

Importance and implications of antibiotic resistance development in livestock and wildlife farming in South Africa: A Review

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(Received 12 August 2017; Accepted 6 December 2017; First published online 24 January 2018)

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Abstract

Antibiotic resistance (ABR) is regarded as one of today's major global health challenges. The development of ABR in nature is a complex phenomenon with many influencing factors, of which the farming industry is labelled a significant contributor. The transfer of ABR to humans, which usually occurs via the food chain, is of concern for human health. A food source that is increasing in popularity is game meat, which is farmed widely in South Africa. The natural environment, including wildlife, is not isolated from the rest of the farm, and thus could be a source of ABR or possibly a transfer vector. It is therefore important to assess the ABR situation in wildlife species and the factors that influence its emergence and transfer. Elements that play a part in the development of ABR in game species include certain harvesting and slaughtering and other farming practices and closer contact with humans and other farm animals. Additionally, natural transfer vectors include wind, water, manure, crops and animals. Worryingly, there is lack of knowledge of this situation owing to inadequate monitoring, documentation and control of antibiotics in the farming industry. The objective of this review was to gain better understanding of this situation, which would aid in the development of surveillance systems and methods to prevent or hinder the development of ABR in wildlife species.

Keywords: Antimicrobial resistance, food-borne pathogens, game meat, surveillance systems, zoonoses

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Introduction

Microbial resistance to antibiotics is growing rapidly. This has brought about increased public concern and scientific interest over the last decade (Wellington *et al.*, 2013; Fair & Tor, 2014; Tanwar *et al.*, 2014). Antimicrobial resistance of bacterial origin, known as antibiotic resistance (ABR), of zoonotic food-borne pathogens is now regarded by the World Health Organisation (WHO) as one of this century's leading global health challenges (Marshall & Levy, 2011; McNulty *et al.*, 2016).

Increasing levels of resistance to antibiotics and the simultaneous decline of new antimicrobial developments pose major threats to global health, leading to a higher rate of treatment failure, increased infection, severity of infection, and a rising occurrence of infections that would otherwise not have arisen in animals and humans. Taken together, these could precipitate a 'post-antibiotic era', ensuing ineffective antibiotic use, whereby diseases caused by resistant bacteria would become untreatable with the traditional range of known antibiotics (Capita *et al.*, 2016). This would create a burden on the public health system as more people require hospitalization and the likelihood of rising mortality rates increases (Angulo *et al.*, 2004).

Initially, it was believed that the development of ABR would be minor, based on the assumption that the emergence of antibiotic resistant mutants would be negligible (Van Hoek *et al.*, 2011). The ability of bacteria to interchange genes through a process known as horizontal gene transfer (HGT) was largely unforeseen. Likewise, the ability of a microorganism to adapt to environmental conditions was overlooked and underestimated.

Bacteria exhibit a number of ABR mechanisms, including i) efflux pumps, which actively pump out the antibiotic from the bacterial cell and thus decrease intracellular antibiotic concentration, ii) enzyme

modification of the antibiotic, which renders it ineffective, iii) degradation of the antimicrobial compound, iv) the use of alternative metabolic pathways to those inhibited by the antibiotic, v) overproduction of the target enzyme, (vi) modification of antibiotic targets, and vii) alteration of cell wall permeability, which stops the antimicrobial agent from entering the cell and reaching the target sites (Bhullar *et al.*, 2012).

The rise in antibiotic resistant bacterial species is a result of a complex mix of factors. Some factors are unavoidable and inherent in nature, such as the ability of bacteria to adapt rapidly to changing environmental conditions because of their short generation time and the intrinsic resistance of certain bacteria (Woodford & Ellington, 2007; Laxminarayan *et al.*, 2013). But some variables are human made, such as the extensive use of antibiotics as growth promoters in the farming industry (Lowy, 2003; Ventola, 2015).

Bacteria can develop resistance to antibiotics via mutation or the acquisition of resistant genes from other bacteria (Wintersdorff *et al.*, 2016). The development of ABR is associated with the use, particularly misuse and overuse, of antibiotics in agriculture and human medicine, which creates selection pressure that favours the development of resistant bacterial strains. Antibiotic resistance can even develop towards antibiotics that have not been used, if the resistance determinants are genetically related (Phillips *et al.*, 2004).

