The One Health stewardship of colistin as an antibiotic of last resort for human health in South Africa

Marc Mendelson, Adrian Brink, Joey Gouws, Nontombi Mbelle, Vinny Naidoo, Troy Pople, Natalie Schellack, Moritz van Vuuren, Helen Rees, on behalf of the South African One Health Stewardship Sub-Committee of the Ministerial Advisory Committee on Antimicrobial Resistance

Increasing reliance on antibiotics of last resort to treat the rising numbers of multidrug-resistant bacterial infections in people has focused attention on how shared-use antibiotics are managed and regulated across human and animal health. Discussions at international and national levels have intensified since the identification of new plasmid-mediated genes for colistin resistance in 2016, first in China and subsequently in many other countries, removing the last line of defense against multidrug-resistant Gram-negative bacterial infections with carbapenem resistance. South Africa has reacted to this threat by doing a situational analysis and review of the existing legislation concerning colistin use in animals and people, to inform which course of action to take. The experiences shared in this Personal View outline the process, institution of governance with widespread stakeholder engagement, surveillance, and interventions that South Africa has taken towards optimising the shared use of colistin. The instigation of stewardship guided by the principles of the One Health concept for shared-use antibiotics at the country level is a crucial component of any action plan to combat antibiotic resistance, and is as relevant to other existing antibiotics and new chemical entities that will be forthcoming from an invigorated antibiotic pipeline as it is to colistin.

Introduction

Increasing bacterial resistance to antibiotics (both natural and synthetic products) has resulted in decreasing treatment options for patients with community-acquired and hospital-acquired infections.[1] Although several options to treat drug-resistant Gram-positive bacteria are available, the increase in Gram-negative bacteria expressing carbapenemase genes, and non-enzyme-related carbapenem resistance determinants, has resulted in the need to use antibiotics of last resort to treat infections caused by multidrug resistant (MDR) Gram-negative bacteria.[2] One such antibiotic is colistin, a polymyxin first introduced in 1959, which became unpopular by the 1980s because of its renal toxicity profile.[3] Since then, colistin has been used predominantly as a veterinary medicine for the treatment of Gram-negative gastrointestinal infections in poultry and pigs. The need to treat MDR Gram-negative bacteria in human beings has caused a reintroduction of colistin use, primarily in critically ill patients in intensive care units and patients with decreased immunity due to cancer chemotherapy or organ transplantation.

The efficacy of colistin is under threat from a novel set of transmissible resistance genes.[4,5] Previously, the understanding of colistin resistance was that it evolved slowly, was chromosomally mediated, and was vertically transmitted.[4] However, in November, 2016, a new plasmid-mediated resistance gene, mobilised colistin resistance (*mcr*)*-1*, and later *mcr-2*, emerged, conferring colistin resistance that could be transmitted between bacteria of the same or differing species through horizontal gene transfer. The subsequent identification of *mcr-1* in livestock in farms and abattoirs and in retail meat on shop shelves, and its ability to colonise the human gastrointestinal tract and cause infection in patients, has brought into focus the consequences of the shared use of antibiotics on human health.[6]

South Africa's consumption of antibiotics has markedly increased since the turn of the century.[7,8] In response to this increase and to the rising prevalence of MDR common bacterial infections in South Africa, we have developed a One Health-based national strategic framework for antimicrobial resistance,[9] an implementation plan,[10] and a mechanism for the governance of stewardship at national, provincial, district, and hospital levels.[11] In this Personal View, we describe how South Africa has responded to the threat of losing colistin as an antibiotic for human health through a programme to advance national stewardship of colistin across the One Health platform—ie, across human, animal, and environmental health. The response is as relevant to other antibiotics of last resort and to new chemical entities as it is to colistin, which is used here as an example.

Stage 1: the formation of South Africa's Colistin Working Group

A triad of factors caused action to address the potential loss of colistin in South Africa: the identification of *mcr-1* in *Escherichia coli* in South African poultry, which threatened the relatively stable prevalence of colistin resistance in veterinary medicine recorded to date; the recognition of *mcr-1*-induced colistin resistance in South African patients; and the mandate to develop a One Health approach to address antibiotic resistance in South Africa's National Strategy Framework for Antimicrobial Resistance, 2014–24.[9]

The South African Medicines Control Council convened the first meeting of South Africa's Colistin Working Group on April 20, 2016, in Pretoria. The objective of the meeting was to understand the status of colistin resistance in the country, to understand the importance of colistin as an antibiotic in human beings and animals, and to begin developing a One Health

