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Review

Antibiotics usage in food-producing animals in South Africa and impact on human: Antibiotic resistance

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The widespread and intensive use of antibiotic agents in modern food production systems is believed to be contributing significantly to antibiotic resistance among bacteria. Antibiotic usage in food-producing animals tend to be increasing and data show that even those that have been banned in other countries such as growth promoters are still being used in South Africa. Moreover, very few relatively recent surveys and reports on antibiotic resistance isolates from food animals in South Africa have been carried out and are crowded in Gauteng province. However, despite poor health status which include a large portion of bacterial infections, as well as HIV/AIDS epidemic and tuberculosis, South Africa has had the most active surveillance for antibiotic resistance of any African country. But, the concern is that it has not yet fully translated available antimicrobial resistance surveillance data into policy. Moreover, a national surveillance programme of antibiotics usage on the food-producing animals and antibiotic resistance is required to help to mitigate the problem of lack of availability of information.

Key words: Antibiotic, food-producing animals, bacteria, resistance, surveillance.

INTRODUCTION

The intensive use of antimicrobial (antibiotic) agents in industrial animal husbandry have spread into developing countries, and the negative impact on human health and food safety have often followed (Garcés, 2002). The impact may vary considerably between countries and regions, influenced by the interaction between human populations, land use, contaminated water sources, animal demography, national policies (production, trade, food security, animal health, etc.), and national and international trade (WHO, 2012). Hence, antibiotic resistance is a major global societal problem (Mellon et al., 2001; Davies and Davies, 2010; WHO, 2012), involving many different sectors example medicine, veterinary medicine, animal husbandry, agriculture, environment and trade (EC 2011). Epidemiological studies have demonstrated a correlation between antibiotic use and antimicrobial resistance (Goossens et al., 2005; Beerepoot et al., 2011, 2012; den Heijer et al., 2012). Goossens et al. (2005) showed that there were higher rates of antibiotic resistance in high consuming countries, probably related to the higher consumption/usage of antibiotics in southern and eastern Europe than in northern Europe. There is a higher report of use of antibiotics in developed countries than in developing countries both for prophylaxis and therapy but, higher therapeutic use than prophylactic use in developing countries

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(Mitema et al., 2001; Byarugaba et al., 2011). Reports point that the international travel and trade in animals and animal products increase the risks of antibiotic resistance world-wide (Acar and Röstel, 2001; Mellon et al., 2001; EC, 2011; Byarugaba et al., 2011; WHO, 2012).

Furthermore, antibiotic resistance has been given a low priority in most developing and many developed countries. Most important, developing countries such as South Africa have received much limited attention regarding this problem (Okeke et al., 2007). Globally, only a few developed countries such as Sweden, Denmark, the United Kingdom, and Netherlands have managed to reduce antibiotic consumption in the community which have sometimes resulted, but not always, in a decrease in resistance (Cogliani et al. 2011; Mackie, 2011; Carlet et al., 2012). Unfortunately, there is no single or simple solution to the problem of bacterial antibiotic resistance because there are many diverse factors that contribute to irrational use of antibiotics including knowledge, perceptions, attitudes and behaviour of policy-makers, prescribers, manufacturers, dispensers and consumers (WHO, 2012). However, the use of antibiotics in livestock production is suspected to be significantly contributing to the antibiotic resistance in species of bacteria which are common to humans and animals (Acar and Röstel, 2001). Mostly, the routine practice of giving antibiotic agents to domestic livestock (that is, preventing and treating diseases, as well as promoting growth) is found to be an important factor in the emergence of antibiotic resistant bacteria that are subsequently transferred to humans through the food chain/or foodstuffs (Perreten et al., 1998; van den Bogaard and Stobberingh, 2000; Schlegelova et al., 2004; Byarugaba et al., 2011).

