THE SOUTH AFRICAN ANTIMICROBIAL RESISTANCE STRATEGY FRAMEWORK

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South Africa faces an overwhelming burden of infectious diseases at the heart of the HIV and tuberculosis pandemic. Largely unnoticed, the rise of antibiotic resistance in our country is now highly visible and tangible to health-care professionals and the public alike. With outbreaks of MDR bacteria closing wards and causing high morbidity and mortality, a strong response as part of the WHO Global Action Plan is required. The adoption of the Antimicrobial Resistance National Strategy Framework is the first step in this response, and can be seen as a blueprint for other middle-income countries. Furthermore, many of the interventions described here are applicable across health resource settings.

Infections constitute South Africa's greatest burden of disease *(1)*. The collision of two pandemics, HIV (12.2% of the population, 6.4 million persons in 2012) *(2)* and tuberculosis (prevalence of ~1,000/100,000 population) *(3)* has dominated the health landscape for over 20 years. In the second national burden of disease study (1997–2009), HIV was responsible for the highest number of deaths (31.2%), ahead of cerebrovascular disease (6.2%), tuberculosis (5.4%), lower respiratory tract infection (5.2%) and ischaemic heart disease (4.4%) *(1)*. Despite nearing elimination, malaria too continues in three of South Africa's nine provinces, and neglected tropical diseases, predominantly schistosomiasis, are a major, yet largely undocumented, burden in many parts of the country. Three quarters of schoolchildren at a junior school in Mbashe district of the Eastern Cape Province were found to have *S. haematobium* in urine *(4)*.

The true burden of bacterial infection (HIV- and non-HIV related) in South Africa remains incompletely documented due a high level of empiric management and an overall paucity of samples being sent for laboratory diagnosis. Although reduction in bacterial disease burden has occurred for some infections *(5)* as a result of South Africa's extended programme of immunization, respiratory, enteric and meningitis-related disease remain the predominant causes of bacterial infection in the country *(6)*. The true burden of fungal infection too is poorly understood, although a greater level of understanding of the burden of deep fungal infection in HIV through enhanced surveillance of cryptococcosis and the identification of new fungal species in the South African population *(7)* is increasing our understanding.

It follows, that with such a high burden of infection, an equally high burden of antimicrobial use occurs and hence, antimicrobial resistance. Over 2.5 million South Africans currently receive antiretroviral therapy (ART), with a significant increase expected once the criteria for initiation eases from CD4 T lymphocyte count of <350, to <500 cells/mm^3. Current rates of transmitted resistance to first line ART remain low in some provinces (<5% in Gauteng and Western Cape), yet are increasing in others (5–15% in KwaZulu Natal, Free State and Eastern Cape), and are predicted to rise as rollout of ART continues *(8)*. A level of 10–17% has been documented in more mature epidemics in developed countries *(9)*. The World Health Organization estimates between 400,000–600,000 cases of tuberculosis occurred in 2012, multi-drug-resistant (MDR) tuberculosis cases comprising 1.8% of new cases and 6.7% of retreatment cases respectively *(3, 10)*. Heightened surveillance for extensively-drug-resistant (XDR) tuberculosis is increasing our understanding of true extent of drug-resistant

Table 1: Antibiotic resistance profiles in human and animal health in South Africa

Human Health

	Resistance profile	Comments
Gram-positive	Methicillin-resistant *Staphylococcus aureus* (MRSA)	>50% of all hospital-acquired *S. aureus* isolated from the blood of sick patients in public hospitals in 2010 were MRSA.[i] MRSA accounted for three quarters of all hospital-acquired *S. aureus* infections in a large tertiary level paediatric hospital.[ii]
	Vancomycin-resistant Enterococci (VRE)	In 2012, there were large outbreaks of VRE in public and private hospitals in South Africa. *Enterococcus faecium* bloodstream isolates from the private sector between Jan–Jun 2012 showed variable sensitivity to vancomycin ranging between 33–100% depending on geographical location.[iii]
Gram-negative	ESBL-producing Bacteria	In studies from 2010 and 2012, up to 75% of *K. pneumoniae* isolated from the blood of hospitalised patients were ESBL.iv
	Carbapenemase-producing Enterobacteriaceae (CPE)	16.2% (115/711) of carbapenem non-susceptible Enterobacteriaceae in private sector contained a carbapenemase producing gene.[v] CPE are now widespread across public and private hospitals in South Africa