Acquired ABR develops as a result of the transfer of resistant determinants between bacteria. Transfer of antibiotic resistant genetic material through HGT is of greater concern than random genetic mutation, because it can occur more often with a more specific outcome. In addition, HGT can occur between bacterial strains, species and even between genera that share the same ecological niche, and, more worryingly, from non-pathogenic to pathogenic bacterial strains (Capita *et al.*, 2016).

Certain conditions and factors favour the probability of the resistant genes being transferred in an ecological niche. The larger the pool of resistance genes in a certain bacterial population, the greater the likelihood of transfer among that population (Capita *et al.*, 2016). Normal gut flora in humans and animals represent an example of a large pool of resistance genes owing to their high bacterial density (Capita *et al.*, 2016). For this reason, *Escherichia coli* (*E. coli*) is most commonly used as an ABR indicator organism owing to its abundance in mammalian gut flora and its ability to exchange genetic material (Adefisoye & Okah, 2016).

Important microorganisms in antimicrobial resistance development

Although viruses are responsible for many food-borne illnesses, bacterial infections cause most of them, accounting for up to 75% of infectious diseases in humans (Nyenje & Ndip, 2013; McNulty *et al.*, 2016). The main causative bacterial agents include *Staphylococcus*, *Salmonella*, *Clostridium*, *Campylobacter*, *Listeria*, *Vibrio*, *Bacillus* and enteropathogenic *E. coli* species (Nyenje & Ndip, 2013). It is therefore important to analyse the prevalence of ABR in food-borne pathogens with regard to human health (Wallmann, 2006).

Staphylococcus species have shown increasing resistance since antimicrobials have been used, especially in hospital-acquired infections. They are already resistant to multiple antibiotics, except vancomycin, which is known as the drug of last resort (Levy, 1998; Blunt, 2000; Doyle *et al.*, 2013). The major concerns of diseases caused by *Staphylococcus* species are those caused by methicillin-resistant *S. aureus* (MRSA) (Chambers & DeLeo, 2009). Methicillin-resistant *S. aureus* has been found to be associated with domestic animals, food-producing animals and various food items such as meat and milk (Porrero *et al.*, 2014). This poses a threat to human health because MRSA is responsible for many nosocomial infections worldwide and could be transferred to humans via the food chain (Nyenje & Ndip, 2013).

Salmonella ABR is a major global health concern owing to the increase in resistance to conventional antibiotics and the rise in multidrug resistance in recent years (Su *et al.*, 2004; Alali *et al.*, 2010). Transmission of *Salmonella* to humans most commonly takes place via contaminated meat, where poultry remains the major transmission vehicle (Alali *et al.*, 2010).

Clostridium difficile is considered the most important *Clostridium* specie with regard to emerging antibiotic resistant bacteria, according to the Centre of Disease Control and Prevention (CDC). The future of human health is threatened by the emergence of these antibiotic resistant strains, which is coupled with the rise of hypervirulent strains that cause severe infections, and their ability to spread rapidly (CDC, 2013; Spigaglia, 2016).

Campylobacter species have shown increased resistance to fluoroquinolones and macrolides, which is recognised as an emerging public health problem. Isolates resistant to macrolides have been found to be of animal origin, where *C. coli* has been most commonly found in pigs and *C. jejuni* in chickens (Nyenje & Ndip, 2013).

Listeria species are distributed widely in the environment. Only *Listeria monocytogenes* (*L. monocytogenes*) is pathogenic to humans and has emerged as a major food-borne pathogen (Teuber,

1999). Listeriosis is an often fatal disease for which antimicrobial treatment is essential, the main transmission route to humans being food borne (Nyenje & Ndip, 2013).