The increase in antibiotics resistance has been reported in both commensal and pathogenic bacteria, this raises an emerging threat to public health and the environment (Marshall et al., 2009; Thaller et al., 2010; Aiyegoro et al, 2011; Byarugaba et al., 2011; Carlet et al., 2012). This high resistance challenge results from two combined factors (Carlet et al., 2012). First, microorganisms are becoming extremely resistant to existing antibiotics, in particular Gram-negative rods (example, *Escherichia coli, Salmonella spp, Klebsiella* spp., *Acinetobacter* spp.), which are resistant to almost all currently available antibiotics in some settings. Second, the availability of new antibiotics has become extremely dry (Hughes, 2011). Several new powerful compounds active against Gram-positive cocci have been made available in the last few years, but this is not the case for Gram-negative bacteria and almost no new antibiotic class active against multi-resistant Gram-negative rods can be anticipated in the near future (Carlet et al., 2012). Therefore, this work summarizes the problem and the impact of antibiotic resistance in relation to antibiotics usage in farm animal husbandry with the consequences on consumer's health. The work also tried to look at some of the efforts which are being done to contain antibiotic resistance which include alternatives to antibiotic usage.

ANTIBIOTIC USE IN AGRICULTURAL SECTOR: FOOD-PRODUCING ANIMALS

Treatment, prophylaxis and growth promoters are the commonly uses of antibiotics in food-producing animals (Table 1) and is essential for a sustainable and economically sustainable animal industry (Acar and Röstel, 2001; Eagar, 2008). However, the application of these antibiotic drugs in animals, particularly in food animals, may lead to a selection of resistant strains of bacteria, which in turn may proceed to infect both animals and human (Mellon et al., 2001). Molecular analysis of antibiotic resistance genes and antibiotic-resistant mobile elements has shown that identical elements were found in bacteria that colonize both animals and humans, suggesting a role for raw foods in the spread of resistant bacteria and resistance genes to humans via the food chain (Teuber, 2001; Van et al., 2007). For example, the use of fluoroquinolones (example enrofloxacin) in food-producing animals has resulted in the development of ciprofloxacin-resistant *Salmonella, Campylobacter* and *E. coli*, which have caused human infections that proved difficult to treat (WHO, 2011).

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 (Henton et al., 2011). Moreover, considering the lack of information on the total quantity of antibiotics produced, it is not surprising that information on quantities used for specific purposes in agriculture and human medicine is also limited. Of all the available antibiotics used in livestock production in South Africa about 29% reported (Eagar, 2008) are in the form of premixes, and represents a large percentage of all the registered antimicrobials. Picard and Sinthumule (2002) together with Eagar (2008) reported that the most frequent uses of antibiotics by weight (as measured by sales) were those for treating and preventing diseases in poultry and pigs, and as growth promoters. In a survey Henton et al. (2011) found that tylosin, one of 4 growth promoters banned in Europe, was the most extensively sold antibiotic in South Africa followed by tetracyclines, sulphonamides and penicillins, respectively. Extensive usage of tylosin in food-producing animals was initially reported by Eagar (2008). In that study it was also found that the mean antibiotic sales for 3 years period (Table 2) from 8 companies were 1.5 million kilograms active ingredient. Where, in terms of total volumes of sales (kg), the macrolides, lincosamides and pleuromutilins represented 42.4% of the antibiotics sold. In the last four years there have been annual increases in unit sales from 25.3 to 29.8 million (Table 3) of broad-spectrum penicillins, fluoroquinolones, carbapenems and penems, carbacephems

Table 1. Some of commonly used antibiotics in food-producing animals.