Animal Health

There is little published data on resistance rates for bacteria in food animals, and even less in companion animals. High rates of tetracycline and sulphonamide resistance in *E. coli*, *Enterococcus spp* and *Salmonella enterica* was highlighted in the South African National Veterinary Surveillance and Monitoring Programme for Resistance to Antimicrobial Drugs (SANVAD) that studied infections between 2002-2004.[vi]

[i] *Bamford et al. SAJEI 2011;26:243-250*
[ii] *Naidoo et al. PLoS One. 2013 8(10): e78396*
[iii] *SASCM Laboratory Surveillance data, Private Sector, Jan-Jun 2012*
[iv] *Bamford et al. S Afr J Epidemiol& Infect 2011;26:243-250. And GERMS-SA Annual Report 2012*
[v] *National Institute for Communicable Diseases. Communicable Diseases Communiqué 2014;13(8):6-7*
[vi] *Henton et al. S Afr J Med 2011;101(8): 583-6*

tuberculosis in South Africa. Drug resistance in both HIV and tuberculosis is already managed within their respective national programmes and HIV resistance in South Africa is discussed elsewhere in this publication.

Despite a national public surveillance programme for bacteria causing specific respiratory, gastrointestinal and central nervous system infections, there are significant gaps in our knowledge of drug resistance in bacteria other than tuberculosis (hereafter termed bacterial resistance) in South Africa. Currently, we are largely unable to identify patterns of community compared to hospital-acquired bacterial resistance due to a lack of linkage between laboratory and clinical data systems. The information available from public and private laboratory surveillance suggests very high levels of MDR-bacterial infections in hospitalized patients (Table 1). In terms of antibiotic consumption, South Africa, as one of the BRICS nations, has recently been highlighted as a major contributor to the global increase in antibiotic use *(11)*. However, detailed surveillance of antibiotic consumption at provincial, local, district and institutional levels is lacking, as integrated information systems that link pharmacy with laboratory and clinical data are not in place.

The initial response to rising antibiotic resistance levels in South Africa

In 2011, the Global Antibiotic Resistance Partnership–South Africa (GARP–SA) performed a situational analysis of antibiotic resistance (ABR) in South Africa *(12)*. A clear need for action was identified and for this reason, and in response to an increasing number of outbreaks of MDR-bacterial infections in health-care institutions, the South African Antibiotic Stewardship Programme (SAASP) *(13)* was formed under the auspices of the Federation of Infectious Diseases Societies of Southern Africa (FIDSSA). SAASP comprises members from public and private sectors, bringing together the necessary skills set of infectious disease physicians and paediatricians, veterinarians, microbiologists, IPC practitioners, pharmacists,

Figure 1: Pillars of the South African Antimicrobial Resistance Strategy Framework

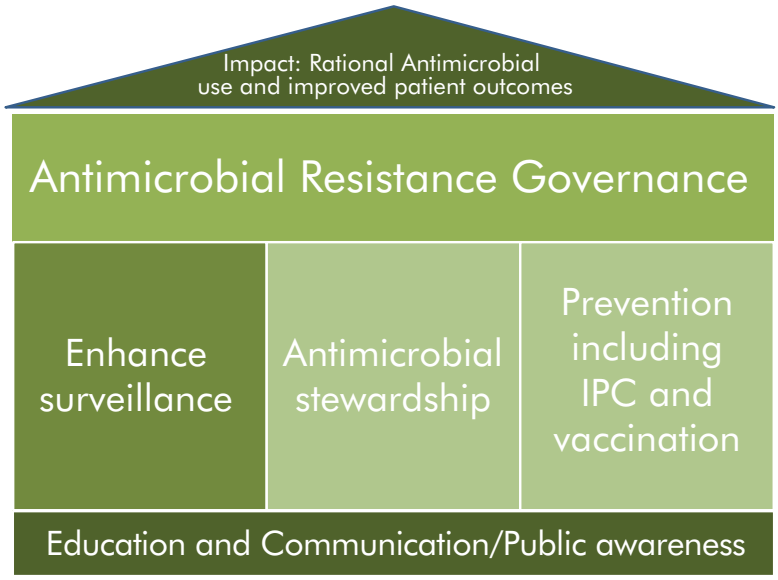


Figure 2: Multidisciplinary intersectoral Ministerial Advisory Committee on Antimicrobial Resistance

pharmacologists, intensivists, surgeons, epidemiologists and quality improvement experts. Its objectives are to promote appropriate antibiotic prescribing, education and engagement with (and in support of) the National Department of Health, as the effector arm of the ABR response. Advocacy by SAASP coupled with encouragement from WHO for Member States to develop a national plan to combat AMR, has resulted in the development of the national strategy framework for AMR.