Vibrio species are found in marine environments. Seafood-associated infections is usually caused by *V. cholera*, *V. parahaemolyticus* and *V. vulnificus* (Raissy *et al.*, 2012). Recent studies have shown that these species have become multidrug resistant (MDR) owing to the misuse of antibiotics in aquaculture production, and are thus major health threats to the public who become infected with seafood-borne diseases caused by antibiotic resistant *Vibrio* species (Elmahdi *et al.*, 2016).

Bacillus species are used widely as probiotics and animal feed additives because of their ability to stimulate the immune system (Adimpong *et al.*, 2012). This has raised concern about the possibility of these feed additives acting as reservoirs of antibiotic resistant genes because *Bacillus* species have been shown to be resistant to several antibiotics (Adimpong *et al.*, 2012).

E. coli is commonly used as an indicator of ABR in microbial populations because it readily exchanges genetic material with other bacterial species and has the ability to harbour several resistant determinants. The prevalence of extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* has been increasing since the 1980s and has been found in healthy food animals and even in wild animals (Poeta *et al.*, 2009). The ESBLs now compromise third-generation cephalosporins for treating gram-negative infections (Hawkey, 2008).

Additionally, antibiotic susceptibility testing of indicator organisms *E. coli* and *Enterococcus* species is commonly carried out to determine the prevalence of acquired ABR. These commensal bacteria are used as indicators of ABR in bacterial populations as they are known to form a reservoir of mobile resistance genes that can spread to other bacteria (McNulty *et al.*, 2016). In addition, the South African National Veterinary Surveillance and Monitoring Programme for Resistance to Antimicrobial Drugs (SANVAD) has noted that *E. coli* and *Enterococcus* species have shown increased ABR, which is consistent with findings from its European counterparts (Eager *et al.*, 2012).

Magwedere *et al.* (2012) and McNulty *et al.* (2016) recommended that the current major zoonotic food-borne pathogens *Salmonella* and *Campylobacter* should be monitored in food animals, as well as emerging zoonotic pathogens such as MRSA, ESBL-*Enterobacteriaceae* and *L. monocytogenes*. Additionally, monitoring of commensal bacteria is recommended as they give good indications of ABR levels in the environment (McNulty *et al.*, 2016).

Antimicrobial resistance in animal production

Antibiotic resistance in the environment occurs in many sectors, from aquaculture, food processing and healthcare to wildlife, companion animals and food animals (Landers *et al.*, 2012; Wegener, 2012). The agricultural industry relies on the use of antimicrobials to improve animal health and productivity, especially in intensively reared species (Moyane *et al.*, 2014; Woolhouse *et al.*, 2015). Therefore, the volume of antimicrobial use in the industry is comparable with that of medicine (Anon., 2015). Worryingly, many antimicrobials that are regarded as important to human health are used in animal food production, such as tetracyclines, penicillins, and sulphonamides (Landers *et al.*, 2012).

The misuse, overuse and inappropriate use of antimicrobials in animal husbandry has created enormous selection pressure, which increases and accelerates the likelihood that bacteria will adapt and multiply to produce a more resistant population. The spread of ABR is facilitated by the high density of animals involved in primary production (Aminov & Mackie, 2007). Consequently, the farming industry has been established as an ABR reservoir 'hotspot' (Essack & Bester, 2010).

To keep up with the enormous scale of global food production and limited resources, food producers have applied new technologies and alternative production methods to industrialize and optimize food production (Koluman & Dikici, 2013). An example involves the use of antibiotics as feed additives to enhance the growth of animals, which are known as growth promoters (Koluman & Dikici, 2013). The mechanisms of growth promoters are still largely unknown, but it has been hypothesized that they work by altering microintestinal flora, which results in more efficient digestion and metabolism, as well as disease and pathogen suppression (Phillips *et al.*, 2004).

The use of antibiotics in the food production chain is usually seen as important in continuing a consistent supply of healthy and substantial animals, leading to greater profitability and efficient production (Capita *et al.*, 2016). The application of mass medication, known as metaphylaxis, and the use of broad-spectrum antibiotics in animal husbandry is common, because it is often impractical to treat animals individually (Capita *et al.*, 2016). This exploitation of antibiotics at low concentration over extended time favours the emergence of ABR.