Antibiotic	Treatment objective	Food animal	Reference
lincomycin	Feed efficiency, growth promoter and disease control	Swine, poultry	Regassa et al. (2008) Kuchta, (2008)
Tylosin*	Feed efficiency and growth promoter	Poultry, cattle	Henton et al. (2011) Jackson et al. (2004) Eagar, (2008)
Penicillin	Feed efficiency, growth promoter and disease control	Swine, poultry	Regassa et al. (2008) Doyle, (2006)
Virginiamycin*	Feed efficiency, growth promoter and disease control	Swine, poultry, cattle	Regassa et al. (2008) Donabedian et al. (2003) Cogliani et al. (2011)
Tetracyclines (chlrotetracyclineoxytetracyline, tetracycline)	Feed efficiency, growth promoter and disease control	Swine, poultry, cattle	Oguttu et al. (2012) Regassa et al. (2008)
'Erythromycin	Disease control	Swine, poultry, cattle, sheep	Jeong et al. (2006)

*Banned in European Union

Table 2. Volumes (kg) of antibiotics used during 2002-2004* as sourced from veterinary pharmaceutical companies.

Class of antibiotic	Volume (kg)			Total (kg) over 3 years
	2002	2003	2004	
Penicillins	49 465	55 677	59 688	165 717*
Cephalosporins	5 470	3 321	3 316	12 107
Tetracyclines	58 342	71 842	58 974	257 755*
Aminoglycosides	3	242	268	1 048*
Macrolides, lincosamides and pleuromutilins	204 325	221 275	223 412	651 690*
Quinolones	582	582	1 082	3 094*
Quinoxalines	30 043	26 468	30 448	86 959
Sulphonamides	35 041	72 277	75 098	190 676*
Polipeptides	27 011	26 985	42 191	69 820
Ionophores	14 736	5 582	43 674	69 820*
Glycolipids	370	425	432	3 936*
Total	**425 388**	**484 676**	**538 583**	**1 538 443***

(Eagar, 2008). * Two of the eight veterinary pharmaceutical companies that provided data were only able to access their data for the whole three year period and not for each year individually.

and glycopeptides in South Africa (Essack et al., 2011). Moreover, counterfeiting of pharmaceuticals is highly problematic in South Africa, with an estimated one in five medicines sold believed to be counterfeit (BMI, 2010). It is reported that the majority of counterfeit medicines have been imported from India and Pakistan and reach pharmacies through illegal means and the South African Medicines and Medical Devices Regulatory Authority (SAMMDRA) have not been successful in combating this problem (Essack et al., 2011). Therefore, sales data may

Table 3. Antibiotic utilisation in units, 2008 – 2011.

Antibiotic	Year	Sum of MAT units,			Count of antibiotics in each class*
	2008	2009	2010	2011	
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 Glycopeptideantibact.	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**

Essack et al. (2011), MAT = Moving Annual Turnover, *Number of drug formulation.

provide a misleading and inaccurate measure of the use of antibiotics because of counterfeiting. Hence, industry data on antimicrobial use in livestock production almost certainly underestimate usage and are far too general to help scientists explore the linkages between various types of farm use and the emergence and spread of resistance (Union of Concerned Scientists, 2001, (www document;http://www.ucsusa.org/assets/documents/food_and_agriculture/hog_chaps.pdf Accessed 04/Sep/2012).

A study by Eagar et al. (2012) found that the majority of consumed antibiotics in animals were from the macrolide and pleuromutilin classes, followed by the tetracycline, the sulphonamide and lastly the penicillin class. Their survey results showed that 68.5% of the antibiotics were administered as in-feed medications. About 17.5% of the total volume of antibiotics utilised were parenteral antibiotics, whereas antibiotics for water medication constituted 12% of the total and other dosage forms (topical and aural dosage) constituted 1.5% of the total. From the figures above, it is not surprising that many chicken farms widely use antibiotics as a prophylactic and a growth stimulant (Medeiros et al., 2011). However, this is particularly problematic because antibiotic for growth promoters are used without veterinary prescriptions or administered for long periods of time at sub-therapeutic concentrations to entire groups or herds of animals (Carlet et al., 2012). These farmers have come to believe that relatively low concentrations of antibiotics in feed and water can help avoid disease-driven losses in livestock with the belief that they increase profit margins despite the lack of well-understood mechanisms (Mellon et al., 2001). However, if the quality of industrial animal farming is improved there would be far less of the problem of disease control and prevention, and hence antibiotic resistance (Garcés, 2002). This is because in most cases overcrowded and unhygienic conditions of industrial animal farming result in the spread and emergence of microbes. Therefore, if conditions were improved, the prophylactic use of antibiotics would not be necessary.

