalosporins in Africa, but such strains will undoubtedly emerge over time, either through importation or *de novo*. All gonococci tested in South African surveys carried out by the STI Reference Centre (STIRC) over the past 5 years have remained fully susceptible to both cefixime and ceftriaxone (D A Lewis, unpublished data).

In terms of other antimicrobials, studies from Gauteng have confirmed that tetracyclines and penicillin should not be used to treat gonorrhoea in South Africa because of a high prevalence of plasmid-mediated tetracycline resistance (36 - 74%) and a lower, but still unacceptably high, prevalence of penicillinase-producing gonococci (16 - 26%).[121,128] Gonococci isolated in Johannesburg in 2008 demonstrate no resistance as yet to azithromycin, spectinomycin and gentamicin (D A Lewis, unpublished data).

Where bacterial STI pathogens are resistant to treatment, patients may be at increased risk of pathogen-associated complications, such as epididymo-orchitis or pelvic inflammatory disease in the case of antimicrobial-resistant *N. gonorrhoeae*. From the public health viewpoint, such patients also remain infectious to others for longer and this may increase transmission of the pathogen within the community. STIs are also important co-factors in HIV transmission, and HIV viral loads are increased in cervicovaginal, seminal and ulcer-derived secretions in the presence of other STIs. In the case of gonorrhoea, for example, studies from Malawi demonstrated that urethritis can elevate the seminal HIV viral load approximately 8 times and, even with effective anti-gonococcal treatment, it may take over 3 weeks for the seminal viral loads to decline to levels seen in HIV-infected dermatology patients (controls).[129] The risk of HIV transmission may be much greater in HIV-infected individuals with antimicrobial-resistant gonorrhoea, particularly in a country like South Africa where there are an estimated 5.3 million HIV-infected individuals aged 15 years and older.[130] Relevant to this argument, the STI Reference Centre demonstrated that the detection of QRNG in men with MUS in Cape Town and Johannesburg was significantly associated with co-infection with HIV.[122]

Finally, treating patients with resistant STIs will require use of more expensive antimicrobial agents and also, when gonococcal resistance to oral cephalosporins emerges in South Africa, increased use of injectable antimicrobials such as ceftriaxone, spectinomycin or gentamicin. The widespread use of intramuscular antimicrobial agents to treat index STI patients and their partner(s) may have a deleterious public health effect by reducing patient and sexual partner access because of fears concerning injections. Widespread

use of intramuscularly administered antimicrobials also heightens the risk of needle-stick injuries for staff working with STI patients, who are at high risk of being HIV infected.

Hospital-acquired infections

Public sector

According to the 2009 National Health Laboratory Service (NHLS) public sector susceptibility data (Table V), *K. pneumoniae* remains

Table V. NHLS public sector susceptibility data (January - December 2009). Courtesy of the NASF, Federation of Infectious Diseases Societies of Southern Africa

	Laboratories							
	GSH	TBH	GP	UNI*	DGM	SBAH	CMJAH	CHBH
***Klebsiella pneumoniae* from blood cultures**								
(*N* = total of isolates)	325	190	113	89	112	440	258	388
Gentamicin (% susceptible)	32	42	41	49	63	48	51	39
Amikacin (% susceptible)	70	87	76	90	98	64	63	59
Ciprofloxacin (% susceptible)	54	60	67	61	80	59	66	72
ESBL (% susceptible)	71	64	56	53	46	60	50	62
Ertapenem (% susceptible)	100	100	-	96	99	100	100	98
Imipenem (% susceptible)	100	100	-	100	100	100	100	100
Meropenem (% susceptible)	100	100	-	100	100	100	100	100
***Escherichia coli* from blood cultures**								
(*N* = total of isolates)	281	131	135	40	62	193	219	417
Ciprofloxacin (% susceptible)	80	83	93	70	81	92	83	78
Gentamicin (% susceptible)	83	82	84	90	84	91	78	76
Amikacin (% susceptible)	88	96	94	98	95	94	69	78
ESBL (% susceptible)	10	11	10	13	16	6	8	48
Ertapenem (% susceptible)	100	100	-	100	100	100	100	100
Imipenem (% susceptible)	100	100	-	100	100	100	100	100
Meropenem (% susceptible)	100	100	-	100	100	100	100	100
***Pseudomonas aeruginosa* from blood cultures**								
(*N* = total of isolates)	94	44	15	14	30	134	93	152
Gentamicin (% susceptible)	66	61	80	64	93	48	84	72
Cefipime (% susceptible)	51	64	80	71	90	52	81	79
Pip-taz (% susceptible)	40	43	40	79	97	60	90	74
Ciprofloxacin (% susceptible)	57	68	73	79	100	52	82	84
Ceftazidime (% susceptible)	66	82	93	86	100	57	85	79
Imipenem (% susceptible)	65	52	13	79	100	48	77	74
Meropenem (% susceptible)	66	70	13	86	97	52	78	75
***Acinetobacter* from blood cultures**								
(*N* = total of isolates)	241	175	21	22	38	173	98	323
Pip-taz (% susceptible)	20	8	38	9	89	20	41	14
Ciprofloxacin (% susceptible)	57	30	71	14	18	26	40	37
Ceftazidime (% susceptible)	57	43	67	0	24	27	42	50
Imipenem (% susceptible)	26	9	43	18	92	32	42	21
Meropenem (% susceptible)	25	9	43	14	79	32	32	27
***Staphylococcus aureus* from blood cultures**								
(*N* = total of isolates)	250	175	121	41	94	476	228	411
Cloxacillin (% susceptible)	65	69	74	71	16	63	57	76
Erythromycin (% susceptible)	69	70	83	66	11	56	56	75
Clindamycin (% susceptible)	70	70	85	68	28	58	65	74

*Data for Universitas are incomplete for certain organisms.
NHLS = National Health Laboratory Service; ESBL = extended-spectrum β-lactamase; GSH = Groote Schuur Hospital; TBH = Tygerberg Hospital; GP = Green Point NHLS Laboratory, Cape Town; UNI = Universitas Hospital, Bloemfontein; DGM = Dr George Mukhari Hospital, Pretoria; SBAH = Steve Biko Academic Hospital, Pretoria; CMJAH = Charlotte Maxeke Johannesburg Academic Hospital; CHBH = Chris Hani Baragwanath Hospital; Pip-taz = piperacillin-tazobactam.

Table VI. Incidence (%) ESBL production (number of isolates) in selected strains of Enterobacteriaceae in private practice in South Africa (all sources), January - June 2006 [136]

City	*K. pneumoniae*	*Enterobacter* spp.	*E. coli*
Overall	26 (7 514)	12 (4 031)	5 (28 412)
Johannesburg	42 (3 010)	11 (1 486)	4 (12 600)
Pretoria	27 (2 244)	10 (1 061)	3 (7 406)
Durban	8 (1 359)	5 (1 093)	4 (5 637)
Cape Town	40 (805)	27 (328)	4 (1 380)
Bloemfontein	15 (96)	6 (63)	12 (1 389)

ESBL = extended-spectrum β-lactamase.

a highly resistant nosocomial pathogen, with more than 50% of all strains producing ESBLs. These isolates were frequently multiresistant, with only 32 - 63% susceptible to gentamicin and 54 - 80% susceptible to ciprofloxacin.

E. coli strains exhibited less resistance than *K. pneumoniae*, with 76 - 91% susceptible to gentamicin, 78 - 92% susceptible to ciprofloxacin and only 6 - 16% producing ESBLs. The very high rate of ESBL production (48%) at Chris Hani Baragwanath Hospital (CHBH) remains unexplained.

Patterns of resistance among *P. aeruginosa* isolates vary between laboratories. Ceftazidime remains the most active agent.

Carbapenem resistance among *Acinetobacter* spp. is common in the 5 hospitals with major intensive care units, with only 20 - 40% of isolates being susceptible to carbapenems.

Approximately 60% of *S. aureus* isolates from blood are sensitive to cloxacillin.

Private sector

For several reasons, including selective pressure from overuse of antibiotics and failure of hospital infection control practices, the incidence of colonisation and infection, particularly with resistant Gram-negative bacteria, in South African private institutions appears to be increasing. In addition, the worldwide emergence and spread of carbapenem-resistant *K. pneumoniae* and *E. coli* and reports of hospital outbreaks owing to such strains is cause for local concern.[131,132] Increased use of carbapenems in the private sector in South Africa is driven by an increase in cephalosporin and fluoroquinolone resistance among ESBL-producing Enterobacteriaceae.[133] Although extensive published data regarding antibiotic susceptibility of community-acquired respiratory tract pathogens especially *S. pneumoniae* are available, including those of invasive isolates, few data have been published for Gram-negative pathogens such as *A. baumannii* or *P. aeruginosa* or for Gram-positive pathogens, particularly *S. aureus*.

The SENTRY international antimicrobial surveillance programme documented the prevalence of ESBL production in *Enterobacter cloacae* among hospitalised patients in several Johannesburg private hospitals as 20% (*N*=11/54) and that of oxacillin resistance in blood-culture isolates of nosocomially acquired *S. aureus* to be 40%.[134,135] A 2006 survey of bacteraemic pathogens isolated from patients in private hospitals in 5 major South African cities conducted by the former National Antibiotic Surveillance Forum (NASF), found that nationwide prevalence of ampicillin resistance in blood culture isolates of *E. coli* (*N*=471) was 84%, and 20% were resistant to fluoroquinolones (Table VI).[136] Cephalosporin resistance among isolates of *K. pneumoniae* (*N*=636) was high; 52% were resistant to cefuroxime. The most active agents in *Enterobacter* spp. (*N*=242) were imipenem/meropenem, ertapenem, ciprofloxacin and levofloxacin, with 100%, 94%, 88% and 87% susceptibility, respectively. Carbapenem resistance in invasive isolates of *P. aeruginosa* (*N*=382) varied between 45% and 42% for imipenem and meropenem and in *A. baumannii* (*N*=190) between 33% and 32%, respectively. The overall incidence of methicillin resistance among *S. aureus* isolates was 36% (*N*=629). The prevalence of ESBL production among all-source isolates of *K. pneumoniae* (*N*=7 514), *Enterobacter* spp. (*N*= 4 031) and *E.coli* (*N*=28 412) was 26%, 12% and 5%, respectively.

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Part V. Surveillance activities

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The critical importance of robust antimicrobial resistance (AMR) surveillance in South Africa cannot be overemphasised. Without knowing what the resistance situation is, it is impossible to develop appropriate antibiotic treatment guidelines and associated essential drug lists (EDLs) and to create and update evidence-based policies both at institutional and national levels. The broader benefits of AMR surveillance data include:

- Determining incidence rates of hospital-acquired infections (HAIs) and identifying the associated causative organisms and their AMR profile to feed into hospital guidelines and more appropriate treatment for infected patients. This in turn allows early interventions by infection prevention and control (IPC) so as to minimise further spread of AMR organisms.
- Profiling local or regional AMR patterns to inform selection of AMR screening practices in specific health care facilities (HCFs).
- Educating health care staff about the impact of AMR and about issues in antibiotic use and misuse.
- Monitoring trends over time to signal whether interventions are having the desired effect.
- Comparing South Africa with other countries in the region and around the world to facilitate sharing intervention experience.

South Africa has a good start at AMR surveillance, but it can and must be improved. For most AMR infections, surveillance data are laboratory and therefore organism centred, which limits the ability to differentiate between colonisation and infection with AMR organisms. It is also not possible to determine the clinical impact of AMR. A major shortcoming is that AMR surveillance is currently limited to a minority of HCFs, which does not reflect the extent of AMR across South Africa. The very limited profiling of AMR in the community needs to be addressed. Finally, the variability of surveillance methodology used makes it impossible to compare rates and trends across institutions.

The first part of this section describes studies that have identified serious AMR issues in South Africa which require urgent monitoring; these have provided compelling evidence of the need, and possible methods, for AMR surveillance.