Lancet Infect Dis 2018

Published Online
April 16, 2018
http://dx.doi.org/10.1016/S1473-3099(18)30119-1

Division of Infectious Diseases and HIV Medicine, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa (Prof M Mendelson PhD, A Brink MMed); **Ampath National Laboratory Services, Milpark Hospital, Johannesburg, South Africa** (A Brink); **South African Medicines Control Council, Department of Health, Pretoria, South Africa** (J Gouws PhD, Prof H Rees MRCGP); **Department of Medical Microbiology** (N Mbelle FCPath), **Department of Paraclinical Sciences, Faculty of Veterinary Science** (Prof V Naidoo PhD), **and Department of Veterinary Tropical Diseases, Faculty of Veterinary Science** (Prof M van Vuuren MMedVet), **University of Pretoria, Pretoria, South Africa; Aspen France, Marly-le-Roi, France** (T Pople EMT Paramedic); **Division of Pharmacy, Sefako Makgatho Health Sciences University, Pretoria, South Africa** (N Schellack PhD); **Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa** (Prof H Rees); **and London School of Hygiene & Tropical Medicine, London, UK** (Prof H Rees)

Correspondence to:
Prof Marc Mendelson, Division of Infectious Diseases and HIV Medicine, Department of Medicine, Groote Schuur Hospital, G16.68 New Main Building, Observatory 7925, Cape Town, South Africa
marc.mendelson@uct.ac.za

	Preparation	Dosing	Consumption
Veterinary use			
Medicines registered under Act 101, 1965			
Colistine 1200* (Virbac, Carros, France; oral powder)	A preparation of colistin sulphate powder registered for the management of gastrointestinal infections, cystitis, nephritis, pneumonia, and bronchitis in calves and piglets; this product is not registered for use in poultry	120 000–240 000 IU/kg for 2–5 days	4 tonnes were sold in 2015†
Potencil (Virbac, Carros, France; parenteral)	A combination of colistin and amoxicillin that is available only via veterinary consultation, and is registered for the management of sensitive bacterial infections in calves; indications include treatment of respiratory tract infections, pneumonia, bronchopneumonia, gastrointestinal infections, and omphalitis	Each 100 mL contains 10 g amoxicillin and 25 MiU colistin, administered intramuscularly at a dose of 1 mL/10 kg	No data
Surolan (Elanco, Bryanston, South Africa) and Terra Cortril* (Zoetis, Johannesburg, South Africa)	Registered for use in dogs for the treatment of external ear infections in fixed dose combinations	A few drops of 5500 IU/mL Surolan (containing polymyxin B sulphate, miconazole nitrate, and prednisolone acetate) into the ear every 12 h for 7–10 days; two to four drops of 10 000 U/mL Terra Cortril* (containing polymyxin B sulphate and hydrocortisone acetate) every 8 h for 7–10 days	No data
Compounded colistin-based medicines			
Colistin compounded for the poultry and porcine industries	Compounded for use as an unregistered medicine for gastrointestinal infections, on veterinary prescription from registered community pharmacies or from veterinarians; also compounded for the prevention of salmonella and *Escherichia coli* infection in poultry	For the treatment of *E coli* infections in young broiler chickens (birds are treated at the discretion and duration determined by the treating veterinarian, based on MIC testing): method 1‡: doxycycline (25 mg/kg body mass) and colistin (0·24 million IU/kg body mass); method 2‡: enrofloxacin (10 mg/kg body mass) and colistin (0·24 million IU/kg body mass); method 3§: sulfadiazine with trimethoprim (40 mg/kg body mass) and colistin (0·24 million IU/kg body mass); for prevention of salmonella and *E coli* infection in poultry: 1200 IU/kg colistin is incorporated into the drinking water of the birds for 7 days (approximately 16 mg/kg per day)	No data
Polymyxin E	Compounded for use as an unregistered medicine for the management of ear infections in dogs	Available as topical drops to be administered directly into the ear canal	No data
Human use			
Colymycine (Aventis Pharma, Paris, France) and colixin (Pharmis, Cascais, Portugal)	Not registered in South Africa, but can be obtained via Act 101, 1965, through a Section 21 application to the Medicines Control Council; the drugs are indicated for the treatment of multidrug-resistant Gram-negative bacteria, including Enterobacteriaceae spp, Pseudomonas spp, and Acinetobacter spp	A loading dose of 12 mU colistin, irrespective of renal function, followed by a total dose of 9 mU colistin per day if the patient has normal renal function, either as 3 mU every 8 h or 4·5 mU every 12 h;[12] adjust for renal function	From 2012 to 2016 the CAGR was 5%, and the corresponding cost increase was 14%¶

Act 101, 1965=Medicines and Related Substances Act, 1965. CAGR=compound annual growth rate. *Product has been voluntarily removed from the market. †Petty D (private poultry consultant), personal communication. ‡Duncan N (Faculty of Veterinary Science, University of Pretoria), personal communication. §Gerber D (V-Tech), personal communication. ¶Pharmaceutical Industry Distribution Data for South Africa—December 2016. Data were sourced from the two pharmaceutical suppliers of colistin in South Africa. Colistin is a Section 21 drug and can only be released following approval from the Medicines Control Council. Data from these two sources were combined and a CAGR analysis was done; CAGR is a useful measure of market growth over multiple time periods.