Numerous studies have shown that the use of antibiotics in food-production animals, especially for nontherapeutic use, is linked to resistance in people who live on and near farms and even the general population via the food chain (Marshall & Levy, 2011). What is more, emerging resistant bacteria are

evolving to adapt to different hosts and environments. For example, since the mid 2000s livestock has become a primary reservoir of MRSA strains that were once found only in nosocomial environments (Soni *et al.*, 2015). A new MRSA variant, CC398, which was first noted in Finland in 2007, has recently been found in animals, especially intensively reared production livestock such as pigs, cattle and poultry, and can be transmitted to humans (Salmenlinna *et al.*, 2010). Transmission is mainly via occupational exposure, resulting in mild to serious infections and even death (Anderson *et al.*, 2003; Salmenlinna *et al.*, 2010; Smith & Wardyn, 2015; Grøntvedt *et al.*, 2016).

Linking resistant bacteria from animals to humans is not simple as there are many possible routes of transmission besides food animals (Phillips *et al.*, 2004). Direct transfer routes include contact with companion animals and wildlife. Indirect transfer routes include contamination of the soil, rivers and streams by farm effluents and manure spreading. These would subsequently contaminate crops and water used for drinking and food preparation, and could spread to wildlife habitats (Landers *et al.*, 2012; Wegener, 2012). Nonetheless, the food chain has been hypothesised as the main route of transmission of antibiotic resistant bacteria to humans.

Effects of antimicrobial resistance on animal food production and thus human health

The potential threat to human health from the misuse of antibiotics in food animals is significant. Its impact has not been fully comprehended because of inadequate research and documentation (Landers *et al.*, 2012). However, numerous studies associate ABR in food animals with antibiotic resistant infections in humans (Marshall & Levy, 2011; Landers *et al.*, 2012; Chang *et al.*, 2015). The most commonly identified food-borne pathogens that have been associated with bacterial resistance genes in humans and farm animals include MRSA, *E. coli*, *Salmonella* and *Enterococcus* species (Marshall & Levy, 2011). Zoonotic diseases, for example anthrax and rabies, account for up to 60% of infections in humans (Karesh *et al.*, 2012). Furthermore, resistant microorganisms have been detected in environments surrounding livestock farms. For example, Graham *et al.* (2009) found that *Enterococci* and *Staphylococci* isolates from flies near poultry farms carried similar antibiotic susceptibility patterns to the isolates from poultry litter on the farms.

Antibiotic resistant zoonotic food-borne pathogens in food-producing animals can spread to humans via consumption of contaminated food or water, and direct contact with animals (McNulty *et al.*, 2016). There are various stages and interactions in the food production chain at which antibiotic resistant bacteria can enter. First, in the physical environment, such as soil, air and water, resistant organisms can spread from animals. An example is the consumption of water that is contaminated because of resistant bacteria from animal waste that is used as fertilizer (Landers *et al.*, 2012). On the farm, there could be more direct transfer of resistant bacteria between animals in a herd and those in close proximity, as well as between farmers and their animals (Landers *et al.*, 2012).

Moreover, bacteria in food that is ABR are likely to be more persistent in food commodities owing to their overall resistance to other environmental stressors, such as preservatives and disinfectants (McMahon *et al.*, 2007). This is due to induction of the mar operon as a result of exposure to environmental stress. The mar operon regulates the expression of many genes, including those that encode for various antibiotic resistant mechanisms (McMahon *et al.*, 2007; Anon., 2016). Therefore, the resistance of bacteria to antibiotics can have an influence on their persistence of bacteria owing to their abilities to withstand the effects of various environmental stressors.

A concern to human health is the transfer of antibiotic resistant bacteria in food to humans and subsequent colonization of the human intestine (Bester & Essack, 2010; Founou *et al.*, 2016). This highlights the importance of correct food handling and preparation by consumers to avoid transmission because the presence of antibiotic resistant bacteria could affect the future of human health adversely as certain infections become more difficult to treat or infections occur if pathogenic antibiotic resistant bacteria are ingested (Bester & Essack, 2010; Founou *et al.*, 2016).