AMR surveillance in South Africa

Surveillance of AMR in South Africa has in the past decade been carried out regularly by two main groups, with contributions from other parties. The involved groups are the National Antibiotic Surveillance Forum (NASF), currently known as the South African Society for Clinical Microbiology (SASCM), and the Group for Enteric, Respiratory and Meningeal disease Surveillance (GERMS). Additionally, the STI Reference Centre of the National Institute for Communicable Diseases (NICD), in collaboration with the National Department of Health (NDoH), performs sexually transmitted infection (STI) antibiotic resistance surveillance. In July 2010, a laboratory-based antimicrobial surveillance system was introduced by the Antimicrobial Resistance Reference Unit (AMRRU) of the NICD for HAI-associated *Staphylococcus aureus* and *Klebsiella pneumoniae* isolates collected from patients at designated sentinel sites throughout South Africa. Full characterisation of the resistance mechanisms of these isolates, as well as their molecular epidemiology, will be determined.

The National Antibiotic Surveillance Forum

The NASF was a voluntary professional organisation of medical microbiologists formed in 2002 with the key objective of monitoring AMR patterns in the public and private health sectors in South Africa. In 2009 NASF was superseded by the SASCM, which incorporated all surveillance activities, as well as involvement in other issues of concern to clinical microbiologists.

AMR surveillance in the public sector

In the public sector NASF/SASCM carries out retrospective laboratory-based surveillance of selected invasive pathogens isolated from blood and cerebrospinal fluid specimens at academic hospitals.

Methodology of the NASF/SASCM public sector AMR surveillance data system

NASF public sector surveillance relies on submission of data from the National Health Laboratory Service (NHLS) laboratories (Table I) that participate on a voluntary basis. The participating laboratories have been principally those serving academic tertiary care hospitals, although there has been some flux in the number of participating laboratories and in their catchment populations.

Table I. Participating NHLS laboratories, public sector

Abbreviation	Name
CHBH	Chris Hani Baragwanath Hospital, Johannesburg
CMJAH*	Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg
SBAH†	Steve Biko Academic Hospital, Pretoria
DGM	Dr George Mukhari Hospital, Pretoria
UNI	Universitas Hospital, Bloemfontein
GSH	Groote Schuur Hospital, Cape Town
TBH	Tygerberg Hospital, Cape Town
GP	Green Point NHLS Laboratory, Cape Town

*Formerly Johannesburg Academic Hospital.
†Formerly Tshwane Academic Hospital.

Laboratories submit AMR data on selected organisms isolated from blood cultures and cerebrospinal fluids by completing a standardised form. These organisms include: *Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Streptococcus* group B, *Enterococcus faecalis, S. aureus, Salmonella* Typhi, non-typhoidal *Salmonella, Escherichia coli, Klebsiella pneumoniae, Enterobacter* spp., *Pseudomonas aeruginosa, Acinetobacter baumanii* complex, *Candida albicans* spp. and *Cryptococcus neoformans*. Only blood culture and cerebrospinal fluid isolates are chosen since it can be assumed

that, even in the absence of clinical information, isolates from these sites almost always represent clinically significant infections. The particulars of the pathogen- antibiotic combinations that are reported on are reviewed and updated regularly by a designated committee. All isolates are tested against a range of specified antibiotics.

All NASF surveillance data depend on the accurate identification and antimicrobial susceptibility testing (AST) performed at local laboratory level as no retesting is carried out at a central or reference laboratory. Different laboratories may use different methods for identification and AST and these methods may change over time. However, all the participating laboratories undertake regular internal and external quality assurance and many are accredited by the South African National Accreditation System (SANAS). Furthermore, all laboratories utilise Clinical and Laboratory Standards Institute (CLSI) criteria to perform and interpret antimicrobial susceptibilities, although different laboratories may implement annual updates of CLSI criteria at varying times.

Within the local laboratory, data are recorded either via software designed for the laboratory information system, or by review of various paper-based record-keeping systems. The available software is labour-intensive and not user-friendly, resulting in potential transcription errors. Extraction of minimum inhibitory concentration (MIC) values is particularly problematic and can be critical if changes in cut-offs complicate determination of temporal trends. Duplicate isolates are excluded to minimise bias due to over-representation of those patients whose cultures were performed most frequently. Only data on final, laboratory-authorised results are included. Monitoring of the quality of data submitted is achieved through self-reported answers to periodic questionnaires.

Data are collected at local level by a medical technologist or by a trainee microbiologist, and checked by an on-site pathologist before quarterly submission to a national co-ordinator. The national co-ordinator receives reports from the individual laboratories, and interrogates the data critically before collating an annual report. The report is reviewed by an editorial committee before dissemination via publications in local journals, or the organisation's website, or scientific presentations at meetings and conferences.

Strengths and limitations of the NASF/SASCM public sector surveillance system

The strengths of the NASF/SASCM public health surveillance system include:

- Because it is a nationwide programme it provides AMR data for all main regions in South Africa and allows for detection of similarities and differences between different areas.
- As it has been in existence for a number of years this allows for comparisons and determination of AMR trends.
- It addresses clinically relevant invasive pathogens and reports AMR to antibiotics that are generally available in the public sector.
- The large number of isolates for which AMR data are collected minimises the effects of errors or unusual patterns of resistance.
- Data are provided by generally competent laboratories.

Important limitations include:

- Because this is a solely laboratory-based AMR surveillance system:
  - there is no way to correlate patient outcomes with AMR data
  - community- versus hospital-acquired infections cannot be differentiated
  - the primary site of infection cannot always be determined
  - submission of specimens for culture is dependent on clinicians whose test request practices may vary between different institutions.
- Uniformity is lacking with regard to data extraction methods.
- Surveillance is limited to large academic centres with an on-site microbiologist and AMR data from many smaller HCFs and rural areas are therefore lacking.
- Because participation is voluntary, time constraints experienced by participating members result in delays in submission of data.

To improve the NASF/SASCM public sector AMR surveillance system, the following resolutions taken at a workshop in September 2010 will be implemented in the next 6 - 12 months:

- Reinforce the importance of timely and consistent implementation of updated CLSI guidelines to facilitate standardisation between laboratories.
- Standardise AMR data collection procedures between the private and public sectors.
- Improve training in the use of computer-based epidemiology software programs, as well as in the interpretation of the data generated.
- Establish contacts with established surveillance programmes such as the European Antimicrobial Resistance Surveillance System (EARSS).
- Disseminate, through an editorial committee, the results of surveillance through brief, targeted and user-friendly reports.
- Investigate the possibility of obtaining surveillance data in terms of detailed information on individual isolates rather than through cumulative susceptibility results.
- Investigate the possibility of improving laboratory request forms to facilitate collection of clinical data.
- Establish centres of excellence for detection of emerging resistance.

Private sector AMR surveillance

Private surveillance data for various pathogens from various sources can be accessed on the website www.fidssa.co.za of the Federation of Infectious Diseases Societies of Southern Africa. AMR data from the private sector in South Africa are compiled from a laboratory information system, Meditech, which is used by all private laboratory groups and enables participating laboratories to extract standardised and reproducible AMR data and relevant parameters. Apart from this obvious advantage, similar limitations for the NASF/SASCM public sector AMR surveillance data pertain to the private sector AMR surveillance approach.

In the past, one private laboratory in Johannesburg, which participated in the SENTRY international antimicrobial surveillance programme, documented the prevalence of extended-spectrum β-lactamase (ESBL) production in *Enterobacter cloacae* and of oxacillin resistance in blood culture isolates of nosocomially acquired *S. aureus* among hospitalised patients in several Johannesburg private hospitals. As these results may not have been representative of the rest of private hospitals in South Africa, a wider study was prompted under the auspices of the NASF. It aimed to examine the susceptibility of important invasive Gram-negative pathogens and *S. aureus* in private health care institutions on a nationwide basis.[1] Included was an investigation of the prevalence of ESBL production in selected Enterobacteriaceae cultured from all clinical specimens. All laboratories in private hospitals in South Africa's five largest cities participated.

The study clearly had several limitations and highlighted problems in the surveillance of pathogens isolated from patients in private hospitals. Susceptibility testing of the study isolates was not performed at a single site, nor was uniform methodology used. Furthermore, multidrug resistance (MDR) among invasive strains was not determined. Other limitations included the low numbers of isolates tested in some smaller centres and, more importantly, a lack

of distinction between community- and hospital-acquired pathogens. Typical of laboratory-based surveillance, no clinical information was documented relating to colonisation or clinical significance, particularly in cases of ESBL-producing Gram-negative pathogens; this included the impact of resistance on outcome. Typing of ESBL-producing isolates was not performed. It is therefore uncertain whether cross-infection or clonal spread may have occurred to possibly account for the differences in ESBL rates in different localities. Additional problems highlighted in this study include the lack of standardisation in detection of glycopeptide resistance among isolates of *S. aureus*.

A second private national study, 'Emergence of extensive drug-resistance (XDR) among Gram-negative bacilli in South Africa – moving a step closer', was reported in 2008.[2] It documented new developments, particularly with regard to increases in ESBL production as well as emergence of carbapenem resistance in invasive strains of *K. pneumoniae*, *E. coli* and *Enterobacter* spp. Once again strains were isolated from patients in private health care institutions, but from seven major centres in South Africa. The methods employed were similar to those described previously.[1] The study was conducted from 1 July 2007 to 31 December 2007, and a total of 1 241 blood culture isolates were tested; *E. coli* (*N*=503) *K. pneumoniae* (*N*=548), and *Enterobacter* spp. (*N*=190).

The study highlighted:

- High levels of resistance to 'key workhorse' antibiotics used against Gram-negative pathogens in the health care institutions surveyed
- Significant prevalence of broad-spectrum antibiotic-inactivating enzymes, in particular ESBLs in some centres, and other resistance mechanisms affecting fluoroquinolones and aminoglycosides in strains of invasive Enterobacteriaceae
- Considerable differences in the prevalence of resistance and ESBL production between the various cities
- The emergence of carbapenem resistance among the species in some centres.

These results emphasised the need for routine antimicrobial surveillance at least at regional level, and preferably at each hospital or even each unit. Based on this report, it is clear that the concept of 'know your bugs' has never been as crucial to guiding and optimising empirical treatment for bacteraemic infections in particular. This also applies to several other common hospital-acquired pathogens such as enterococci, where current comprehensive data on vancomycin resistance in private institutions are largely lacking. The true incidence of *Clostridium difficile* infections is also unknown. These challenges must all be urgently addressed to improve future private sector HAI pathogen and AMR surveillance.

The Group for Enteric Respiratory and Meningeal disease Surveillance in South Africa (GERMS-SA)

GERMS-South Africa is an active laboratory-based surveillance programme for bacterial and fungal pathogens of public health importance. Funded by the NHLS and Centers for Disease Control and Prevention (Atlanta, USA), it receives clinical isolates and specimens from a nationwide network of 270 public and private sector laboratories throughout the country. Laboratories submit clinical isolates according to specific case definitions, together with basic demographic data. In addition, enhanced surveillance activities take place at 16 sentinel sites servicing 25 hospitals. In these locations, dedicated surveillance officers collect additional clinical and epidemiological information on all laboratory-confirmed cases.

GERMS-SA has four main areas of interest, namely AIDS-related opportunistic infections, epidemic-prone diseases, vaccine-preventable diseases and nosocomial infections. The various reference units of the NICD monitor the number of cases of 11 specific bacterial and fungal organisms isolated by participating laboratories, and conduct additional laboratory phenotypic and genotypic characterisation studies. The pathogens of interest are *Salmonella* spp., *Shigella* spp., *Vibrio* spp. and *Cryptococcus* spp. isolated from any site; diarrhoeagenic *E. coli* isolated from a stool or rectal swab; *Pneumocystis jirovecii* isolated from a respiratory tract specimen; and *S. pneumoniae*, *N. meningitidis* and *H. influenzae* isolated from any normally sterile body site. As mentioned earlier in this section, a new reference unit has been established specifically for the study of AMR in nosocomial pathogens. This unit will focus initially on *K. pneumoniae* and *S. aureus* isolates from blood culture.