Table 1: **Colistin and polymixin-based preparations, indications, dosing, and consumption data for veterinary and human use in South Africa**

stewardship strategy for colistin. Participants included the chairperson of the South African Medicines Control Council, the chairpersons of its Veterinary Clinical Committee, Clinical Evaluations Committee, and Pharmacovigilance Committee, representatives of the South African Veterinary Council, the Registrar of Medicines (Act 101, 1965) and a technical adviser to the Registrar of Stock Remedies (Act 36, 1947), the chairperson of the Ministerial Advisory Committee for Antimicrobial Resistance, and representatives from the Sector-Wide Procurement governmental department. A situational analysis was presented, including details of the available medicines containing colistin that had been or were being used in animals and people in South Africa, and the crude consumption data of the antibiotic (table 1), which the Colistin Working Group felt were the most important factors to understand, to take action and monitor progress.

Legislation controlling the use of colistin for veterinary and human use in South Africa

Animal production in South Africa represents 47·2% of the gross agricultural production value.[13] In particular, poultry and beef are the agricultural enterprises that contribute the most to the South African agricultural gross domestic product. Poultry accounts for 16·04% of the production share, beef 11·29%, sheep and goats 2·69%, pigs 2·09%, and the rest is made up of other animal products.[14]

In terms of the production size, in 2013 the number of broiler chickens in South Africa was approximately 110 million. Cattle herds in South Africa have remained pretty stable over the past decade at around 14 million animals, with nearly 40% of these being owned by smallholders and subsistence producers, and sheep flocks have more or less stabilised at around 24 million animals. The intensive pig industry includes approximately

100 000 breeding sows, with an unknown number of pigs being owned by subsistence farmers.[14]

The Department of Health administers the Medicines and Related Substances Act, 1965 (Act 101, 1965), which addresses the regulatory oversight of human and veterinary medicines to ensure that they are of acceptable safety, quality, and efficacy, and are manufactured, distributed, and used without compromising human and animal health. Medicines that are classified as antimicrobials and intended for use in animals are listed in Act 101, 1965 as a Schedule 4 substance (these are prescription-only medicines that are available from the pharmacy dispensary, and can be repeated for 6 months), and can only be prescribed by a veterinarian. Little surveillance data are available on antibiotic use in animals over the past 14 years. However, we know that between 2002 and 2004, 28% of antimicrobials that were used for the treatment of food-producing and companion animals were prescribed according to the provisions of this Act.[15]

By contrast, based on historical provisions that are still in force in the Fertilisers, Farm, Feeds, Agricultural Remedies, and Stock Remedies Act (Act 36, 1947), some antimicrobials can be purchased without a veterinarian's prescription. This list of antimicrobials, which does not include colistin, is limited to tetracyclines, sulphonamides (and trimethoprim), some topical intramammary antibiotics for dairy cows, and growth-promoting antimicrobials. Stock remedies accounted for 72% of the antimicrobials for animal use in South Africa between 2002 and 2004.[15] The use of antimicrobials for growth promotion and prophylaxis or metaphylaxis is regulated by this Act, which allows these products to be purchased over the counter by the public (mainly farmers). The National Department of Agriculture, Forestry, and Fisheries administers Act 36, 1947, and has a responsibility to ensure that farmers have access to veterinary drugs for disease control and improved food production, while safeguarding human health by monitoring drug residues in the products of food-producing animals (including antibiotics). This governmental department is also responsible for preventing zoonoses and controlling notifiable diseases.

The prescription of colistin for human use is controlled by the terms of Section 21 of Act 101, 1965, which mandates the Medicines Control Council to approve the use of an unregistered medicine. A doctor wishing to prescribe colistin (or any other Section 21 medicine) must provide their personal details, those of the person, company, or institution importing the unregistered medicine, those of the patient (including their diagnosis, concomitant diseases, and treatments), the exact details of the colistin product to be used, and importantly they must obtain informed consent from the patient. Lastly, a progress report form detailing the outcome of the treatment must be completed by the treating doctor. Colistin availability is restricted to tertiary hospitals under the National Essential Medicines List, and its use is encouraged only when an antibiogram indicates that no other antibiotic option is available.

	n	Sensitive	Intermediate	Resistant
*E coli**	401	290 (72%)	42 (10%)	69 (17%)
All *Salmonella* spp	138	132 (96%)	4 (3%)	2 (1%)
Pseudomonas spp (other than *P aeruginosa*)	54	41 (76%)	1 (2%)	12 (22%)
P aeruginosa	186	150 (81%)	24 (13%)	12 (6%)
All *Pseudomonas* spp	240	191 (80%)	25 (10%)	24 (10%)
All *Shigella* spp	2	2 (100%)	0	0
All *Haemophilus* spp	59	54 (92%)	3 (5%)	2 (3%)
A pleuropneumoniae	45	42 (93%)	3 (7%)	0
All *Pasteurella* spp	126	107 (85%)	6 (5%)	13 (10%)

2500 samples were tested from three of South Africa's nine provinces, and included avian species, cattle, cats, dogs, fish, horses, pigs, primates, reptiles, and goats. Samples were obtained from most body surfaces and organs either during clinical examination before treatment, or during necroscopy, and were submitted for testing by clinicians and pathologists. Reproduced from the Colistine 1200 technical document,[16] by permission of Virbac RSA (Pty) Ltd. *E coli=Escherichia coli. P aeruginosa=Pseudomonas aeruginosa. A pleuropneumoniae=Actinobacillus pleuropneumoniae.* **E coli* was sampled from cases of calf and piglet diarrhoea.