During food production, processing steps such as farming activities, slaughtering practices and transportation of food animals could introduce resistant bacteria into the food chain (McEwen & Fedorka-Cray, 2002; Landers *et al.*, 2012; Founou *et al.*, 2016). Spraying meat carcasses with organic acid solutions to decontaminate them may result in the survival of acid-resistant pathogens. This could consequently cross-contaminate food and 'colonize' the food-manufacturing environment, undermining cleaning and sanitization effectiveness (Berry & Cutter, 2000; Anon., 2006). Moreover, contamination during food preparation and consumption of contaminated meat and other food products results in a more direct transmission route of antibiotic resistant bacteria (Landers *et al.*, 2012). Residual antibiotics in raw meat could result in the development of antibiotic resistant bacteria in the human gut (Kjeldgaard *et al.*, 2012).

Consequently, the food-borne route is where most of the ABR can be transferred from animals to humans. Likewise, most infections with bacterial pathogens occur via the food chain (Wegner, 2012). A number of recent antibiotic resistant pathogens have emerged in the food chain, namely ESBL-producing

Salmonella and *E. coli*, quinolone-resistant *Salmonella* and *E. coli* and livestock-acquired methicillin-resistant *Staphylococcus aureus* (LA-MRSA) (Wegner, 2012). These cases are associated with antimicrobial use in feed for animals.

Research has shown that environmental organisms that are non pathogenic can be a reservoir of resistance genes that could be transferred to pathogens (Bhullar *et al.*, 2012). These reservoirs of ABR genes in bacterial communities have been shown to be stable, even when selective pressure is not created by the presence of antibiotics (Looft *et al.*, 2012). It is therefore considered important not to misuse the application of antibiotics so that the selection of resistant elements and their subsequent movement through microbial communities can be avoided, or at least hindered (Bhullar *et al.*, 2012).

Numerous techniques can be implemented to help reverse or slow down the development of ABR in various environments, which has largely been caused by the misuse of antibiotics (Khachatourians, 1998; McNulty *et al.*, 2016). Increasing farm hygiene and good herd management, vaccines, decreasing the practice of metaphylaxis, and education about and implementation of the correct use of antibiotics and monitoring systems are techniques that can be used in South African farming to prevent the development of a 'post-antibiotic era' and thus preserve the effectiveness of antibiotics as we know them today (Fedorka-Cray, 2002; Doyle *et al.*, 2013; McNulty *et al.*, 2016). Additionally, an effective wild game traceability system in southern Africa should be developed at all harvesting levels. Improvement of current surveillance and control strategies should be employed. This would assist in monitoring the ABR and disease situation to assist in better control of emerging diseases in food animals. Animals at the wildlife-livestock interface, free-roaming wildlife that are harvested for trophies or meat, and those captured from translocation would provide the most suitable samples for a representation of the human health risks associated with wildlife and livestock production (Magwedere *et al.*, 2012).

The concern of ABR to human health is the transfer of resistant bacteria between animals and humans. Case studies have reported evidence of resistant *Campylobacter*, *Salmonella*, MRSA and *E. coli* causing diseases in humans that originated from animals (Phillips *et al.*, 2004; Bengtsson & Greko, 2014). It is alarming that the same classes of antibiotics are used for veterinary and human medicine, namely β -lactams, sulphonamides, tetracyclines, macrolides, lincosamides, streptogramins, and quinolones (Phillips *et al.*, 2004). Efforts should focus on minimizing the transmission of food-borne pathogens via the food chain, despite their antibiotic susceptibility profile by adopting good hygiene practices at all stages of food production, including food marketing and food preparation by the consumer.