GERMS-SA conducts regular audits at participating laboratories to ensure the quality and completeness of isolates submitted. The stored isolates form a valuable isolate bank that can be accessed for additional special studies conducted periodically. GERMS-SA produces an annual report, as well as a quarterly surveillance bulletin and numerous publications. As a result of their surveillance activities, GERMS-SA has developed an extensive database relating to communicable diseases in South Africa, which is used to inform public health decision making.

Enteric Diseases Reference Unit

The Enteric Diseases Reference Unit (EDRU) at the NICD was started in 1997, under the guidance of a pathologist and a part-time technologist. Currently, the EDRU participates in a national, active, laboratory-based surveillance programme through its involvement with GERMS-SA.

The EDRU collects data on patients presenting throughout South Africa with both invasive and non-invasive disease caused by diarrhoea-causing bacteria, *Salmonella* spp. (including *S. enterica* serotype Typhi, hereafter referred to as *S.* Typhi), *Shigella* spp., *V. cholerae* and diarrhoeagenic *E. coli* that meet the EDRU's predetermined case definitions. The EDRU collates all the patient and isolate information in a single record and it is these data that GERMS-SA is able to report on. The EDRU under GERMS-SA have patient and isolate records captured into a secure electronic database from 2003 to the present.

In an attempt to make these data representative and reflective of the disease burden in each province in the country, all diagnostic laboratories throughout the country are motivated to voluntarily submit limited demographic details and isolates to the EDRU. In exchange, the EDRU offers serogrouping, serotyping and AST at no cost. Epsilometer tests (E-tests) are used to determine the MIC of each isolate to antimicrobial agents, according to CLSI, formerly the National Committee on Clinical Laboratory Standards (NCCLS), guidelines.

The unit has the capacity to perform genotypic characterisation of isolates, which is particularly useful in outbreak situations. The molecular epidemiology of these bacterial pathogens is continually being elucidated, specifically that of outbreak or epidemic-prone pathogens such as *S.* Typhi, *Shigella dysenteriae* type 1 and *V. cholerae*. A multiplex polymerase chain reaction (M-PCR) is used to identify the presence of toxin genes in diarrhoeagenic *E. coli*. In addition the EDRU's molecular research laboratory is involved with characterising the molecular basis for AMR in these pathogens.

STI Reference Centre

While no STI surveillance systems exist in the private sector, the numbers of total STI syndrome episodes and new episodes of male

urethritis syndrome (MUS) are recorded at all public sector primary health care clinics (PHCs); however, no data are routinely recorded for other STI syndromes. For this reason, a national sentinel clinical STI syndrome surveillance system was launched in November 2003. This surveillance system, designed by the STI Reference Centre and implemented in collaboration with the NDoH, operates at 270 clinical sites across South Africa. The STI Reference Centre analysed and reported the data for the first year of the sentinel survey (April 2004 - March 2005); subsequent to this, the clinically based sentinel surveillance system has been managed in its entirety by the NDoH.

The STI Reference Centre is part of the NICD, a division of the parastatal NHLS established in 2001. The current activities of the STI Reference Centre are in keeping with the mission of the NICD, which is to be a resource of knowledge and expertise in regionally relevant communicable diseases to the South African Government, to Southern African Development Community countries and to the African continent at large, in order to assist in the planning of policies and programmes and to support appropriate responses to communicable disease issues. The STI Reference Centre's main operational focus concerns STI surveillance, research, training and teaching. The Centre's current goals are to strengthen microbiological surveillance in South Africa and to establish, in collaboration with the World Health Organization (WHO), a Gonococcal Antimicrobial Surveillance Programme (GASP) network across Africa to provide a more complete regional AMR profile for STIs.

The Centre has performed aetiological and AMR surveys in most of South Africa's nine provinces over the past 5 years. Patients with MUS, vaginal discharge syndrome (VDS) and genital ulcer syndrome (GUS) with informed written consent provide anonymous samples, labelled with a unique survey number, for laboratory work-up. All patients who are enrolled into surveys receive syndromic treatment for their STIs, are given contact slips for partner notification and are offered on-site HIV counselling and testing.

For MUS or VDS patients, urine or urethral swabs (men) or endocervical swabs (women) are collected to detect *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis* and *Mycoplasma genitalium* by real-time M-PCR assay. Vaginal smears from VDS cases are Gram-stained to detect the presence of *Candida* spp. and/or the presence of bacterial vaginosis. Ulcer swabs are tested for herpes simplex virus (HSV), *Treponema pallidum*, *Haemophilus ducreyi* and *C. trachomatis* L1-L3 by real time M-PCR. Giemsa-stained ulcer smears are examined to diagnose granuloma inguinale. Syphilis, herpes simplex virus (HSV) type 2 and HIV serology is additionally performed on sera from each patient.

AST for bacterial STI pathogens is only performed with *N. gonorrhoeae* isolates cultured from urethral swabs. Following presumptive and confirmatory identification, MICs are determined for cefixime, ceftriaxone and ciprofloxacin by E-test. The gonococci are also stored in cryovials, preferably at -70°C, and transferred to the STI Reference Centre at the end of each survey for subsequent agar dilution MIC determinations using a wider panel of antimicrobial agents.

The STI Reference Centre is playing a leading role in the development of GASP in Africa, which will feed into the WHO's global GASP. In relation to GASP activities, the Centre first assisted the Namibian Ministry of Health and Social Services to conduct aetiological and AMR surveillance in 2007. At present, the Centre is supporting health ministries and laboratories in Zimbabwe, Madagascar and Tanzania with ongoing or planned AMR surveys in terms of technical assistance with protocol writing and training of both laboratory and clinical staff.

Conclusion

To address the challenge of increasing resistance in these diseases, it will be necessary to begin AMR testing for a wider range of organisms, possibly following the GASP model. Because these pathogens are easily transmitted, it is particularly important that clinicians prescribe effective antibiotics capable of eradicating the pathogen during infection. This is particularly important for strains resistant to other antimicrobials. As most prescribing for these infections is empirical, an important element in appropriate prescribing is knowledge of resistance. It is therefore important that comprehensive laboratory surveillance of these diseases, sufficient to provide data representative of national disease epidemiology, is undertaken to monitor changes in AMR, particularly the evolution of MDR.

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Part VI. Antibiotic management and resistance in livestock production

Authors: **M M Henton, H A Eagar, G E Swan, M van Vuuren**

Keywords: **livestock; agricultural animals; veterinary antibiotic; growth promotion; antibiotic (antimicrobial) resistance; surveillance**

The antibiotic use and levels of antibiotic resistance found in animal populations in South Africa are reviewed: firstly, the framework for antibiotic management in livestock production; secondly, patterns of consumption by sector and application; and thirdly, what is known about bacterial resistance rates. The bacteria discussed are pathogenic to animals, zoonotic organisms and commensal bacteria.

Framework for antibiotic management and supply chain

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 National Department of Health (NDoH). Antibiotics intended for use by the lay public (chiefly farmers) are registered under Act 36 as stock remedies and are available over the counter. Because veterinarians were scarce when Act 36 was promulgated, farmers had to have access to remedies for common ailments affecting livestock. Stock remedies are intended for use by untrained consumers, and the only antibiotics that are registered under Act 36 are those that have been shown to be efficacious when used for specific conditions by such a person, as well as being safe for both the person administering the antibiotic and the animal that is treated. Veterinary medicines are controlled by the Medicines and Related Substances Control Act (Act 101), which primarily controls human medicines. Antibiotics intended for use in animals and registered under Act 101 may only be administered or prescribed by a veterinarian.

This situation has led to some anomalies. The older antibiotics, such as tetracyclines, which are also used for tick-borne protozoal infections, may be registered, depending on the formulation, both as stock remedies and veterinary medicines. Stock remedies are freely available, and no record is kept of their use. Veterinary medicines are under the control of veterinarians, who follow guidelines laid down in the veterinary regulations. Most newer antibiotics, which are also used in human health, fall under Act 101 and are controlled by veterinarians.

Fig. 1 is a simplified version of the supply chain for veterinary prescription-only antibiotics.[2] Veterinarians may administer the antibiotic directly or prescribe and dispense the medicine to the client, who can also obtain the antibiotic from a veterinary wholesaler or distributor. Veterinarians can dispense medicines without a dispensing licence, but are subject to legislation determining the conditions of use of medicines in animals.

Over-the-counter antibiotics (stock remedies) are subject to quality control inspections, must be registered for sale, and are distributed to veterinary wholesalers, distributors, farmers' co-operatives, feed mix companies or veterinarians by the manufacturer. Farmers can purchase the stock remedy based on its required indication without a prescription.

South Africa has several deficiencies when compared with the 1998 World Health Organization (WHO) best practice systems: (*i*) the dual system of regulating veterinary products only partially addresses clear, transparent manufacturing requirements (while antibiotics listed under Act 101 must be authorised with a Good Manufacturing Practice (GMP) licence, stock remedies under Act 36 are not); and (*ii*) most authorised veterinary antibiotics are over-the-counter stock remedies and often administered by farmers. The WHO recommends that only trained and licensed professionals decide when and how to use antibiotics.

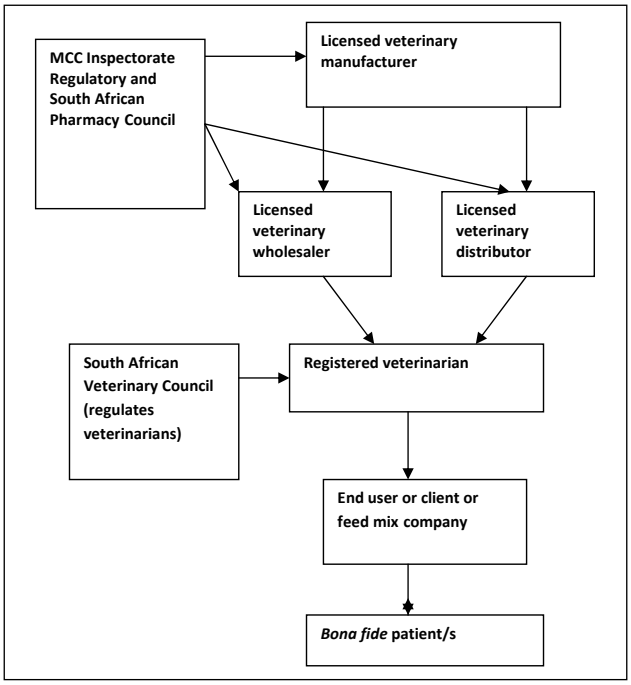

Fig. 1. Supply route of authorised scheduled veterinary antimicrobials (MCC = Medicines Control Council). Source: Eager HA,[2] p. 63.

Antibiotic use in livestock production

Data on the volume of antibiotics used in livestock production are scarce in South Africa, and information is lacking about the patterns of antibiotic consumption in food animals. Because antibiotic use in animals is controlled by two very different Acts, and because pharmaceutical companies protect sensitive information, it is very difficult to obtain an accurate estimate of the amount of antibiotics used in livestock production. The percentage of antibiotic used for non-food-producing animals, such as pets and horses, is also unknown. A study found that mean antibiotic sales per year from 2002 to 2004 were 1 538 443 kg of active ingredient[2] (and H A Eagar, G E Swan, M van Vuuren – personal communication). Macrolides and pleuromutilins constituted the majority, followed by tetracyclines, sulphonamides and, lastly, penicillins (Fig. 2). All the classes were authorised for use in food animals, including growth promoters such as ionophores, macrolides, quinoxalines, polypeptides, streptogramins, glycolipids, oligosaccharides, phosphonic acids and polymeric compounds, all of which have been banned from use in the European Union. In South Africa, 29% of all available antimicrobials were in the form of premixes, and represented a large percentage of all the registered antimicrobials. Chloramphenicol and the nitrofurans were the only types of antimicrobials not available for food animals.

Patterns of use by sector

The greatest volume of antibiotic use is in intensively farmed poultry (including broilers for meat and layers for eggs) and pigs. These animals are kept indoors at a high density, which promotes the rapid transmission of bacterial infections, primarily affecting the respiratory and intestinal tracts.