Table 2: **Colistin sensitivity in tissue samples of veterinary clinical cases assessed by the Onderstepoort Veterinary Institute, South Africa, 1997–99[16]**

Resistance to colistin in bacteria isolated from animals in South Africa

The reported colistin minimum inhibitory concentrations (MICs) between 1997 and 1999 (table 2) suggest that colistin resistance (clinical breakpoint 2 µg/mL) was around 17% for *E coli* during this period. In a non-peer-reviewed study by the community veterinary pharmacy V-Tech, resistance to *E coli* (MIC breakpoint ≥2 µg/mL) was approximately 20% in 2013 (figure).[17] These results suggest that in the 15–18 years between the surveillance periods, the incidence of colistin resistance has remained fairly constant. Although some caution is required when interpreting the second V-Tech study (because the sampling and laboratory methods could have differed from the first study), this observation is in line with international trends in chromosomally acquired colistin resistance in animal isolates, which indicate slow development of colistin resistance.[18]

Although initially in 2012 the prevalence of colistin resistance was still very low (about 3%), in 2014 this prevalence had increased substantially to 13%. On the basis of this observation, V-Tech tested for the presence of *mcr-1* in historical cultures that were obtained from pathological lesions of sick birds during post-mortem examinations. Of 147 samples, collected between August, 2010, and February, 2012, three of the cultures tested were found to be resistant to colistin, but none contained the *mcr-1* gene. By contrast, in the last 20 samples from 2015, the test results showed that the prevalence of *mcr-1* had increased substantially to 95% (19 of 20 colistin-resistant isolates).[19]

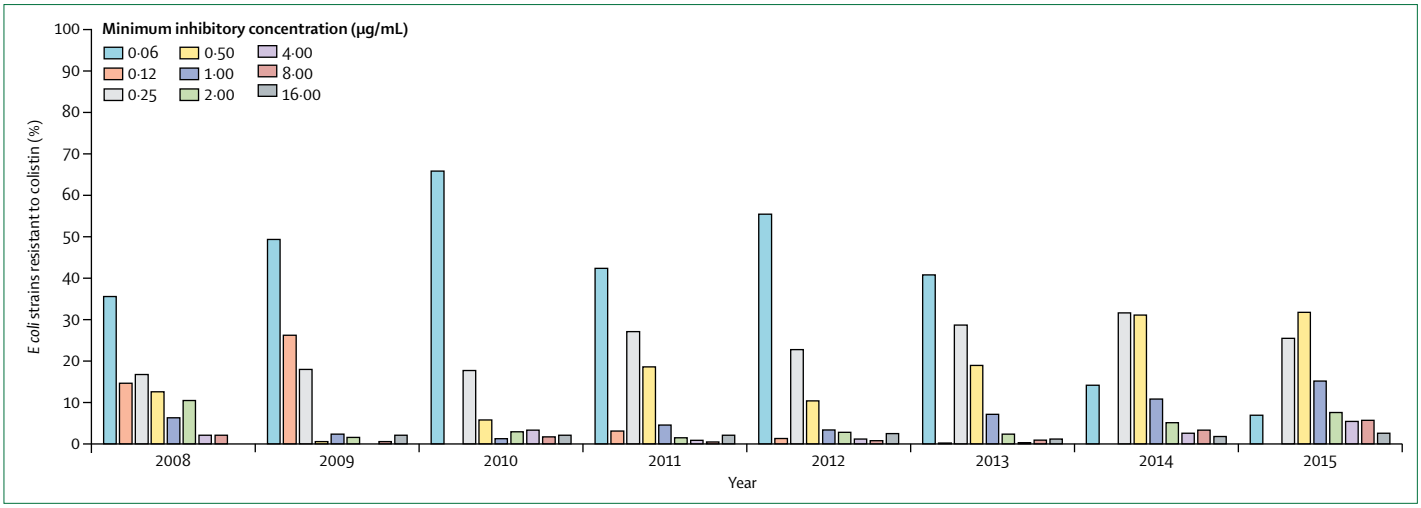

Figure: **Colistin resistance in pathogenic *Escherichia coli* strains isolated from poultry farms in South Africa, 2008–15**
The number of colistin-resistant bacterial strains identified per year were as follows: 48 in 2008; 391 in 2009; 244 in 2010; 486 in 2011; 688 in 2012; 1027 in 2013; 1253 in 2014; and 797 in 2015. Reproduced from an article in VetNews,[17] by permission of the South African Veterinary Association.