The South African Antimicrobial Resistance Strategy Framework

Antimicrobial surveillance and reporting, antimicrobial stewardship (AMS) and improved infection prevention and control (IPC) form the three pillars of the national AMR strategy framework (Fig. 1). Under-pinning these, are plans to strengthen existing health systems, educate the workforce and public, and to stimulate local research and development into therapeutics, diagnostics and preventative measures. The framework describes a strong governance model to ensure success of each measure, and is supported by a rich legislative framework (Table 2).

Governance

Antimicrobial stewardship, which is cross-cutting within departments, programmes, hospitals and districts, needs to be positioned at a high level within a National Department of Health, where leadership can be provided to influence policy development and implementation. A multi-disciplinary, intersectoral Ministerial Advisory Committee (MAC) comprised of key stakeholders (Fig. 2), provides oversight for central interventions, to:

- Enhance national surveillance and reporting systems for MDR pathogens and AMR in the human health and agriculture sectors;
- Guide the selection of antimicrobials in the Essential Medicine List based on resistance patterns;
- Provide leadership and guidance to implement effective systems of AMS at national, provincial, state and institutional level;
- Define improvements in prevention strategies focusing on IPC and enhanced vaccination programmes;
- Advise on core curricula for AMR, patient advocacy and awareness campaigns to reduce the inappropriate use of antimicrobials in human and animal health.

At the operational level, governance is provided through Provincial structures, which monitor pharmaceuticals and therapeutics, AMS and IPC. Institutional CEOs and District Managers govern AMR activities at the coalface. A set of

Table 2: **Legislative framework for the South African AMR strategy**

The Constitution of South Africa (Constitution)	Guides the substantive content of all laws and policies through its Bill of Rights. The Constitution provides for health policy and practices that respond to the needs of South Africans. In terms of Section 27 of the Constitution access to health care in itself is a basic human right. All reasonable measures must be taken to ensure that this right is protected, promoted, and fulfilled within the limits of available resources.
The National Health Act (Act 61 of 2003)	Provides the framework for a structured uniform health system within South Africa. The Act specifically provides for the establishment of "a system of co-operative governance and management of health services, within national guidelines, norms and standards, in which each province, municipality and health district must address questions of health policy and delivery of quality health care services".
The Medicines and Related Substances Act (Act 101 of 1965)	Provides the legislative framework to ensure that medicines are safe, efficacious and of good quality. It also provides for control of veterinary medicines in such a way as to ensure that they are produced, distributed and used without compromising human and animal health. Antimicrobials intended for use in animals and registered under Act 101 can only be administered or prescribed by a veterinarian.
The Public Finance Management Act (Act 1 of 1999)	Ensures that all revenue, expenditure, assets and liabilities of all levels of governments are managed efficiently and effectively and provides for the responsibilities of persons entrusted with financial management to support, among others, sustainable access to health care and medicines.
The National Drug Policy (NDP)	Health objectives are to ensure the availability and accessibility of essential drugs to all citizens, to ensure the safety, efficacy and quality of drugs, to promote the rational use of drugs by prescribers, dispensers and patients through provision of the necessary training, education and information and to promote the concept of individual responsibility for health, preventive care and informed decision making.
The Fertilizers, Farm, Feeds, Agricultural Remedies and Stock Remedies Act (Act 36 of 1947)	Governs the use of antimicrobials for growth promotion and prophylaxis/metaphylaxis, and the purchase of antimicrobials over the counter (OTC) by the lay public (chiefly farmers). The National Department of Agriculture, Forestry and Fisheries has a responsibility to ensure that farmers have access to veterinary drugs for disease control and improved food production and to safeguard man by monitoring residues (including antibiotics) in products of food-producing animals, preventing zoonoses and controlling notifiable diseases.
The Health Profession Act (Act 56 of 1974)	Provides for control over the education, training and registration for and practicing of health professions registered under this act.
The Veterinary And Para-Veterinary Professions Act (Act 19 of 1982)	Provision for the compounding and or dispensing of any medicine which is prescribed by the veterinarian for use in the treatment of an animal which is under his or her professional care

national core standards has been developed for both AMS and IPC to ensure a standardized approach. Every institution will have an AMR committee and AMS team(s) to effect good practice and oversee appropriate antimicrobial prescribing.