Feedlot cattle and dairy cows are the next group in terms of the amount of antibiotics used. Slaughter cattle are generally raised under extensive conditions on farms, and then sent to a feedlot for rounding off before going to the abattoir. Feedlot cattle are prone to respiratory disease, caused by *Mannheimia (Pasteurella) haemolytica, Pasteurella multocida, Histophilus (Haemophilus) somni* and *Mycoplasma,* and mastitis, usually caused by *Staphylococcus aureus.*

Other ruminants (sheep and goats) are extensively farmed, together with the bulk of the population of cattle in South Africa. The main source of food is veld grass, and the density levels are low. Extensively kept ruminants are far healthier than those kept under intensive conditions, and suffer from far fewer bacterial infections.

South Africa is drought-prone and there are few aquaculture ventures. Fresh water farms for trout are only found in the Lydenberg, Drakensberg and Western Cape areas. Suitable rivers are scarce and, where a river is capable of supporting farmed fish, there may be more than one farm on the river. Downstream farms can become infected with bacteria from fish farms in the upper reaches. Marine aquaculture ventures are also scarce, considering the extensive coastline of South Africa. There are a few abalone farms in the Hermanus area, and along the West Atlantic coast a total of 8 at present. The water flow rate in an abalone farm is too rapid for antibiotic administration. Ornamental fish are mostly imported, and little breeding is carried out in South Africa.

Patterns of use by purpose

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.[2,3] Tylosin, one of 4 growth promoters banned in Europe, was the most extensively sold antibiotic in the survey. It is primarily administered through animal feed at sub-therapeutic levels and is available as an over-the-counter stock remedy. About two-thirds of the antibiotics surveyed were administered in feed. The second-, third- and fourth-largest groups of antibiotics sold in the study – tetracyclines, sulphonamides and penicillins – are also readily available and have a wide spectrum of antimicrobial activity against common infections.

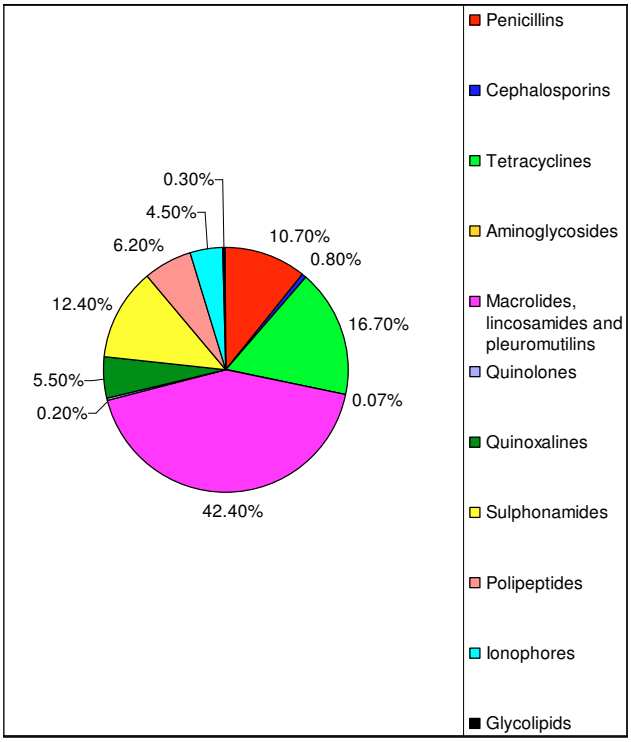

Fig. 2. Percentages of volume for sales of antimicrobials, 2002 - 2004. Source: Eager HA,[2] p. 45.

The volume of antibiotics used for treating and preventing disease is unknown and difficult to assess. Intensive farming systems have a rapid turnover rate, and profit margins are generally low. Infectious diseases have a negative effect on profitability, but the high cost of administering antibiotics to all the animals in the barn (metaphylaxis, i.e. sick as well as healthy animals, or prophylaxis, where antibiotics are given to prevent disease before it occurs) also affects profitability. Chronically ill animals are usually culled and not treated.

Antibiotic resistance

Individual studies

Few recent surveys and reports about 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, and vary in choice of antibiotics tested and other parameters. We review them here, but cannot draw firm conclusions.

In a limited number (varying from 1 - 8 isolates per antibiotic tested) of *Escherichia coli* isolates from poultry, 2/7 (28.6%) were resistant to chloramphenicol and 4/6 (66.6%) to avoparcin (related to vancomycin).[3] Since the 1990s, neither antibiotic has been allowed in food-producing animals in South Africa. Less than 20% were resistant to amoxicillin, fluoroquinolones and the aminoglycosides.

Oguttu *et al.*[4] (2008) reported on drug resistance in *E. coli* isolated from broilers raised on feed containing antimicrobials and from poultry abattoir workers. Isolates from broilers carried an exceptionally high level of resistance to tetracyclines (98%), fluoroquinolones (75.6%) and sulphonamides (78.7%). The levels of resistant *E. coli* from abattoir workers were only slightly higher than those isolated from the general population, and these were lower than the resistance levels of broiler-derived *E. coli*. Although cephalosporins are not used in poultry, 39.9% of the broiler *E. coli* isolates were resistant to ceftriaxone, which may be due to the transfer of a multidrug-resistant plasmid, or to extended-spectrum beta-lactamase (ESBL) production. Neither possibility was examined in the study.

Picard[5] (2010) reported that *E. coli* isolates from poultry were resistant to amoxicillin and trimethoprim-sulpha combinations (60%), tetracyclines (95%) and enrofloxacin (40%).

Georgnaras and von Holy[6] (2001) found high resistance to tetracycline in all *S. aureus* and some *Listeria* species (not *L. monocytogenes*) and *Salmonella* (except *Salmonella enteritidis*) isolates from a poultry abattoir and no resistance to danofloxacin.

Antibiotic resistance in *Campylobacter jejuni* isolated from chicken abattoirs in KwaZulu-Natal was high (>95%) for tetracyclines and ceftriaxone.[7] Broiler isolates were resistant to ciprofloxacin (9%), as were 24% of the isolates from layers. *C. jejuni* isolates from layers were also more likely to be resistant to gentamicin (19%) than those from broilers (2%). In this survey, about 45% of *C. jejuni* isolates were resistant to erythromycin, ampicillin and nalidixic acid.

Jonker[8] (2009), regarding *C. jejuni* and *C. coli* isolates from pigs and poultry (broilers), showed that *C. jejuni* tended to show more resistance than *C. coli*. *C. jejuni* isolates from Gauteng showed 95.5% resistance

to tetracylines, and those from the Western Cape, 70% resistance. Resistance to amoxicillin was 82.4% and to ceftiofur 94.4% in *C. jejuni* from Gauteng. Resistance was also found to macrolides (especially in pig isolates) and fluoroquinolones (especially in poultry isolates).

Of *E. coli* isolates from diarrhoea in calves and mastitis in cows, >40% were resistant to amoxicillin, and almost 60% were resistant to cephalosporins (cefuroxime and cephalexin) and tetracyclines.[3]

Of *S. aureus* and other species of *Staphylococcus* isolated from mastitis in cattle, >60% were resistant to penicillin and amoxicillin, and >40% were resistant to tetracyclines. Levels of resistance were far lower in the South African National Veterinary Surveillance and Monitoring Programme for Resistance to Antimicrobial Drugs (SANVAD) 2007 surveillance, where only 10% resistance to the 3 antibiotics was found.[1] Far less resistance was noted to other commonly used mastitis remedies. In contrast, about 80% of *S. pseudointermedius* isolates from pyoderma and other infections in dogs were resistant to amoxicillin, and about 20% were resistant to first-generation cephalosporins.[3] Petzer *et al.*[9] (2007) found resistance rates of 45% for penicillin, 37% for ampicillin, and 23% of tetracyclines in *S. aureus* isolates from milk.

Pasteurella, Mannheimia, Histophilus and related bacteria usually isolated from cattle respiratory infections showed a <20% resistance rate to commonly used antibiotics for such infections, such as penicillin, amoxicillin, ceftiofur, florfenicol (related to chloramphenicol) and tetracycline.[3]

Surveillance systems for antibiotic resistance

SANVAD monitors antimicrobial resistance in the country. The programme is the result of an appeal made by the *Office International des Épizooties* (OIE) to member countries to establish national programmes for managing antimicrobial resistance.[1] The OIE Regional Commission for Africa, at their 14th Conference in 2001, appealed to member countries to actively promote the prudent use of antimicrobials in animals and to establish national programmes for the management of antimicrobial resistance. To develop and standardise a surveillance and monitoring programme in South Africa, a research proposal was submitted to the National Research Foundation (NRF) for funding under the Bilateral South Africa-Sweden Scientific Collaboration Agreement. Funding resulting from this application provided the resources to set up a network of participating laboratories and to provide training to laboratory technologists.

In accordance with the OIE guidelines, South Africa's surveillance programme is based on 3 categories of bacteria: indicator bacteria, zoonotic bacteria and animal pathogenic bacteria. These categories provide the best opportunities to detect resistance where selective pressures are applied, carrier animals of zoonotic bacteria are treated, and clinically ill animals are treated, respectively.

The results of the 2007 SANVAD surveillance yielded levels of resistance that were generally higher than those reported in Europe for *E. coli* and *Enterococcus*. *E. coli* showed a 67% resistance to one or more commonly used antimicrobials, especially tetracyclines, fluoroquinolones and sulphonamides.[1] Poultry and pigs showed the highest levels of resistance, and commensal strains of *E. coli* showed higher rates of resistance than those associated with disease. This is probably due to prophylaxis or metaphylaxis.

Resistance levels in *Enterococcus* isolates were particularly high for tetracyclines, sulphonamides and neomycin. *E. faecalis* showed less resistance (12.5%) to vancomycin than did *E. faecium* (20%).

S. enterica showed resistance to tetracyclines and sulphonamides, and isolates from pigs also to chloramphenicol. The general levels of resistance were similar (except for pig isolates) to those quoted from most countries, except Sweden, where a concerted effort in eradicating *Salmonella* is reflected in a far lower resistance pattern in isolates.

Current disease control strategies

Vaccines

The principle of vaccination against bacterial diseases is firmly entrenched in agriculture in South Africa. Most farmers greatly prefer an effective vaccine to using antibiotics. One of the first veterinarians in South Africa, Arnold Theiler, founded the Onderstepoort Veterinary Institute and its main focus has always been the development and production of vaccines. Onderstepoort produces an extensive list of vaccines, and many imported vaccines are also available. Many of these vaccines are registered under the Stock Remedies Act 36, and are therefore freely available for laymen to use. Most available vaccines are very cost-effective, which also makes them an attractive prospect for farmers.

Infection control

Worldwide and in South Africa, veterinary medicine for treating food animals is changing profoundly.[10] Veterinarians are perceived by the public as possessing a narrow set of skills focused on treating companion animals that are ill or injured. The number of veterinarians required for primary health care on farms is decreasing because of an increased focus on preventive medicine. The need for veterinarians specialised in preventive medicine in food-producing animals is increasing. These encompass all segments of food production systems, environmental management, bio-security, disease eradication, laboratory diagnostics and regulatory bodies. This situation should change the way in which veterinary students are recruited and trained, although all South African veterinarians are already conversant with the basic principles of preventive medicine.

There are few large hospitals for animals in South Africa. Apart from the academic hospital at the Faculty of Veterinary Science at Onderstepoort, and those associated with charitable organisations, all the others are in private hands as part of a veterinary practice. The practice owners have a vested interest in keeping infection levels low. Veterinary practices are registered by the Veterinary Council, and they and their associated hospitals are regularly inspected by veterinarians designated by the Veterinary Council. The basic principles of infection control in the practice form part of the inspection.

Extensively farmed animals are usually treated on the farm of origin, and there is no standard for the facilities provided by the farmer. The animal may be treated in a field, a crush or a stable. Infection control under these circumstances is in the hands of the veterinarian, who has to educate the farmer if necessary.

A common intensive farming practice in South Africa is the 'all in, all out' system. The entire barn or house is filled with animals of a similar age which are then grown out to slaughter age or, in the case of layers, to the stage when they no longer produce eggs profitably. All the animals are then sent for slaughter, and the barn is depopulated, cleaned, disinfected and left empty for a week or two. This strategy decreases the build-up of resistant bacteria in a population of intensively kept food animals.