ANTIBIOTIC USE IN FARM ANIMALS AND IMPACT ON HUMANS

Certain antimicrobial drugs have been reported to stay in the meat and/or milk of food animals for extended periods of time (Nisha, 2008; McDermid, 2012; Lozano and Trujillo, 2012). For example, chicken are being fed with antibiotics and in some cases hormones which can never be fully broken down and excreted from its body before it is slaughtered, this may result in very concentrated by-products and residues in chicken meat (Compassion in World Farming South Africa (CIWFSA) 2012, (www document,http://www.animal-voice.org/antibiotic-residue-is-in-our-chickens/ Accessed 14/Nov/2012). And it is said that South Africa does not have a regulated process of antibiotic residue testing in meat (McDermid, 2012). Data released by the Compassion in World Farming South Africa in September 2009, showed that every single chicken purchased at supermarkets tested positive for tetracycline residue which is one of the most depended upon antibiotics in human health. Part of the Chicken sample displayed a residue of 55% over the legal limit in terms of South African Law (CIWFSA, 2012). Furthermore, the study found that 10 freshly dead carcasses from the Phillippi cull outlet showed 100% antibiotic resistant bacteria on the skin surface including *staphylococci* and *enterobacteriaciae* (CIWFSA, 2012). The antibiotics to which the bacteria were 100% resistant were penicillin and ampicillin, both of which are used for a broad spectrum of human illnesses (Schrag et al., 2002; CIWFSA, 2012).

Concerns about use of penicillins and other antibiotics is the withdrawal period (Eagar et al., 2012). The high content of antibiotic residues such as that of tetracycline (and penicillins, etc.) in food animal products is of great concern since it has been established that these compounds also remain chemically detectable even after cooking, as cooking only decrease its amounts (Javadi, 2011). A comparative study in Nigeria showed penicillin (14%) was the drug with the highest rate of occurrence in meat samples followed by tetracycline (8%) and streptomycin (4%). These antibiotic traces have harmful effects on consumer's health, such as allergic reactions, liver damage, yellowing of teeth and gastrointestinal disturbance (FAO/WHO, 2002; Jing et al., 2009). Another fact is that over time, through continued consumption of meat products containing these antibiotic residues (indirect consumption of antibiotic residues), people's body will start to develop resistance to that antibiotic molecule which can impact their lives (Andrew, 2003; Nisha, 2008; McDermid, 2012; Lozano and Trujillo 2012). Whereby, these residues produces potential threat with direct toxic in human, second the low levels of antibiotic exposure will result in alteration of microflora, causing disease and the possible development of resistant strains which cause failure of antibiotic treatments (Nisha, 2008).

On the processing point of view, Kjeldgaard et al. (2012) examined how acceptable levels of antibiotics in meat influence fermentation. Their results show that commonly used bacterial starter cultures were sensitive to residual antibiotics at or near statutorily tolerable levels, and as a result, processed sausages may contain high levels of pathogens. Furthermore, their findings provided a possible explanation for outbreaks and disease cases associated with consumption of fermented sausages and offered yet another argument for limiting the use of antimicrobials in farm animals. With no doubt, there is a need to investigate the role of the availability of antibiotics over the counter for use in animals in South Africa in the development of resistance among humans (Oguttu et al., 2012).