	E coli		*K pneumoniae*		*P aeruginosa*		*A baumannii*	
	n	% resistant	n	% resistant	n	% resistant	n	% resistant
Eastern Cape	280	0%	435	1%	91	2%	151	1%
Free State	138	0%	332	0%	76	0%	190	0%
Gauteng	1354	1%	2372	1%	545	1%	1124	1%
Kwa-Zulu Natal	757	1%	1180	4%	205	2%	448	4%
Limpopo	44	0%	179	2%	18	10%	21	0%
Mpumalanga	131	NR	239	0%	41	0%	86	0%
North West	66	0%	230	0%	31	0%	15	0%
Northern Cape	79	0%	43	0%	13	0%	29	0%
Western Cape	998	1%	569	1%	185	2%	277	4%

E coli=Escherichia coli. K pneumoniae=Klebsiella pneumoniae. P aeruginosa=Pseudomonas aeruginosa. A baumannii=Acinetobacter baumannii. NR=not reported.

Table 3: **Colistin resistance reported from blood culture isolates by South African province in 2014 and 2015**

See Online for appendix

Human resistance to colistin in South Africa

As reported by the National Institute for Communicable Diseases,[20] for 2014 and 2015 combined national surveillance of blood culture isolates of *E coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Acinetobacter baumannii* showed that the prevalence of colistin resistance was low (table 3). Information is now available on the mechanisms that led to the development of colistin resistance during these years. Notably, although resistance in *K pneumoniae* isolates varied, the mechanisms leading to colistin resistance include a single aminoacid change in protein PmrB,[21] hetero-resistance associated with alterations in the PhoPQ regulatory system,[22] and various mutations in the *crrB* gene among carbapenemase-producing strains.[23] More recently, *mcr-1* was detected in resistant *E coli* clinical isolates from nine patients in two provinces of South Africa.[24,25] Three patients were admitted to hospital and five patients presented to primary care physicians and were managed as outpatients. Importantly, except for one patient with an abscess, all community-acquired cases presented with urinary tract infections, and had not previously been exposed to colistin.

Stage 2: converting analysis to action

During the first meeting of the Colistin Working Group held in April, 2016, which was jointly chaired by the chair of the National Department of Health's ad-hoc working group on antimicrobial resistance and the chair of the Medicines Control Council, the need for broader consultation was recognised. As a result, for the second meeting of the Colistin Working Group on July 13, 2016, the representation of stakeholders was expanded (appendix). In the interval between the first and second meetings, the European Medicines Agency published updated evidence and advice on colistin products for the European Union.[26] Important findings confirmed that colistin resistance can be transmitted via consumption of food or environmental contact, and that this poses a serious risk of death for people. Recommendations from the report included a reduction of the use and sales volume of colistin as a central principle of risk management, and restriction of colistin use to when sensitivity testing of appropriate microbiological samples sent to the laboratory proves that it is necessary in both humans and animals. Veterinary sales of colistin were recommended to be reduced to the feasible minimum. The Colistin Working Group considered the European Medicines Agency report and agreed that although a national risk assessment before a ban on colistin use in food-producing animals in South Africa would be ideal, the country would be unable to undertake such an assessment in a timely manner. Therefore, the group agreed that the European Medicines Agency's assessment

	Notes
Short term recommendations	
Cancel the registration of Colistine 1200 (Virbac France, Carros, France; oral powder) by the MCC under the terms of the provisions of Act 101, 1965, but retain registration of Potencil (Virbac France, Carros, France; injection) for veterinary use	Cancellation of Colistine 1200 registration by the MCC allows procurement exclusively via Section 21, which eliminates its routine use for animal growth promotion
Prohibit registration of colistin in farm feeds	Registrar of Act 36, 1947, to reduce the opportunity for colistin use in animal growth promotion and prophylaxis by prohibiting registration for these uses
Introduce Section 21 conditions of use for colistin in animals under the terms of Act 101, 1965	Veterinarians should apply for the use of colistin for a specific animal, a specific quantity, and a specific period under terms of Act 101, 1965
Increase the schedule of colistin active pharmaceutical ingredient to Schedule 6, and the medicine final product to Schedule 4 for human or veterinary use	Both Schedule 4 and 6 require a prescription from a medical practitioner or a veterinarian, and are only available from a pharmacy; Schedule 6 demands a higher level of regulatory control
License all manufacturers, importers, and distributors of APIs according to the provisions of section 22A of Act 101, 1965	Licensing will allow for greater regulatory oversight over the distribution chain of APIs
Develop two tariff codes from the DTI and ITAC	Two tariff codes will allow the DTI to identify and monitor colistin as an API and as a final product independently
Amend Act 54, 1972, to align it with the current Codex Alimentarius	Amend the General Regulations to Act 54, 1972, to bring the residue levels in line with the Codex Alimentarius directive
Publish the list of restricted substances relating to colistin	Joint communication by the veterinary, medicine, and food control directorates will be actioned
Prevent compounding of medicines containing antibiotics and colistin for food-producing animals	Any veterinarian who wishes to compound medicine must obtain a license from the Director General of Health
Medium term recommendations	
Increase surveillance of colistin residues in food	The Department of Health Food Control Directorate should increase the surveillance of colistin residues under regulations of Act 54, 1972, with the aim of working towards a zero residue policy. Amend the foodstuffs regulation to bring it in line with current codex requirements
Develop a comprehensive communications strategy surrounding the use of antibiotics in food-producing animals	This strategy should be developed in line with the South African National Strategy Framework, 2014
Review legislation related to the use of colistin across the One Health platform	Review Acts 101 (1965), 54 (1972), 36 (1947), 35 (1984), 40 (2000), and 108 (1997) and coordinate changes for corrective action
Long term recommendations	
National risk assessment for all antimicrobials used in food-producing animals	Phasing out of all antibiotics for animal growth promotion
Strengthen surveillance of antibiotic use in animals	Increased surveillance would help meet goals of all colistin use being directed by sensitivity testing
Develop a programme for sludge management on farms	The management programme would be developed in association with the Department of Water and Sanitation