Biosecurity on farms is another strategy. Control of visitors to a farm, showering and changing clothing before and after entering animal houses, disinfection of lorries delivering feed, good fences properly maintained, and the quarantine and testing of newly introduced animals are all part of a farm's infection control measures.

Dairy cattle pose a special problem. Cows are bred throughout the year, to ensure a continuous supply of milk. Milking parlours are expensive to build, and so there is usually only one parlour on a farm.

Cows are usually milked twice a day, but high-producing cows are milked 3 times a day. These factors make infection control difficult, as the milking parlour is only empty for a few hours between the end of one milking and the next, every day of the year. There are continuous deliveries of feed and other supplies, as well as collections of milk, which complicates biosecurity measures. Cows also need to be kept in small camps close to the milking parlour, as they cannot walk long distances twice a day to the parlour and back to the grazing.

The supplier of fresh milk is paid a premium for milk with a low bacterial load, even though milk in South Africa is pasteurised before bottling. This ensures that the dairy producer implements effective hygienic principles and, as each batch of milk is usually tested for contamination, there is continuous monitoring of hygiene on the farm. This has an effect on infectious agents as well, and contributes to mastitis control. Milk used for other purposes, such as the preparation of dried milk powder, is subjected to far lower requirements, and farmers are also paid far less for their milk. Hygiene may be a problem on such farms.

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Part VII: Interventions

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Antimicrobial resistance (AMR) surveillance activities in South Africa have been described in Part V of this report. Surveillance – knowing the levels of resistance and the trends around the country and in different types of institutions – is essential, but is only useful to the extent that the data influence practice. That link is not made automatically, nor is it always easy. Choices must be made among the available interventions based on what will work best in a given situation, and taking into consideration feasibility, cost, likely impact, acceptability to patients and providers, political will, etc.

Clearly, surveillance and recent studies can inform revisions of the essential drugs list (EDL) and standard treatment guidelines (STGs). What is more difficult but still possible is that these data can influence and change antibiotic prescribing practices and result in policy formulation geared to limit inappropriate antibiotic use and, consequently, AMR and its spread. However, so far the efficacy and clinical outcomes of both EDLs and STGs have, since their implementation, not been adequately evaluated.

Reducing the burden of infectious diseases also reduces the need for antibiotics but, primarily, prevents illness. Vaccination and infection prevention and control in hospitals and other health care facilities are the two critical interventions in this category.

In this section, the status and challenges of all these interventions in South Africa are reviewed.

Prescribing practices and available treatment guidelines

When considering the problem of AMR and how to address the issue, it is important to look at it from two perspectives. Both laboratory and clinical practice play an important role and each will be addressed separately, although the two are not mutually exclusive.

From a laboratory perspective a critical deficiency in the South African setting is the adaptation of laboratory testing in the provision of relevant results. It is common practice in South Africa to adapt practice according to reports in the literature from abroad, without first assessing the situation locally. Unfortunately the state of AMR is not universally applicable and it is imperative that local data are made available, which may then either corroborate or refute the problems of resistance experienced elsewhere in the world.

A concerted effort to investigate the problem of resistance in nosocomial pathogens in a systematic and periodic manner is critical. Research funding needs to be invested in this endeavour, and the results of such investigations must be disseminated locally in such a way that will influence clinical practice.

Correct choice of antibiotic and adequate dosing is important in curbing the development of resistance, and the application of pharmacological principles, including pharmacokinetic and pharmacodynamic parameters, is critical in determining what the optimal drug and dose should be. Unfortunately, these criteria are seldom applied and the choice of antibiotic is often based on a laboratory report and familiarity with a particular agent. The reality is that the medical practitioner of today often does not have the time to read around the issues of antibiotic pharmacodynamics, and consequently inappropriate prescribing practices are common.

Specialist staff, including clinical microbiologists, clinical pharmacologists, hospital pharmacists and infectious disease sub-specialists, need to be part of a management team, especially for managing critically ill patients requiring antimicrobial therapy. Staff constraints are a serious hindrance to this approach, which will require not only the training of more specialists but also a change in mindset. The concept of a team approach and seeking of advice from others needs to be engendered, with broader consultation and acknowledgement of the consequences of inappropriate prescribing.

Great scope exists to improve overall antibiotic management in South Africa. The overuse of antibiotics extends to both the public and private sectors, and to all types of health care facilities (including physician offices). Not only are antibiotics prescribed for cases that do not require them (e.g. for viral illnesses, which do not respond to antibiotics), but also for prolonged duration, and two or more together inappropriately; there is a virtual absence of de-escalation. A recent nationwide survey in academic, public and private institutions (Prevalence of Infection in Intensive Care in South Africa study (PISA) – unpublished) revealed that all of these practices were rife.

What is needed is a formal, strategic programme of sustained reduction in consumption of all classes of antibiotics over the long term, and the strategies may be different in public and private hospitals because of differences in their organisation and governance. In this regard the results of the survey of antibiotic consumption practices in several private hospitals identified as pilot sites in the recently launched 'Best Care … Always!' (BCA) campaign (http://www.bestcare.co.za – see below) are eagerly awaited.

In private institutions in South Africa, it appears that the antibiotic prescribing fraternity has not yet accepted stewardship of the emerging problem of multidrug and extensive drug-resistant Gram-negative bacilli (refer to Part IV of this report). Currently, doctors in private institutions can decide, without consulting guidelines or other policies, whichever antibiotic they wish to prescribe, at whatever dose and for how long. In this regard, clinical pharmacists have now been employed in some private institutions in Johannesburg. The aim, in conjunction with clinical microbiologists (or in future, infectious disease sub-specialists), is to actively intervene in cases of inappropriate antibiotic selection, dose and duration as an integral aspect of an 'antibiotic care bundle' as opposed to adoption of antibiotic restriction policies. Unfortunately, this is not policy everywhere and structures to enforce such changes are still being tested.

Vaccination and its impact on infectious diseases – the South African experience

Vaccination has not only significantly reduced morbidity and mortality of a range of infectious diseases – its primary benefit and a great achievement – but the absolute reduction in infection rates secondary to widespread vaccination coverage also reduces the necessity for antimicrobial therapy. Less antibiotic use means slowing the spread of antibiotic-resistant bacteria. Vaccination is an integral part of reducing global trends in progressive AMR, and the consideration of whether to employ new vaccines should take this into account, as well as their primary benefits.

Historical overview

Edward Jenner heralded the start of the vaccine era in 1792 through demonstration of protective immunity to smallpox by active immunisation. Less than 200 years later, smallpox was the first (and still singular) communicable disease to be declared eradicated by the World Health Organization (WHO).[1] Since then, the repertoire of vaccine-preventable diseases has increased considerably.

Six vaccine-preventable diseases (diphtheria, measles, pertussis, poliomyelitis, tetanus and tuberculosis (TB)) are significant contributors to infant and child mortality. Before 1974, fewer than 5% of children worldwide had access to these vaccines.[2] This led to the launch of the WHO's Expanded Programme on Immunization (EPI), in collaboration with various organisations including UNICEF, with the aim of supplying vaccines targeting these six diseases to every child by 1990. By 1990, approximately 80% of children were reached (i.e. had received at least the third dose of diphtheria-tetanus-pertussis (DTP3) vaccine), preventing an estimated [3] million deaths annually. By 2007, 82% of children were being vaccinated. In the USA, the Centers for Disease Control and Prevention (CDC) reported in 1999 that cases of nine vaccine-preventable diseases had been reduced by at least 95% (Table I).[3] Vaccines work. Despite this demonstration of success (repeated in Europe and in a few other countries), vaccination rates vary significantly around the world. For example, DTP3 coverage rates for industrialised countries are estimated at 96%, but in sub-Saharan Africa and South Asia, rates are much lower.[4]

In 2000, the Global Alliance for Vaccines and Immunization (GAVI) was formed to facilitate a broader availability and administration of vaccines in developing countries.[5] South Africa is classified as a middle-income country and so does not qualify for financial support from GAVI and similar associations.[6] In addition to supplying low-income countries with vaccines, GAVI has assisted in accelerating the development and deployment of new (rotavirus, pneumococcal conjugate and human papillomavirus) vaccines and underused (hepatitis B and *Haemophilus influenzae* type B (Hib) vaccines.[4]

South African Expanded Programme on Immunisation (EPI)

The EPI was initiated in South Africa in 1995, which included vaccines against the six major vaccine-preventable diseases mentioned above.[7] Hepatitis B vaccine was promptly included within the first year of EPI initiation, followed by Hib vaccine in 1999. Bacillus Calmette-Guérin (BCG) vaccination was converted from the percutaneous route of administration to intradermal in 2000. South Africa was declared free of polio in 2006, with the last case reported in 1989.

The South African EPI has greatly impacted on childhood morbidity and mortality, significantly reducing the incidence of a variety of childhood diseases (Table II).

The South African EPI was significantly restructured in 2009, with the addition of 7-valent pneumococcal conjugate vaccine (PCV-7), rotavirus vaccine (Rotarix) and the pentavalent combination vaccine Pentaxim (which includes acellular pertussis and parenteral poliomyelitis components).[1] Furthermore, a pneumococcal booster dose at 9 months and Hib booster dose at 18 months were introduced.[1] The new EPI aims to contribute to reaching the fourth Millennium Development Goal by reducing mortality among children under the age of 5 by 66% for the period 1990 - 2015.

Production, distribution and cost

The worldwide demand for vaccines has been increasing exponentially, almost doubling in the past 5 years.[9] Manufacturers typically attempt to anticipate market demands 5 years in advance. Despite this, short-term needs remain unpredictable and are particularly problematic if manufacturing timelines are considered. Production is tightly governed in South Africa through the Medicines and Related Substance Act (Act 101 of 1965) and regulated by the Medicines Control Council as the statutory body.[10]

The South African governmental budget for vaccination in 2010 exceeded R1 billion.[11] Vaccines are procured from various multinational companies (Sanofi-Pasteur, Statens Serum Institute, Pfizer, GlaxoSmithKline, Herberbiovac and Novartis) under the auspices of the Biovac Institute, a private-public partnership situated in Cape Town. From this point, vaccines are either directly distributed by Biovac (Western Cape and areas of Gauteng) or to medical depots of the National Department of Health (NDoH). The Biovac Institute carries the contract for supply and distribution of vaccines in South Africa up to December 2016.[11,12]

Table II. Impact of EPI vaccination on childhood diseases in South Africa, 1980 - 2006[8]

	Cases reported to NDoH per year			
	1980	1990	2000	2006
Measles	19 193	10 624	1 459	86
Neonatal tetanus	166	58	11	6
Poliomyelitis	112	5	0	0
Diphtheria	57	34	2	1

NDoH = National Department of Health.

Table I. Decrease in cases of vaccine-preventable disease in the USA through 1998 as reported by the US Centers for Disease Control and Prevention[3]

Disease	Cases at baseline	Cases in 1998	Reduction (%)
Smallpox	48 164	0	100
Diphtheria	175 885	0	100
Pertussis	147 271	7 405	95
Tetanus	1 314	41	97.9
Paralytic polio	1 316	0	100
Measles	503 282	100	100
Mumps	152 209	666	99.6
Rubella	47 745	364	99.3
Haemophilus influenzae type b	20 000	63	99.7

The previous EPI vaccines were procured at a cost of approximately R 81.90 per child.[8] One of the major hurdles to introduction of new vaccines was the cost (remembering that South Africa is not a GAVI-supported country). Despite this, the new EPI was introduced and incorporated a range of new and underutilised vaccines. The revised 2009 EPI schedule costs R 1 338.00 per child in the public sector (based on government tender prices) and R 4 103.00 per child in the private sector, where the consumer pays in most cases through medical aid schemes.[6] Although this is a significant cost, vaccines in general are considered a highly cost-effective method of reduction of mortality, second only to supply of clean water.[2]

Coverage and mass vaccination campaigns

According to Health Systems Trust Statistics, DTP3 vaccination coverage in South Africa for 2009 was estimated at 101.7% ranging from 78.5% in the Free State to 121.5% in Gauteng (Table III).[13] Rates in excess of 100% reflect vaccinations over and above routine administrations, typically as part of mass vaccination campaigns. Individuals therefore received more than the routine amount of vaccine administrations.