ROLE OF FOOD IN DISEASE TRANSMISSION: RESISTANCE AND DISEASE

There is limited information of disease caused by antibiotic resistant bacteria in South Africa, due to the fact that causes of illnesses and deaths are not well counted, as is often the case in low-resource countries (Crowther-Gibson et al., 2011). According to a report from the International Federation for Animal Health (IFAH, 2011), it is estimated that of the 1,500 diseases that affect people, almost two-thirds can pass between animals and humans. The transfer of *Staphylococcus aureus* isolates between humans and animals, especially in the case of livestock-associated Methicillin-resistant *S. aureus* (MRSA) ST398, has recently gained particular attention (Smith and Pearson, 2011). The ST398, which is the swine-associated MRSA, and ST398 human infections, has been recognized in several countries (NIAA, 2011). It is suggested that livestock associated MRSA originally were methicillin-susceptible commensal strains in pigs, whose spread was facilitated by the abundant use of antibiotics in pig and cattle farming (Voss et al., 2005). *S. aureus* is a major human pathogen, a relevant pathogen in veterinary medicine, and a major cause of food poisoning (Sobral et al., 2012). A joint ECDC/EFSA/EMA (2009) scientific report demonstrated that pigs are a major reservoir of a new emerging type of MRSA and concluded that the extensive use of antibiotics for prevention of disease appears to be an important risk factor for the spread of MRSA. With South Africa having a high burden of infectious diseases, including a large portion that are of bacterial origin (Crowther-Gibson et al., 2011), these resistant microorganisms pose a serious health concern in the country where there is a high rate of HIV/AIDS and TB infection. Bacterial infections are quite frequent in HIV-infected patients (Carrega et al., 1997). This is because HIV-induced immunosuppression amplifies the risk of bacterial infections, TB and non-tuberculosis, often involving antibiotic-resistant strains, with severe and/or recurrent potential (Stoian, 2013).For example, infections such as respiratory failure in HIV infected patients are bacterial *pneumonias* which have been reported to be caused by *Pseudomonas*, *Staphylococcus aureus* and other bacteria (Bajwa and Kulshrestha, 2013).In 2009 an estimated 29% (over 5.5 million) of people were infected with the HIV virus (Crowther-Gibson et al., 2011). Moreover, some evidence indicate that antibiotic resistance rate to nosocomial pathogens are generally high in South Africa (Nyasulu et al., 2012).

Poultry meat has been reported as an important vehicle in foodborne diseases and some studies have suggested that chicken can be a source of antibiotic resistant *Salmonella* spp. in humans (Medeiros et al., 2011). In their study Medeiros et al. (2011) found that the prevalence of *Salmonella* spp. was relatively low. However, there were a high proportion of multidrug-resistant strains, including third generation cephalosporins used to treat invasive salmonellosis. Test results from randomly selected spent hens; sold live to residents in Khayelitsha, a community near Cape Town revealed that the hens were contaminated by a range of disease-causing bacteria (Garcés, 2002). The concern is that the study showed that the bacteria in both the hens and study community were 100% resistant to most common (oxacillin, vancomycin and methicillin) antibiotics. Therefore, this entails that certain antibiotics would be ineffective in the treatment of people who get infected by eating such hens. Moreover, resistance shown to vancomycin is particularly worrying. As it is a front-line antibiotic used to treat all sorts of infections in humans including chest and heart muscle infections (Nierenberg and Garcés, 2005).

Most of the concern about human health consequences of antibiotics use has focused on growth promotion (which boosts the utilisation of the genetic potential for growth of pigs and poultry, improve feed conversion and reduce waste product output from intensive livestock production) rather than disease prevention (WHO, 1997). The rationale is that the benefits of growth promotion are purely economic and often compensate for and encourage unsanitary conditions (Mellon et al., 2001).