Optimization of surveillance and early detection of AMR

Surveillance of four components of AMR is to be strengthened within the strategy framework:

- Antimicrobial resistance patterns;
- Antimicrobial consumption;
- Antimicrobial drug quality;
- Medication errors.

A centralized data warehouse (CDW) will collate public and private national resistance data. Specific drug resistance patterns are to become statutorily notifiable. This will include both statutory notifications of resistance patterns for common bacterial infections that are already at high prevalence such as methicillin resistant *Staphylococcus aureus* (MRSA) and extended spectrum beta-lactamase (ESBL) producing bacteria, and sentinel notification of the most serious resistant MDR bacteria currently at low prevalence, e.g. carbapenemase-producing Gram-negative

Table 3: **Antimicrobial Stewardship Toolkit**

Intervention	Comment
Antibiotic Prescription Chart	Stand alone or incorporated into the Provincial or institutional prescription chart
AMS Ward Round	Each institution and district will have its own AMS team(s) to perform ward rounds. The composition of participants will vary depending of level of health-care and human resources. The nucleus of the AMS team should be a prescriber "champion" and a pharmacist
Antibiotic prescribing guidelines	Essential Medicines List, Structured Treatment Guidelines and the SAASP antibiotic prescribing guidelines will provide direction to prescribers
Antibiotic prescribing license	Along the same lines as Advanced Trauma (or Cardiac) Life Support courses, which are mandatory for certain medical practices, a compulsory antibiotic prescribing course which mandates passing to be allowed prescribing rights is under discussion with the Health Professions Council of South Africa and providers. A biennial, renewable, web-based qualification is envisaged.
"Train the Trainer" AMR residential courses	A two-week residential course combining theory and AMS ward rounds target under-served Provinces, which do not have an AMS programme running. This provides an opportunity to rapidly up skill AMR "champions"
Restrictive interventions	Restrictive interventions show inter-Provincial, intra-Provincial and inter-institutional variation. Formulary restriction and pre-authorisation are options for health care programmes within institutions

bacteria. Sentinel reporting will act as an early warning system for AMR outbreaks.

In addition, CDW data has been de-duplicated and transformed to generate an electronic tuberculosis and drug resistant tuberculosis surveillance system for monitoring trends in disease burden *(14)*.

The National Institute for Communicable Diseases (NICD) conducts surveillance for human bacterial and fungal diseases of public health importance. Such surveillance platforms have already demonstrated significant declines in invasive pneumococcal disease cases caused by bacteria resistant to one or more antibiotics, a very valuable added benefit of immunization *(5)*. Performing susceptibility testing on submitted invasive fungal pathogens such as Cryptococcus and Candida, and tracking antifungal resistance patterns is an important component of NICD surveillance. While antifungal resistance in Cryptococcus remains very unusual, azole resistance in bloodstream Candida isolates has emerged as a major problem in some parts of South Africa *(15)*.

A recent addition to NICD's surveillance platform is the prospective sentinel surveillance programme for Xpert MTB/Rif diagnosed rifampicin resistant tuberculosis cases. This is being expanded to include integrated tuberculosis/HIV surveillance. An early warning system for detection of recent transmission clusters and outbreaks with predictive geospatial capability in selected, high burden, drug-resistant districts is also being piloted.