Table III. Statistics from the Health Systems Trust depicting DTP3 and Fully Immunized Child (FIC) data for 2009

	DTP3	FIC (<1 year)
Eastern Cape	87.8	90.7
Free State	78.5	86.6
Gauteng	121.5	115.4
KwaZulu-Natal	95.3	84.9
Limpopo	118.6	99.2
Mpumalanga	107.7	92.2
Northern Cape	111.7	92.3
North West Province	92.4	86.2
Western Cape	95.7	102.5
South Africa	101.7	95.5

Current data from the WHO paint a slightly less optimistic picture with countrywide DTP3 rates estimated at 91%, translating to just under 900 000 infants out of a population of 985 000 receiving full DPT3 coverage,[11] but these figures must be considered very encouraging.

In 2010, the South African government embarked on mass vaccination campaigns focusing on three major pathogens – measles, poliomyelitis and influenza. The measles campaign was launched in response to the recent outbreak, predominantly in the Gauteng area. The epidemiology of this outbreak showed an age distribution different to that typically seen. In the Tshwane area, adolescents were most severely affected, while Johannesburg seemed to have the majority of cases reported among infants younger than 1 year of age (4 220 infants within total of 12 499 total reported cases). Polio was targeted in view of cases of wild-type polio in Angola and Nigeria.[14] Despite current vaccination practices, South Africa has not yet reached coverage for measles or oral polio vaccine (OPV) exceeding 90%. Furthermore, pockets exist with significantly lower coverage and data obtained from certain areas are very unreliable.[14]

The influenza campaign was the first of its kind in South Africa. The main rationale for this intervention was the already significant disease burden associated with annual infections, as well as the H1N1 outbreak since 2009, which caused 93 confirmed deaths. Despite the obvious advantages to making trivalent influenza vaccine widely available, only 1.3 million doses could be procured for an estimated high-risk population group of 6.6 million persons.[15]

These mass immunisation programmes are generally conducted every 3 - 5 years as a supplement to routine EPI activities. The main aim remains to reduce the number of susceptible hosts from crossing the epidemic threshold, and thereby reducing the possibility of outbreaks occurring.[14] The reduction in antibiotic demand is a secondary, though important, benefit.

Vaccines targeting bacterial disease

Pertussis. Despite the availability of an effective vaccine, 16 million cases of pertussis are still reported annually. The majority of these are found in developing countries, leading to almost 200 000 child deaths. The biggest impact on disease control has been through establishing vaccination campaigns. The so-called cocoon strategy was first proposed by the CDC in 2006 in an attempt to curb spread that was not covered with routine immunisation strategies. This involves giving a preschool booster dose and immunisation of adolescents,[16] coupled with vaccination of child minders, health care workers and contacts of newborns.[17] However, this practice is not currently advocated by the WHO.[11]

Streptococcus pneumoniae. The pneumococcus is a major pathogen of childhood worldwide,[1] and has been estimated to cause infection in 349 per 100 000 children annually in South Africa.[18,19] It is well established that the incidence of invasive pneumococcal disease has declined significantly with the introduction and use of pneumococcal conjugate vaccine (PCV) in children. The protective effect of childhood vaccination has been proven to extend to adults, reflecting the effects of herd immunity.[20,21] Although vaccine efficacy seems to be lower among HIV-1-infected children, impact may still be sufficient to significantly reduce the incidence of invasive disease and thereby the need for antimicrobial therapy.[22,23]

Tetanus. Neonatal tetanus still caused a staggering 59 000 deaths worldwide in 2008, with the majority of cases reported from Africa and southern and eastern Asia. The biggest impact on this disease has been through maternal vaccination, as treatment once infection has been established is exceedingly difficult, with mortality often approaching 100%.[4,24]

***Haemophilus influenzae* type B.** South Africa was the first African country to introduce Hib vaccine into its national EPI in 1999.[25,26] Since its introduction, rates of invasive infection have declined significantly. The most recent 2009 EPI schedule includes an additional booster dose at 18 months[1] in an attempt to further reduce rates of breakthrough invasive disease occurring after infancy.

Soweto as a setting for research into global infectious diseases priorities

Sociopolitical forces have played a major role in shaping the state of health and burden of disease in South Africa, and the township of Soweto is no exception to this rule. Soweto, a peri-urban township near Johannesburg, was established in the 1930s as a consequence of policies that sought to segregate the population on the basis of race. The population of Soweto is currently estimated to be 1.3 million predominantly black South Africans (although some estimates propose a figure of 3.5 million).[27,28] The far-reaching consequences of apartheid policy provided a platform for socio-economic instability that is still felt, despite South Africa's transition to democracy in April 1994; an estimated

28% of households earn less than R800 per month and 40% of household heads are unemployed.[27] Most Sowetans do not have access to private health care facilities, and an estimated 90% of children in Soweto use the local public health facilities.[29]

The under-5 mortality rate in South Africa was estimated to be 63 per 1 000 in 1995, and rose to 79 per 1 000 in 2005,[30] the increase being attributed to the HIV epidemic.[31] The strongly criticised inertia of the South African government to face the realities of the HIV/AIDS catastrophe until April 2004, when the national roll-out of antiretroviral therapy (ART) commenced, only served to increase the toll of HIV-related morbidity and mortality in this community.[32]

HIV prevalence among children admitted to Chris Hani Baragwanath Academic Hospital (CHBAH), the only secondary/tertiary public hospital serving Soweto, rose from 3% to 20% between 1992 and 1995,[33] with a 21% increase in in-hospital child mortality during the same period.[34] HIV prevalence among children admitted to the paediatric wards at CHBAH remained at 30% between 2000 and 2008.[35-37] It is now estimated that 54% of HIV-infected children in need of ART have access to this therapy in South Africa,[38] with 74% of Sowetan HIV-infected children in need of ART accessing appropriate care in the public health sector in the township.[39]

Because of the unique social and health care status and high HIV-1 prevalence in Soweto, CHBAH and Soweto serve as a pertinent, geographically defined area from which important research to evaluate the local burden of infectious diseases and possible strategies for infectious disease prevention has emanated over the past 15 years.

The Respiratory and Meningeal Pathogens Research Unit (RMPRU), formerly known as the Pneumococcal Diseases Research Unit, was established in 1995. The RMPRU, which was initially focused on researching pneumococcal disease, is now mandated to perform research aimed to evaluate: (*i*) antimicrobial resistance in respiratory pathogens; (*ii*) research and development of pneumococcal conjugate and common protein-antigen vaccines; (*iii*) the impact of the local HIV-1 epidemic on respiratory and invasive diseases, e.g. otitis media, sinusitis, pneumonia and meningitis; and (*iv*) respiratory viruses and their interaction with bacteria in respiratory infections.

Childhood pneumonia aetiology studies conducted in Soweto in the 1990s indicate that *Streptococcus pneumoniae* is the commonest bacterial cause of community-acquired pneumonia in HIV-infected and uninfected children under 5 years of age in Soweto.[40] Similarly, *S. pneumoniae* was observed to be the most important aetiological agent in HIV-infected children admitted to CHBAH with bacterial meningitis.[41]

In 1998, RMPRU embarked upon a pivotal double-blind placebo-controlled study of 9-valent pneumococcal conjugate vaccine (PCV) in Soweto, in which 39 000 infants were enrolled with the aim of describing the efficacy of the vaccine in a setting with high HIV prevalence. This study demonstrated a highly significant 85% reduction in invasive disease caused by vaccine-serotype pneumococcal strains, and for the first time demonstrated the safety and efficacy of PCV in HIV-infected children.[29] The findings of the Soweto PCV study, and a similar study conducted in The Gambia in 2000 to 2003,[42] provided compelling evidence for the incorporation of PCV into the EPI schedules of developing countries, despite initial concerns regarding the cost of the vaccine.[43] In August 2008, 26 countries offered PCV vaccination as part of their EPI[44] which increased to 43 countries by January 2010.[45] PCV was included in the South African EPI in April 2009.

Additional vaccine probe studies arising from the PCV trial have implicated the pneumococcus as being a significant co-pathogen in children presenting with radiographically confirmed pneumonia, viral pneumonia, and culture-confirmed TB at the study site.[46-54]

The CHBAH-based research unit has since focused more closely on other vaccine-preventable diseases, and now includes a vaccine-preventable diseases research dimension. Madhi and colleagues have published widely on the differences in vaccine response between HIV-infected and uninfected children to PCV, [29,53,55-60] Hib conjugate vaccine,[61-64] rotavirus vaccine,[65,66] parainfluenza virus type 3 live-attenuated vaccine,[67] and novel vaccine preparations[68] through studies conducted at the site. Vaccination strategies in adults have also been explored in studies conducted by the unit, and efficacy and safety data of trivalent inactivated influenza vaccination in HIV-infected adults has recently been described.[69] Influenza vaccination studies in pregnant women are in progress, and plans are under way to conduct an *S. agalactiae* vaccination study in pregnant women attending antenatal clinics in Soweto.

Prevention strategies other than vaccination have also been explored in studies conducted by the RMPRU. The use of chlorhexidine vaginal wipes to prevent early-onset neonatal sepsis in infants born to mothers giving birth at CHBAH was recently explored by Cutland and colleagues,[70] who demonstrate that chlorhexidine has no advantage over water wipes of the external external genitalia before delivery. A further prevention strategy, that of providing primary isoniazid preventive therapy (IPT) to HIV-1 infected children with access to ART in order to prevent them from developing active TB, was evaluated as part of a multicentre study; the results of this trial failed to demonstrate an advantage of IPT over placebo in protecting against the primary outcome of TB disease-free survival in the intervention group.[71]

A significant future direction for research planned by the unit includes involvement in a multinational case-control study to determine the aetiology of childhood pneumonia in the era of HIV-1 infection, access to ART, urbanisation, and current vaccination policy.

Soweto is beset by overwhelming challenges, including the high burden of disease. A wealth of research activity aimed at delineating the major infectious diseases affecting children has been conducted in this setting. This research has impacted positively not only the individuals residing there, but has had a major impact on the health status of children and adults in South Africa, Africa and the developing world.

Summary: Vaccination as a means of limiting AMR

Vaccination has not only significantly reduced morbidity and mortality of a range of infectious diseases, but the absolute reduction in infection rates also reduces the necessity for antimicrobial therapy. Its role in reducing global trends in progressive AMR should be recognised formally, as a secondary but important benefit.

The current status of infection prevention and control in South Africa

Infection prevention and control (IPC) is a neglected field of medicine in South Africa that is now gaining new prominence. This area has been identified by the national Minister of Health, Dr Aaron Motsoaledi, as one of the priorities in health care in South Africa. The country faces increasing demands on its health care services, driven at least in part by the HIV-1 and TB epidemics. Antibiotic resistance is a major concern,[72,73] and with the lack of new antimicrobials on the market, IPC becomes even more important as a strategy to combat the threat and expense of antibiotic-resistant organisms.

Infection prevention relates to practice targeted at decreasing health care-associated infections while infection control refers to the management of nosocomial outbreaks. This document outlines the currently available resources for IPC and highlights current activities in the field. Areas of emphasis are:

- staffing
- policies
- training
- additional resources
- current problems
- potential solutions.

There is a dearth of information in the public domain regarding many of the above, and much of the information cited here has been sourced from personal contacts, as well as first- and second-hand experience. Where possible, original sources have been acknowledged.

South Africa has a public and private health care structure. Public health care serves approximately 85% of the population, so much of this document deals with infection prevention and control in the public sector. However, the private sector faces similar challenges; where possible, information from the private sector is included.