Act 101, 1965=Medicines and Related Substances Act of 1965. MCC=Medicines Control Council. Act 36, 1947=Fertilisers, Farm, Feeds, Agricultural Remedies, and Stock Remedies Act of 1947. API=active pharmaceutical ingredient. DTI=Department of Trade and Industry. ITAC=International Trade Association Commission. Act 54, 1972=Foodstuffs, Cosmetics, and Disinfectants. Act 35, 1984=Animal Diseases Act. Act 40, 2000= Meat Safety Act of 2000. Act 108, 1997=Water Services Act of 1997.

Table 4: **Interventions to ensure One Health national stewardship of colistin in South Africa**

could be used to guide South Africa's action plan, and provided detailed recommendations for action to be taken by the South African Government and stakeholders to mitigate colistin resistance (table 4).

In December, 2016, governance of the Colistin Working Group was transferred from the Medicines Control Council to the newly constituted Ministerial Advisory Committee on Antimicrobial Resistance, and the One Health Stewardship Sub-Committee was formed to take the work further. Stakeholder expansion incorporated the Department of Trade and Industry (to deal with the regulatory oversight of the importation of chemicals, including active pharmaceutical ingredients), the Department of Environmental Affairs (to provide input into the proper control of on-farm effluent systems through applicable environmental legislation), the Department of Agriculture, Forestry, and Fisheries (to monitor animal disease control and antimicrobial resistance relating to animal health, and to oversee the administration of Act 36, 1947), and the Department of Health and Food Control Directorate (to address food safety and food security issues). The importance of ensuring broad stakeholder participation when setting up a One Health stewardship programme that will determine antimicrobial use was an important lesson for the Colistin Working Group, and one that should be considered by any country at the very beginning of the process.

An essential intervention towards reducing the use of colistin in food-producing animals came in the form of a letter sent to all members of the veterinary profession by the South African Veterinary Council—the veterinary statutory body—on Nov 14, 2016.[27] The letter stated as

follows: "It is recommended that colistin not be used in food producing animals at all, unless the veterinarian can justify its use at the hand of a sensitivity test and as a very last resort to treat an animal. Any conduct to the contrary would be regarded by Council as unprofessional conduct." The letter represents what is tantamount to a ban on colistin use in food-producing animals.

One of the weaknesses identified in the data available in South Africa was the scarcity of data on colistin resistance in the environment. Research done by the South African Water Research Commission identified sustained levels of antimicrobials (colistin was not included in the analysis), agrochemicals, and personal care products in the effluent from three drinking water production facilities in Gauteng and North West Province.[28] Additionally, the results also showed that antibiotic-resistant bacteria were present in the same water from these drinking water production facilities, which is cause for concern. A monitoring and evaluation programme (which would include colistin) needs to be instigated on a larger geographical scale, with options for corrective action to be taken. The programme will be further developed with the support of the Ministerial Advisory Committee on Antimicrobial Resistance, with an agreed monitoring and evaluation framework in collaboration with South Africa's Water and Research Commission. Although environmental surveillance data is scarce, the One Health Stewardship Sub-Committee of the Ministerial Advisory Committee on Antimicrobial Resistance felt that the data that we have on colistin resistance in human beings and animals was sufficient to justify the implementation of the programme of change.

Conclusion

National One Health stewardship of colistin is pertinent to all shared-use antibiotics across the One Health platform. Colistin was used here as an example, because it is an antibiotic of last resort for multidrug resistance in Gram-negative bacteria, including resistance to carbapenems in human beings. The approach could equally apply to new chemical entities, although, given the public health needs relating to antibiotic resistance, new products for treating MDR in Gram-negative bacteria are perhaps more likely to be prioritised for human use alone, which could be achieved by registration under Act 101, 1965. Alternatively, access for human use only could be ensured through Section 21 applications, also available under Act 101, 1965, which enables clinicians to prescribe and use medicines to treat patients that are not yet registered by the Medicines Control Council.