CASES OF ANTIMICROBIAL RESISTANCE IN SOUTH AFRICA

Only a few relatively recent surveys and reports on antibiotic resistance in isolates from food animals in South Africa have been conducted and they are very few and bunched in Gauteng province (Gelband and Duse, 2011). A number of clinical and environmental data suggest that the rate of antimicrobial resistance is high in South Africa. A current systematic review of published literature (Nyasulu et al., 2012) of antimicrobial resistance surveillance among nosocomial pathogens revealed resistance to commonly used antimicrobial drugs in population: for *S. aureus*, resistance to cloxacillin was 29% and to erythromycin 38%; for *Klebsiella pneumoniae,* resistance to ciprofloxacillin was 35% and to ampicillin 99%; and for *Pseudomonas aeruginosa,* the mean resistance to ciprofloxacillin was 43% and to amikacin 35%. Ateba and his co-authors have also reported antibiotic resistance in dairy and poultry products (Ateba et al., 2010). It is reported that penicillin resistance in South Africa remains mainly intermediate in level, with a low prevalence of fully resistant isolates (Crowther-Gibson et al., 2011).

CURRENT EFFORTS TO CONTAIN/REVERSE ANTIBIOTIC RESISTANCE

South Africa is part of the four countries (including India, Vietnam and Kenya) forming the Global Antibiotic Resistance Partnership (GARP). GARP-South Africa was launched on 8 February 2010 at a meeting attended by 40 experts (Suleman and Meyer, 2012). It aims to address the antimicrobial resistance through the situational analysis of antimicrobial resistance in South Africa and collaborating countries. The situational analysis was published as a special supplement to the South African Medical Journal, (SAMJ, 2011). Thereby, the data obtained was said to be used to inform and develop policy and advocacy for antimicrobial resistance-related issues in each of the collaborating countries (Gelband and Duse, 2011). Therefore, GARP is to recognise those issues and recommend policy alternatives that are right for the time and place. Despite poor health status, South Africa has had the most active surveillance for antibiotic resistance of any African country (Gelband and Duse, 2011). However, it has not yet fully translated available antimicrobial resistance surveillance data into policy (Suleman and Meyer, 2012). Hence, there is no evidence of any on-going antimicrobial resistance surveillance for pathogens in South Africa (Nyasulu et al., 2012).

Crude plant extracts have been a promising alternative and potential resistance modifying agents in fight against antibiotic resistance (Sibanda and Okoh, 2007; Aiyegoro et al., 2009; Savoia 2012). Aiyegoro et al. (2009, 2011) proposed that extracts of the leaves of *Helichrysumpedunculatum* and *Afzeliaafricana* stem barkcould be of relevance in combination therapy and as a source of resistance modifying principles that could be useful as treatment for microbial infections. Therefore, these breakthroughs are the promising signs that in the next years some different molecules discovered by ingenious screening programs and obtained from different plant oils and extracts will become useful therapeutic tools (Savoia, 2012).

RECOMMENDATIONS

More work on a national surveillance programme of antibiotics usage on the food-producing animals and the surveillance programme on antibiotic resistance in bacteria must be established in South Africa. These programmes should collect a well arranged data on usage, such as the usage per animal species (drugs type, daily doses) or usage on farm level. It should also include the testing (quantitative susceptibility tests and molecular analysis of resistant genes) of a wide range of bacteria from animals and food products. This information will help to mitigate the problem of lack of availability of information on the amount of antibiotics which are currently being used in livestock production in South Africa. Moreover, a consumer risk perception study on the use of antibiotic in livestock should be conducted, as it is an important factor because it reflects the subjective assessment that people make on the use of antibiotics in food-producing animals as it affect the food they consumes.

Conclusion

Data from studies indicate that South Africa is using large amount of antibiotic in food-producing animals, this includes a number of antibiotics that have been banned for use in other countries. It is evident that there is a real growing problem of antibiotic resistance in South Africa and with high burden of infectious diseases, including a large portion of bacterial origin, as well as HIV/AIDS epidemic and tuberculosis this put people's life at high risk. Therefore, more effort is needed if South Africa is determined to overcome this global problem of antibiotic resistance among pathogens.

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