Numbers of IPC practitioners

According to draft legislation,[74] the currently recommended staffing levels for IPC practitioners (IPCPs) is 1 per 200 beds. There is some debate about the validity of this ratio,[75] as some feel that it should be revised to take into account the nature of the hospital and its bed allocation (the complexity of the cases admitted), with higher level hospitals possibly requiring more IPCPs. The NDoH recently completed a survey of IPCP numbers throughout the country (T Apalata – personal communication). Of the hospitals responding (Western Cape data were missing at the time of writing), 253 IPCPs were identified; no facility surveyed had the required number of trained IPCPs based on the recommended ratio. A survey in the Western Cape in 2005[76] found that in tertiary hospitals, the ratio of IPC nurses to acute beds was 1:400, while it ranged from 1:250 to 1:300 in smaller hospitals. No official figures were obtained from the private sector, but every hospital has a designated person tasked with the IPC function. In most hospitals, this person has a combined post, usually with occupational health and safety (OHS). While the IPCPs certainly add value to managing key OHS risks to staff, the additional functions detract from the time available for traditional IPC activities. In hospitals with more than 300 beds, there is a full-time equivalent (FTE) dedicated IPCP post. The IPCP manpower is further supplemented by the designation of an IPC link nurse in all units.

In the recent NDoH survey, 116 of the 253 IPC staff were not employed primarily as IPCPs at all and were performing their infection prevention function either 'on the side' or out of interest. There is a lack of a clearly defined career path for formally employed IPCPs, resulting in IPCPs moving to other areas of nursing (e.g. theatre management), a situation that will probably continue unless this issue is addressed.

Even among staff employed formally as IPCPs, there is a common feeling in both the private and public sector sthat IPCPs are regularly assigned duties that intrude on the time available to perform IPC functions. These extra duties include acting as unit managers, OHS officers, practitioners and theatre scrub nurses. It is also worth bearing in mind that many international recommendations regarding the ratio of IPCPs to bed numbers assume the presence of an epidemiologist and/or microbiologist in the infection control team. In South Africa, many hospitals do not have microbiologists or epidemiological support on site, and the IPCP therefore has additional responsibilities (for which they are not specifically trained) related to infection control.

Dedicated infection control units

There are three academic centres in South Africa with dedicated infection control units: Stellenbosch University, the University of the Witwatersrand and the University of KwaZulu-Natal (UKZN). These are involved in infection prevention activities as well as outbreak control. In addition, the University of Cape Town and National Health Laboratory Service (NHLS) have started a satellite National Institute for Communicable Diseases (NICD) epidemiology unit that will offer laboratory and clinical epidemiological services to assist with outbreak investigations in Cape Town (and potentially further afield). Whether the presence of these units provides sufficient resources for the entire country is difficult to assess; a detailed analysis of what resources are required, and what resources are offered by the units, is necessary.

Training in infection control

There are currently three academic centres offering postgraduate training in infection control:

- University of the Witwatersrand (IPC certificate and postgraduate diploma)
- Stellenbosch University (IPC certificate and postgraduate diploma)
- UKZN (IPC certificate and BSc Hons degree).

In addition, a number of centres offer IPC certificates, including the Netcare, Life Healthcare and MediClinic private hospital groups and the University of Limpopo (previously known as Medunsa). At present these courses are not recognised by the South African Nursing Council for career development purposes, although efforts are being made to change this. The content of the courses is also not standardised nationally.

In many provinces formal training in IPC is not a prerequisite for appointment to the post of IPCP, either in the public or private sector. Of the 253 IPCPs identified by the NDoH survey, 149 (58.9%) had no formal training in infection control. Of those that did, 78 had a certificate in IPC, 14 an IPC diploma and 12 a BSc Hons in IPC.

In a survey conducted in the Western Cape[76] provision of infection control training to general staff was also poor, with only 10% of staff in hospitals with <200 beds having received any formal IPC training in the preceding 4 years. In hospitals with >400 beds, 40% of staff had received this training. These figures are consistent with those described in a national survey performed by the Human Sciences Research Council looking at HIV/AIDS in the workplace. They found that just over 35% of staff had received training in standard (universal) precautions.[77] Although many IPCPs may have no formal training in the field, it is likely that many have accumulated a number of years' worth of experience. It is unclear whether this experience would be sufficient to include a 'grandfather' clause should recognised formal IPC training become a prerequisite for appointment as an IPCP.

A compromise may be to offer experienced, but untrained, IPCPs priority and funded places in training programmes.

Management and oversight

In the public sector, IPC falls under either the quality assurance directorate or directly under nursing management. In the private sector, IPCPs mostly report directly to nursing management. The reporting therefore varies from hospital to hospital, which causes confusion. There are plans within the NDoH to discuss these arrangements. Clearly, a standardised management and reporting structure implemented nationally would be ideal.

Each province should have a provincial infection control committee with the mandate to ensure adherence to national and provincial policies, review such policies, review surveillance data, evaluate infection control needs, etc. It is not known how well these committees are functioning.

Each hospital should have an infection control advisory committee. The audit performed by the NDoH showed that the membership of these committees consisted primarily of nursing staff, medical officers and pharmacists, followed by microbiologists and environmental health staff. An important point noted by this audit was the poor representation by hospital administration and management. Without adequate representation by hospital management on infection control committees, recommendations made by these committees are unlikely to be implemented.

At present there is draft legislation governing communicable diseases (which includes infection control).[74] There are also a number of national and provincial policies related to infection control, published by the NDoH as well as by various academic centres. These include policies related to prevention of nosocomial transmission of TB, prevention of health-care-acquired infections, requirement for infection control, an IPC manual (in press), guidelines for prevention of ventilator-associated pneumonia (VAP), guidelines for prevention of nosocomial infections, etc. On the face of it there is therefore adequate information available regarding IPC. The only concern is that there may be too many guidelines, sometimes giving conflicting messages. Standardisation of these guidelines is therefore required.

Many facilities in the public sector draft their own infection control policies, based on national and/or provincial guidelines. This is an appropriate approach in order to ensure that policies are relevant to each facility. However, it is not clear whether these policies adhere to the principles in the national guidelines, how often policies are updated or how accessible the policies are to staff in the facilities. To the best of our knowledge, there have been very few well-conducted surveys to evaluate these issues.

Other IP resources/structures

Infection Control Society of Southern Africa (ICSSA)

ICSSA's mandate is to promote infection control throughout the country, mainly through the formation and support of local 'chapters'. However, sustaining these local chapters is proving difficult. At present, there are three established local infection control societies: Western Cape, Gauteng and Pretoria. The corresponding society in the Free State communicates with members electronically, but no longer holds meetings that individuals can attend. The KwaZulu-Natal chapter has undergone a setback since the IPCP tasked with re-forming the chapter moved to theatre management. This confirms the problem related to lack of career paths for IPCPs.

The local chapters function primarily by holding seminars and other educational activities and provide a forum for IPCPs to discuss policy and practice. More recently, members of the Western Cape Infection Control Society have been represented in the Provincial Infection Control Committee of the Western Cape. The KwaZulu-Natal Provincial Committee has recently been placed under the IPC unit at the UKZN. To date, members of the Gauteng and Pretoria infection control societies have not been included in their provincial committees.

Surveillance

There is no formal, standardised reporting scheme for nosocomial infections in the public sector in South Africa. Ongoing active surveillance cannot be managed, given the shortage of IPCPs in the majority of facilities. Point prevalence surveys have been conducted occasionally, but again, without these being performed regularly, it is difficult to measure trends or to use the data effectively.

Few surveys of IPC practices are available in the public domain. One conducted in the Western Cape[76] found a number of breaches of what would be considered standard practice. These included needles left in multidose vials in 10% of the wards surveyed, overfull sharps containers in 12% of the wards, and blood splatters around sharps containers in 20% of the wards. Encouragingly, 95% of the wards had provision for hand disinfection – however, the study did not examine compliance with hand hygiene.

A study conducted at Red Cross War Memorial Children's Hospital found hand hygiene compliance rates to be approximately 60%, and that hand hygiene compliance was better after patient contact than before.[78] A survey of disinfection of nasopharyngoscopes found that more than half of respondents did not follow published guidelines for disinfection of these instruments.[79] This again points to the disconnection between knowledge and practice. A survey of infection control in dental practices found that, despite adequate provision of knowledge, there was poor compliance with recommendations, particularly with respect to hand hygiene, use of eye protection, and cleaning and disinfection of dental equipment.[80]

Other evidence of shortfalls in infection control practice can be gleaned from the various reports of outbreaks of nosocomial infection from South Africa hospitals. However, this is a poor surrogate, as it provides a snapshot of practices when a problem occurs, which may not necessarily reflect what is being done routinely. However, it could be argued that if infection control processes were being followed properly and consistently, the outbreaks would have been less likely to occur.

A common breakdown in IPC that has been identified during outbreak investigations is that of contamination of parenterally administered fluids or solutions by multiple use of single-dose parenteral supplements.[81-83] The Western Cape has recently issued guidelines about the use of multidose vials, as has at least one of the private health care groups, but as with all policies or guidelines, the degree to which they are enforced is not clear.

Movement of patients and staff between hospitals has been implicated in transmission of resistant organisms in more than one study.[84,85] This practice, while certainly likely to contribute towards transmission of organisms, may be very difficult to prevent, as movement from one facility to another is often essential for effective clinical management of patients, but it does mean that resistance problems may be shared in the community, and thus provide a rationale for community action.

Overcrowding has been described in many published outbreak investigations,[82,86] as well as in a report on an outbreak of *Klebsiella* sepsis and necrotising enterocolitis at a Gauteng Hospital (2010). While it is not always possible to prove that overcrowding is the sole reason for an outbreak, it is hard to argue against the likelihood of overcrowding resulting in a breakdown in IPC practices.

Some strategies for optimising IPC in hospital settings are working. The BCA campaign, which links the public and private sectors and facilitates communication across the sectors, is thought to be having an impact.

Best Care…Always! (BCA) as a model for optimising IPC practice

Health-care-associated infections (HAIs) are among the most common and serious adverse events in hospitals globally, occurring in about 1 in 10 admissions overall. A recent meta-analysis provides evidence that the problem of HAIs is much bigger in the hospitals of developing countries than in the industrialised world.[87] The prevalence of HAIs is 15.5 per 100 patients, at least double the overall rate in Europe, and the incidence of HAIs acquired in intensive care units (ICU) is 34.2 per 1 000 patient-days, triple the rate in the USA. Regardless of the setting, infections such as surgical site infections (SSIs), VAP, catheter-associated urinary tract infection (CAUTI), and central-line-associated bloodstream infection (CLABSI) cause considerable morbidity and mortality, waste precious resources and can clearly be reduced if not entirely eliminated. Prevention of HAIs therefore deserves high priority in all health systems.

Although HAI prevention targets are quantitative, the institutional culture in health care facilities is harder to quantify than are infection rates. However, improvement of safety is facilitated by improvement of the safety culture, which can be measured. A standardised safety culture survey can be used to assess the attitudes and beliefs of frontline teams about the environment in which we expect high performance but less often achieve it.[88] Another important element at the heart of improvement science is the use of carefully designed checklists, which can, as Atul Gawande, lead researcher in WHO's safer surgery programme puts it, 'get the dumb stuff out of the way'.[89] That safety can be dramatically enhanced by the appropriate use of checklists has been demonstrated in recent landmark surgical studies.[90,91] However, sustained effort over time is required, not to 'tick the boxes' but to make sure that the correct steps occur in key clinical processes, every time. Most hospitals that achieve success take 1 - 2 years to get to the desired level of performance.

For these reasons it was mandatory for South Africa to implement a campaign with urgency.

Aims of the BCA campaign in South Africa

Launched at the 3rd joint Federation of Infectious Diseases Societies of Southern Africa (FIDSSA) Congress in Sun City (20 - 23 August 2009), the BCA campaign is a uniquely collaborative effort among health care organisations, clinical teams and supporting stakeholders and organisations across South Africa including funders, vendors and professional societies, including FIDSSA. It advocates a non-punitive, 'just culture' approach and emphasises measurement (not only to establish a baseline but more importantly to monitor the effects of interventions), shared learning and continued iterative improvement through the implementation of a relatively small number of simple, evidence-based tasks aggregated in 'bundles' that should be performed every time on every eligible patient.