We believe that our approach of convening intersectoral stakeholders across the One Health platform to develop a national strategy for the stewardship of antibiotics provides valuable lessons for future work in South Africa, and that such a method could be useful in other countries. If we are to achieve the phasing out of antibiotics that promote animal growth in South Africa, and control the administration of prophylaxis or metaphylaxis by enforcing application strictly under veterinary oversight, the national strategy should be continuously guided by a prioritised research, surveillance, and regulatory agenda. Noting the importance of national risk assessments for the use of all antibiotics in food-producing animals, low-income and middle-income countries should be offered technical and financial support to undertake these essential studies.

Contributors

MM, NM, JG, VN, MvV, and HR participated in the initial working group and subsequent committees. Data on the human use of colistin were provided by TP, AB, and NS, and data on the animal use of colistin by VN and MvV. MM wrote the first draft of the paper, although all authors reviewed and provided input into the interpretation of the data, and all edited the final report.

Declaration of interests

We declare no competing interests. *Co-chairs*: Helen Rees (chairperson of the Medicines Control Council [MCC]) and Marc Mendelson (chairperson of the Ministerial Advisory Committee on Antimicrobial Resistance). *Members*: Shabir Banoo (chairperson of Names and Scheduling), Marius Collins (Department of Trade and Industry, International Trade Association Commission), Kim Faure (technical advisor to the National Department of Health-Antimicrobial Resistance), Joey Gouws (registrar for the MCC, Act 101, 1965), Bayers Hoek (chairperson of the Clinical Evaluations Committee, MCC), Ruth Lancaster (Sector-Wide Procurement, Essential Drugs Programme), Nontombi Mbelle (microbiologist and member of the MCC), Mike Modisane (chief director of Act 35, 1984, and of Department of Agriculture Forestry and Fisheries [Animal Production and Health], and president of the World Organisation for Animal Health), Ernest Mokantla (technical advisor to registrar for Act 36, 1947, Veterinary Control Council, and MCC member), Margaret Molefe (Department of Environmental Affairs, Hazardous Chemical Management, Department of Environmental Affairs), Vinny Naidoo (chairperson of the Veterinary Clinical Committee of the MCC), Camilla Patterson (Act 36, 1947, Department of Agriculture Forestry and Fisheries), Derryn Petty (Veterinary Control Council Poultry Biosecurity Issues and Disease Epidemiology), Darshana Reddy (representing director of Animal Health and director of Veterinary Public Health, Act 35, 1984), Gerry Swan (MCC and Veterinary Control Council member), and Moritz van Vuuren (Veterinary Control Council microbiologist and Ministerial Advisory Committee on Antimicrobial Resistance committee member). *Secretariat*: Jeanette Lotter (Medicines Evaluation and Research), Alice Sigobodhla, Suraiya Suliman, Kefiloe Mompati, and Mahlodi Mohlala (Vet Unit), Portia Nkambule (Clinical Evaluations and Trials), Shyamli Munbodh, and Adelaide Molatuli (Section 21 Unit), Griffith Molewa and Lesiba Moshiga (Law Enforcement Unit), Khotso Bokaba (Inspectorate Unit), and Maryke Herbst (Food Control, Chemicals Management Unit).

References

1 Mendelson M, Røttingen JA, Gopinathan U, et al. Maximising access to achieve appropriate human antimicrobial use in low-income and middle-income countries. *Lancet* 2016; **387:** 188–98.

2 Holmes AH, Moore LS, Sundsfjord A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet* 2016; **387:** 176–87.

3 Koch-Weser J, Sidel VW, Federman EB, Kanarek P, Finer DC, Eaton AE. Adverse effects of sodium colistimethate. Manifestations and specific reaction rates during 317 courses of therapy. *Ann Intern Med* 1970; **72:** 857–68.

4 Liu Y-Y, Wang Y, Walsh TR, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *Lancet Infect Dis* 2016; **16:** 161–68.

5 Xavier BB, Lammens C, Ruhal R, et al. Identification of a novel plasmid-mediated colistin-resistance gene, mcr-2, in *Escherichia coli*, Belgium, June 2016. *Euro Surveill* 2016; 21.

6 Al-Tawfiq JA, Laxminarayan R, Mendelson M. How should we respond to the emergence of plasmid-mediated colistin resistance in humans and animals. *Int J Infect Dis* 2017; **54:** 77–84.

7 Van Boeckel TP, Gandra S, Ashok A, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis* 2014; **14:** 742–50.

8 Center for Disease Dynamics, Economics & Policy. The state of the world's antibiotics, 2015. 2015.https://www.cddep.org/wp-content/uploads/2017/06/swa_edits_9.16.pdf (accessed March 6, 2018).