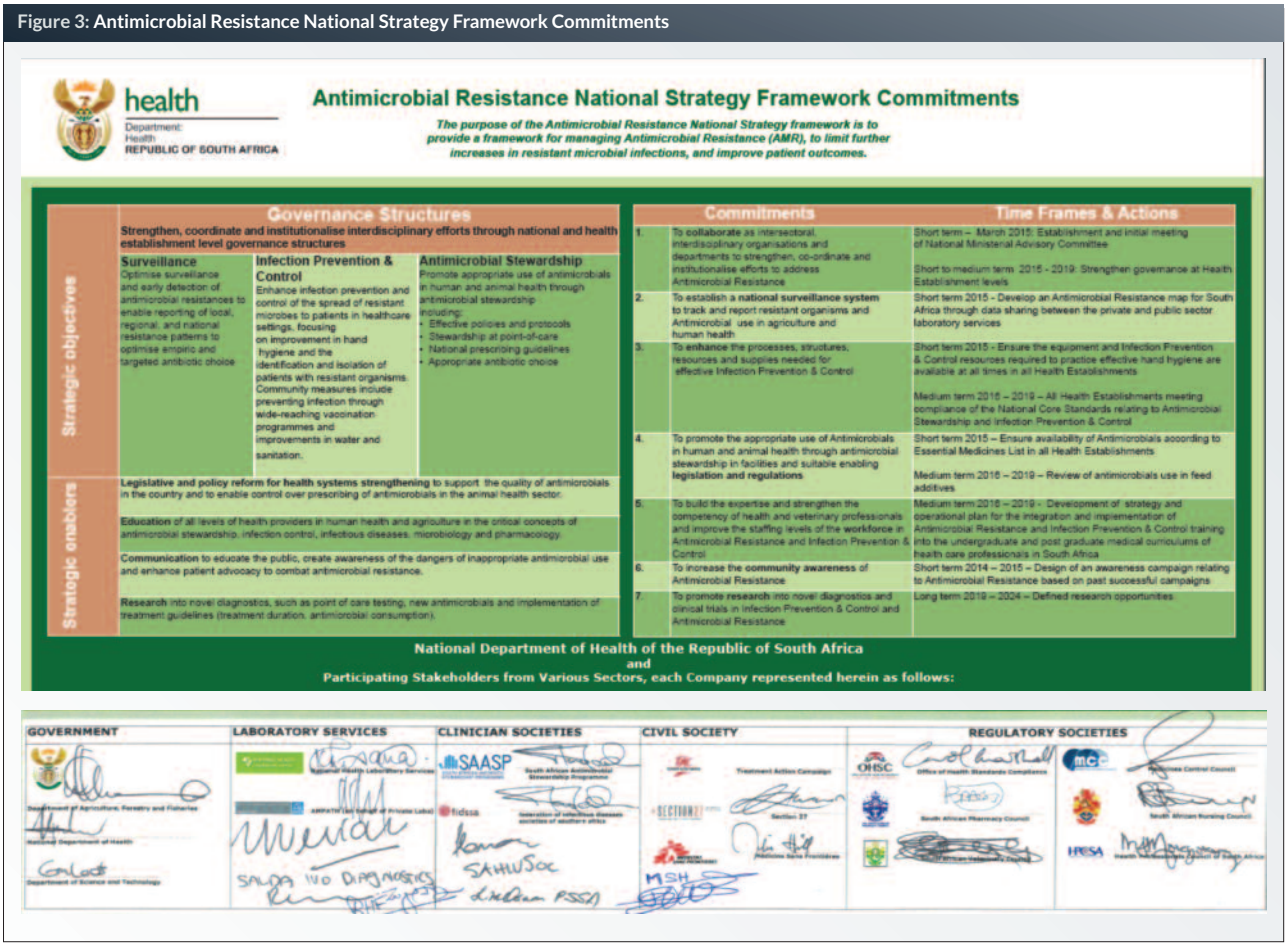
Surveillance and reporting of bacterial resistance in feed and companion animals is an equally important component of the national strategy framework. Prior to 2007, a surveillance programme active in all nine of South Africa's provinces was reporting data. However, the programme lost funding and was discontinued. This will be resurrected in conjunction with the Faculty of Veterinary Sciences at University of Pretoria and the Department of Agriculture, Forestry and Fisheries (DAFF).

In line with World Health Assembly resolution 67.25 *(16)*, South Africa is forging international collaborations to strengthen surveillance and reporting. An antimicrobial resistance map of the country is being developed as a collaborative project between the Center for Diseases Dynamics, Economics and Policy (CDDEP), SAASP, NICD and the South African Society for Clinical Microbiology. In addition, a Commonwealth twinning project with Public Health England is planned to strengthen laboratory support within South Africa.

Promotion of appropriate use of antimicrobials in human and animal health

Uninterrupted access to affordable antimicrobials means adopting appropriate prescribing practice. The quality of

Figure 3: **Antimicrobial Resistance National Strategy Framework Commitments**



medicines will be strengthened through the use of laboratory systems to monitor quality assays and pharmacovigilance reporting systems monitored by the Medicines Control Council, which will also include veterinary medicines.

The strategy framework aims to institutionalize AMS, not only through the adoption of national core standards, but by incorporating AMS activities into job descriptions, performance appraisals and continuing professional education activities. The national development of an integrated information technology system to link pharmacy, laboratory and clinical information is similarly vital in this regard. An audit of patient information systems at primary care level revealed that only 22 out of 37 systems in all nine provinces were functional and operational, but could be scaled up (unpublished observations). A similar audit is underway at hospital level.