There are four BCA infection prevention interventions (CAUTI, CLABSI, SSI and VAP, mentioned above) that collectively represent the majority of HAIs for which local versions of internationally developed care bundles have been endorsed by the BCA task force and expert panel. Measurement tools have also been developed, adopted or adapted. These tools do not require a sophisticated data infrastructure. Bundle implementation coupled with a programme to improve safety culture produces results. For example, in Michigan, USA, central-line infection rates have been driven to zero in many of the 100 or so ICU members of the Keystone initiative.[92] Importantly, low infection rates can be sustained through continued effort. Such programmes have a high return on investment, in both lives and money saved.

Another aim of BCA in the future is to introduce antibiotic stewardship programmes as an integrated component of the campaign. One goal is the development of an 'antibiotic use bundle' to reduce inappropriate antibiotic prescribing in an attempt to promote appropriate choice, dosing and duration of antibiotic therapy. The ultimate aim is to optimise microbiological and clinical outcomes while simultaneously minimising the development of antibiotic resistance.

The BCA approach does not dispense with individual accountability or with education, but recognises that education and the diligent effort of solitary individuals cannot by themselves effect sustained improvement in practice or outcomes. What is needed instead is to redesign clinical processes for greater reliability.

Progress with implementing the BCA campaign in South Africa

In the private sector, hospital groups that have implemented all or some of the BCA bundles include the Life Healthcare, Netcare, Medi-Clinic and National Hospital Network (NHN) groups of hospitals. In the public sector, 14 Gauteng hospitals, several in the Free State and 9 in the Western Cape have joined the campaign, making a total of 192 BCA-affiliated hospitals in South Africa. Over 600 active infection prevention interventions have been introduced in these hospitals as follows: VAP (74%, *N*=143), SSIs (78%, *N*=150), CLABSI (75%, *N*=144), CAUTI (80%, *N*=154). Furthermore, at least 7 hospitals in the private sector have launched antibiotic stewardship programmes involving clinical pharmacologists who, in conjunction with clinical microbiologists, prospectively audit antimicrobial use with intervention and feedback.

Within the BCA network, many of the early adoption hospitals have provided mentorship to those who started later. A website (http://www.bestcare.org.za) has been established as a vehicle for learning and obtaining implementation material, to share best practices and as a discussion forum for staff in participating hospitals. Monitoring and evaluation has obviously been a strong focus for the campaign, with almost all participating hospitals now measuring at least one intervention on an ongoing basis. There is an ongoing journey towards improvement involved in establishing reliable best practice. Participating hospitals are learning the science of monitoring and evaluation for improvement, which uses different statistical tools and concepts than traditional measurement for research.

Selecting and defining measures within the constraints of the public sector has been a critical focus of provincial government in South Africa. Successfully implementing measures for CLABSIs and VAP, based on 'incidence per 1 000 intervention days', has been a serious challenge because of the difficulty of collecting

device-day denominator data. Hence hospital teams in Gauteng have developed their own outcome measures for each of the bundles. One example is the measurement of days between CLABSIs in the neurosurgical ICU of the Steve Biko Academic Hospital in Pretoria (Fig. 1).

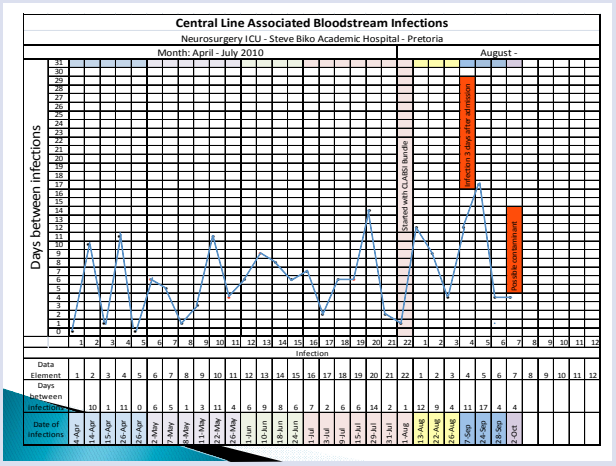

Fig. 1. CLABSI infection rates depicted as 'days between infections' (courtesy of EM de Bruin, Operational Manager, Neurosurgery ICU, Steve Biko Academic Hospital, Pretoria).

The aim is to develop a process that will ultimately result in viable measures for tracking the impact of the BCA bundles on the incidence of HAIs in public hospitals. Lessons learnt may also be applicable to the private sector, especially in making the data more accessible to front-line staff.

Many organisations worldwide have implemented strategies, campaigns and programmes in hospitals to improve patient safety and to support 'best practice; obtaining results is difficult. Knowledge and guidelines are widely disseminated but are at best inconsistently applied, and it often takes years before routine incorporation into practice and improved clinical results occur. For example, in developed countries patients receive 'recommended (evidence-based) care' only about half of the time.[93] During hospital admissions 10 - 17% of patients suffer an adverse event, and around half are considered preventable. The changes needed in organisational, team and individual clinical practice for real, sustained improvement are a challenge for all health care systems.

BCA is potentially a significant contributor to the development of widespread clinical systems improvement capacity in both private and public hospitals, and for a future health care system in which public and private care divisions may be less clear and the unifying focus is on quality of care.

Summary: IPC as a means of limiting HAI

It seems clear that infection prevention and control is not being practised adequately in South Africa. The key reasons for this are most probably a lack of IPCPs, as well as a lack of training among a significant number of IPCPs. Underlying reasons for the lack of training are probably mutifactorial, including poor job descriptions, a lack of training opportunities (particularly in the past), no perceived need among management for such training, and lack of time to receive training. The solution to these problems sounds easy – employ more well-trained IPC staff. However, for this to happen prior training in IPC should ideally be a prerequisite for employment (taking prior experience into account), and clearly thought out and well-communicated career paths should be implemented. Furthermore, employing extra IPC staff will require additional funding, and it is not known whether this is available. Creative approaches should be sought, and there may be a need to move away from the paradigm of dedicated IPCPs and involve more staff employed in other sectors in infection control responsibilities. Ideally, there needs to be a comprehensive review of the systems involved in infection control to inform new thinking on infection prevention systems, structures and roles, which is beyond the scope of this document.

There is a need for more data related to the incidence of nosocomial infections. Ideally, there should be a national strategy to collect data in a standardised, systematic fashion, and the means of doing this using current resources needs to be discussed. Given current staffing concerns, active surveillance is unlikely to be sustainable in the long term, and better use of existing infrastructure, such as the hospital and laboratory information technology systems, may be more realistic. Existing infection control units and societies should take the lead in this, and, in conjunction with the NDoH, as well as other interested organisations, discuss and make recommendations for surveillance that is cost-effective, reliable and of clinical value.

Conclusion

In this paper, we have sought to describe the barriers which exist to curtailing the problem of AMR in public and private health care facilities in South Africa. It is likely that, if current practices of indiscriminate antibiotic prescribing, suboptimal IPC practice, and reluctance to involve nursing and medical staff with higher degree training in infectious disease management in patient care are not dealt with in the next few years, patient outcomes may well be severely impacted upon. Promising primary preventive interventions that will assist in halting the spread of AMR organisms do exist, however. A concerted public/private partnership, with strong leadership by the NDoH, has the potential to have a lasting and positive impact on the issue of emerging AMR. The expertise base exists in South Africa, and needs to be broadened through up-training of nurses and doctors with special interest in the management of infectious diseases. The time to act is now.

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Part VIII. Future directions for GARP

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Underlying the creation of the Global Antibiotic Resistance Partnership (GARP) as a global alliance was the recognition that antibiotic resistance is a global problem, that some of the tools needed to understand and manage it could be shared globally, but that actions to control it and to ensure access to antibiotics when they are needed must take place at the national level. South Africa is fortunate in having a well-developed cadre of health care professionals already addressing antibiotic use, evident from the wealth of programmes and information included in this report but, even so, resistance is a growing problem. In countries that lack a strong medical system, the challenges are even greater.

Even in South Africa, information is not generally known across sectors, e.g. there has been little awareness of the details of agricultural antibiotic use and resistance among hospital professionals and vice versa, and the knowledge base needed for policy making has large gaps. During this first stage, a GARP South Africa Working Group was established (see Part I), including the range of relevant sectors and interests, and the current situation was analysed, resulting in this report and a desire to follow on with policy recommendations.

In the second phase of GARP's global agenda, work will continue in the four GARP phase 1 countries (India, Kenya and Vietnam, in addition to South Africa), with the Working Groups leading in honing the recommendations and developing 'critical paths' for implementation. This includes commissioning demonstration projects and gap-filling research, where those are part of the critical paths. (The information generated in these small studies will either support or halt the continued progress of recommendations.)

At the same time, a new set of GARP countries will be identified, and work will begin to assess the existing information and ongoing programmes, and to recruit multidisciplinary Working Groups to lead these, as has been the case in GARP phase 1 countries. South Africa is a model for new GARP countries, because it has had relatively lesser direct involvement from the Center for Disease Dynamics, Economics & Policy (CDDEP) than have India and Kenya, and fewer resource inputs than Vietnam. GARP is sustainable only to the extent that work is conducted locally with minimal (but not zero) external funding.

The other force that will drive the continued existence and progress of GARP country efforts is the global network that is evolving. Over the past 3 years, connections have been made among the 4 Working Groups, and lessons have been shared among countries. We anticipate that this network will strengthen over the years, including the formal GARP country efforts, international organisations (especially the World Health Organization), groups like ReAct-Action on Antibiotic Resistance (http://www.reactgroup.org/), and the many individual programmes and researchers involved in antibiotic-related work.

The First Global Forum on Bacterial Infections: Balancing Treatment Access and Antibiotic Resistance (www.globalbacteria.org) will cap GARP phase 1. This major international scientific meeting for scientists, clinicians and policy makers from all over the world – mainly from low- and middle-income countries – takes place in New Delhi on 3 - 5 October 2011. At the Global Forum, the GARP Working Groups will discuss their recommendations and plans to move forward, as well as exchange information and ideas on persistent challenges. The Global Forum is attracting policy makers as well as those of us who produce evidence toward policy change, as a step toward bringing these threads together.

Future directions

Finally, it is important to identify future challenges regarding antimicrobial resistance (AMR) in South Africa that must be addressed going forward. All the individual steps identified here build toward placing AMR on the public health policy agenda, stressing the health consequences of antibiotic resistance and its current and rising economic costs. The evidence provided through GARP should support a stepwise response that is co-ordinated and achievable, given the current South African realities. If this report and the GARP effort are to have any significance, they must be translated into policy changes that will conserve the usefulness of antimicrobials going forward into the future.

Some of the specific challenges and information needs are to:

- determine the true economic impact of antibiotic use and misuse and AMR on our population, a task that requires global collaboration on methods and local data
- conduct a careful analysis of the appropriateness of antibiotic-prescribing patterns in various health care delivery settings. This will be facilitated by developing ready mechanisms to access antibiotic-prescribing information via hospital and community pharmacies, health care funders and others, and providing incentives for data to be analysed.
- calculate the costs and benefits of vaccination v. antibiotics for infectious disease prevention, including the 'antibiotic-sparing' effect of a lesser infectious disease burden
- strengthen the current AMR surveillance systems and fix identified weaknesses. This involves adding surveillance capacity in regional, district and primary (including rural) health care facilities that are not currently represented in the system, which is dominated by academic centres and private pathology microbiology laboratories.
- pay greater attention to hospital-acquired infections, firstly determining the national prevalence and, secondly, tracking the incidence of these infections. Enhanced AMR surveillance of the most dangerous organisms is a priority.
- updates of standard treatment guidelines and the essential drugs list with relevant AMR data
- collaborate more closely, participate in joint research projects, and share data on antibiotic consumption, supply chain and resistance – clinicians and veterinarians – not just for AMR, but for a broader set of zoonotic diseases
- support the Infection Prevention and Control (IPC) programme through training, specialist registration with the South African Nursing Council, clear job descriptions and allocation of relevant responsibilities. We need to build and empower a cadre of current and future IPC practitioners.

It is envisaged that many of these challenges will form part of research activities that will be more clearly defined for eager young researchers in the AMR field. Together with the strong GARP South Africa Working Group, we will be able to advance the process systematically, working through these issues.