9 South African National Department of Health. The South African antimicrobial resistance strategy framework 2014–2024. http://www.health.gov.za/index.php/antimicrobial-resistance?download=679:a5-antimicrobial-resistance-national-strategy-framework-2014-2024-final (accessed Oct 4, 2017).

10 South African National Department of Health. Implementation plan for the South African antimicrobial resistance strategy framework 2014–2019. http://www.health.gov.za/index.php/antimicrobial-resistance?download=1175:implementation-plan-for-the-antimicrobial-resistance-strategy-framework-in-south-africa-2014-2019 (accessed Oct 4, 2017).

11 South African National Department of Health. Guidelines on implementation of the antimicrobial strategy in South Africa. One Health approach and governance. http://www.health.gov.za/index.php/antimicrobial-resistance?download=2194:antimicrobial-stewardship-guidelines-governance-june2017 (accessed Oct 4, 2017).

12 Laubuschagne Q, Schellack N, Gous A, et al. Colistin: adult and paediatric guidelines for South Africa, 2016. *South Afr J Infect Dis* 2016; **31:** 3–7.

13 Henton MM, Eagar HA, Swan GE, van Vuuren M. Part VI. Antibiotic management and resistance in livestock production. *S Afr Med J* 2011; **101:** 583–86.

14 Bureau for Agricultural Policy Baseline. Agricultural outlook 2016–2025. www.bfap.co.za/documents/baselines/BFAP_Baseline_2016.pdf (accessed Oct 11, 2017).

15 Eagar H, Swan G, Van Vuuren M. A survey of antimicrobial usage in animals in South Africa with specific reference to food animals. *J S Afr Vet Assoc* 2012; **83:** 16.

16 Virbac RSA. Colistine 1200. In: Virbac Technical Document. Gauteng, South Africa: Virbac RSA 2000: 14–15.

17 Gerber D. Colistin resistance in *E. coli* in broiler operations in South Africa. *VetNews* (V-Tech, Midrand, South Africa), November, 2016: **8–9.**

18 Bialvaei AZ, Samadi Kafil H. Colistin, mechanisms and prevalence of resistance. *Curr Med Res Opin* 2015; **31:** 707–21.

19 Perreten V, Strauss C, Collaud A, Gerber D. Colistin resistance gene *mcr-1* in avian-pathogenic *Escherichia coli* in South Africa. *Antimicrob Agents Chemother* 2016; **60:** 4414–15.

20 National Institute for Communicable Diseases. Antimicrobial resistance national surveillance maps for South Africa. http://www.nicd.ac.za/index.php/httpscdwmicrostrategy-nhls-ac-zamicrostrategyaspmain-aspxservernhlssandmicsi03projectnhlsbiport0evt2048001srcmain-aspx-2048001documentid10c27d0e4b424b217efdc086730cd76dcurrentvie/ (accessed March 6, 2018).

21 Jayol A, Poirel L, Brink A, Villegas M-V, Yilmaz M, Nordmann P. Resistance to colistin associated with a single amino acid change in protein PmrB among *Klebsiella pneumoniae* isolates of worldwide origin. *Antimicrob Agents Chemother* 2014; **58:** 4762–76.

22 Jayol A, Nordmann P, Brink A, Poirel L. Heteroresistance to colistin in *Klebsiella pneumoniae* associated with alterations in the PhoPQ regulatory system. *Antimicrob Agents Chemother* 2015; **59:** 2780–84.

23 Jayol A, Nordmann P, Dubois V, Brink A, Villegas M-V, Poirel L. High level resistance to colistin mediated by various mutations in the crrB gene among carbapenemase-producing *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2017; **61:** e01423–17.

24 Coetzee J, Corcoran C, Prentice E, et al. Emergence of plasmid-mediated colistin resistance (MCR-1) among *Escherichia coli* isolated from South African patients. *S Afr Med J* 2016; **106:** 35–36.

25 Poirel L, Kieffer N, Brink AJ, et al. Genetic features of MCR-1-producing colistin-resistant *Escherichia coli* isolates, South Africa. *Antimicrob Agents Chemother* 2016; **60:** 4394–97.

26 European Medicines Agency. Updated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health. Draft. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/05/WC500207233.pdf (accessed Nov 10, 2017).

27 South African Veterinary Council. Colistin use by veterinarians. http://www.fidssa.co.za/newsletter_FIDSSA/RSA_Use_of_Colistin_SAVC_and_MCC.pdf (accessed Dec 7, 2016).

28 South African Water Research Commission. A scoping study on the levels of antimicrobials and the presence of antibiotic resistant bacteria in drinking water. http://www.wrc.org.za/Pages/DisplayItem.aspx?ItemID=11823&FromURL=%2Fpages%2FResearch.aspx%3Fdt%3D%26ms%3D%26d%3DA+scoping+study+on+the+levels+of+antimicrobials+and+presence+of+antibiotic+resistant+bacteria+in+drinking+water%26start%3D1 (accessed Dec 7, 2016).