A series of antimicrobial stewardship interventions are being put in place as part of the strategy framework (Table 3). Central to these is the AMS ward round, which has been shown to reduce antibiotic prescribing in South Africa, without affecting patient safety *(17)*. Coupled with dedicated antibiotic prescription charts, these activities focus attention on antimicrobial prescribing and is an effective means of transferring skills to trainees. Information on appropriate prescribing in the form of the South African Essential Medicines List and Standard Treatment Guidelines has been augmented by an algorithmic clinical guideline on appropriate antimicrobial prescribing *(18)*.

Enhance infection prevention and control (IPC)

Prevention of infection through wide-reaching vaccination programmes and improvements in water and sanitation are important prevention strategies to reduce AMR. South Africa's extended programme of immunization will be augmented by increased coverage of influenza vaccination, which has been shown elsewhere to reduce influenza-associated antibiotic prescribing *(19)* and by fast-tracking expanded immunization of pneumococcal conjugate vaccination in high-risk adults. In the context of South Africa, this includes HIV-infected adults.

A key enabler to effective IPC includes sufficient, suitably qualified, and competent IPC practitioners (IPCPs) with defined core competencies. Human resource planning to meet international norms for IPCPs in South Africa is a required component of the strategy framework. Although

Table 4: **Strategic enablers towards the antimicrobial resistance national strategy framework.**

Intervention	Comment
Legislative and policy reform for health systems	AMS and IPC national core standards are prescribed as regulated standards that accompany the National Health Act, and the promulgation of the Office of Health Standards Compliance (OHSC). OHSC inspectors will ensure compliance countrywide.
Education and Workforce Development	DAFF are undertaking a comprehensive review ofthe Stock Remedies Act 36 of 1947, which regulates the use of antimicrobial feed additives (AFAs) used for growth promotion, and those used for metaphylaxis. Impact studies on the phasing out of AFAs with respect to food security and production are to be undertaken, so that the use of antimicrobials in food production may be aligned with international norms and standards.
	Annual reporting of antimicrobial use in animal health will be instituted under the direction of DAFF.
	In collaboration with the Department of Education, curricula for school learners, medical and paramedical undergraduates, as well as post-graduate continuing professional development programmes will be reviewed to augment AMR content.
	Targets for human resource development, especially in terms of IPCPs and pharmacists are important enablers to the rollout of AMR programmes nationally, as are the required number of Infectious Diseases specialists and Microbiologists needed to support the national strategy. Current levels are inadequate.
Communication	Capitalizing on heightened awareness of infectious disease transmission in the wake of the Ebola epidemic, a national hand hygiene campaign has begun to inform the public of simple infection prevention measures. Annual influenza vaccination campaigns will be strengthened to include messaging around antibiotic use.
Research	Initial priorities will include studies on the impact of proposed changes to prescribing practices in the animal feed sector, piloting electronicprescribing and integration of pharmacy/clinical and laboratory data systems to inform rational antibiotic prescribing.
	South Africa has a long tradition of excellence in research. The recent characterization of a novel antimalarial drug,*(18)* which is currently in phase I trials highlights the role of academia.The Biovac Institute*, a private-public partnership between the South African Government and the Biovac consortium will play a vital role in manufacturing affordable quality vaccines for South Africa, the continent,and the developing world.

**The Biovac Institute. http://www.biovac.co.za*

more challenging, interventions to mobilize communities with respect to basic infection prevention and hand hygiene are currently underway as part of a private-public partnership with local celebrities *(20)*. As world attention is currently focused on transmission of Ebola in West Africa, community awareness around infection and transmission has been heightened, and offers a receptive audience for health messaging around infection prevention.

Strategic enablers of appropriate antimicrobial prescribing

We recognize four strategic enablers to achieve our objectives; legislative and policy reform for health systems strengthening, education, communication and research (Table 4). These enablers form an integral part of the strategy framework, which was presented to a national AMR Summit held in Johannesburg on 16 October 2014. The Antimicrobial Resistance National Strategy Framework Commitments (Fig. 3) were formally adopted by Government departments and all relevant stakeholders at the Summit

Summary

South Africa faces an overwhelming burden of infectious diseases at the heart of the HIV and tuberculosis pandemics. Largely unnoticed, the rise of antibiotic resistance in our

country is now highly visible and tangible to health-care professionals and the public alike. With outbreaks of MDR-bacteria closing wards and causing high morbidity and mortality, a strong response as part of the WHO Global Action Plan is required. The adoption of the Antimicrobial Resistance National Strategy Framework is the first step in this response, and can be seen as a blueprint for other middle-income countries. Furthermore, many of the interventions described here are applicable across health resource settings.

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