Antimicrobial resistance in wildlife species

The fate of antibiotic resistant bacteria in more remote ecosystems is largely unknown, but the emergence of resistance genes in these environments could affect antibiotic efficacy in human medicine and agriculture. Antibiotic resistance in humans is interlinked with ABR in other populations and in the wider environment. Resistance, specifically mobile genetic elements, can pass between these populations in nature (Woolhouse *et al.*, 2015). It has been hypothesized that wildlife play a significant role in the development of antibiotic resistant bacteria in nature because a variety of wildlife species carry antibiotic resistant bacteria and cover large territories throughout their lifespan (Magwedere *et al.*, 2012; Vittecoq *et al.*, 2016;). Various wild animals could be considered natural reservoirs and potential spreaders of antibiotic resistant microorganisms throughout their environment, including birds of prey, wild ungulates, arctic birds, and wild rodents (Kozak *et al.*, 2009; Sousa *et al.*, 2014).

Although ABR in wild animals is expected to be low owing to low-level exposure to antibiotics, studies have shown that 75% of zoonoses related to emerging human infectious diseases are associated with wildlife animals (Magwedere *et al.*, 2012). It is evident from these studies that ABR among wild animals is becoming a public health concern owing to increased wildlife contact with humans, livestock and domestic animals, as well as increased co-habitation with other animals. This increased contact and co-habitation intensifies the likelihood of ABR traits in microorganisms transferring among ecosystems (Sousa *et al.*, 2014). Indirect contact between wildlife species and humans can occur among those that live near rearing estates or if contaminated food or meat is consumed by humans (Magwedere *et al.*, 2012). Direct contact occurs most frequently with hunters, trappers and veterinarians (Vittecoq *et al.*, 2016).

Moreover, various studies have found that antibiotic resistant bacteria in wildlife species are often resistant to antibiotics of natural origin, and thus can be considered natural reservoirs and transfer vectors of antibiotic resistant bacteria of environmental origin (Cole *et al.*, 2005; Jeters *et al.*, 2009; Guenther *et al.*, 2010; Wellington *et al.*, 2013). The origin of many ABR genes seems to reside in naturally occurring antibiotic synthesising organisms. Alternatively, the ABR genes are native to organisms where the resistant gene has a physiological function, but is 'silent' in the sense of not showing a detectable form of resistance, since its function is to protect the host's own metabolism (Gilmore *et al.*, 2008). For example, the chromosomal penicillin binding proteins that confer resistance to penicillins were originally involved in

bacterial cell wall synthesis. Resistance is due to a mutation or overproduction of penicillin binding proteins (Chadha, 2012).

In addition, there is a growing trend of consumption of wild game meat and meat from farmed game, with the game farming industry growing at 2.5% per annum (Hoffman, 2007; Hoffman & Cawthorn, 2012). Furthermore, the variety of human activities in natural habitats has increased over recent years through the construction of game reserves, conversion of land for crops to wildlife habitats, and the expansion of communities, causing an increased risk of disease transmission to and from wildlife (Magwedere *et al.*, 2012; Katakweba *et al.*, 2015).

The application of antibiotics in various situations, from agriculture to the food industry, has resulted in a constant release of low-level antibiotic concentration into the water and soil through wastewater treatment plant effluents, sewage, agricultural waste and the application of manure fertilizer to fields and gardens, among others (Anon., 2006; Dias *et al.*, 2015). This environmental pollution, together with co-habitation of livestock and wild animals and increased human contact, allows antibiotic compounds to reach more remote natural habitats. This alters the population dynamics of microorganisms, encouraging the development of ABR in microbiological communities of wild animals through heightened selection pressure of resistance (Martínez, 2008; Dias *et al.*, 2015). Importantly, water is a major transmission vector for antibiotic resistant microorganisms. Pathogens such as *S. aureus*, *E. coli*, *Klebsiella pneumonia* and *Salmonella* species can survive in aqueous environments (Vittecoq *et al.*, 2016).

Another important ABR vector is manure as it is a reservoir of antibiotic compounds and resistant bacteria. A concern with the spread of ABR is that 30–90% of antibiotics are often excreted unchanged and thus can easily enter the environment via manure to be spread among exposed bacterial populations (Marshall & Levy, 2011). Manure has been shown to promote HGT in soil, as it carries large amounts of broad-host-range plasmids which are major vectors of HGT (Heuer *et al.*, 2011; Woolhouse *et al.*, 2015).

Therefore, water, soil and manure can be considered major potential pathways of ABR transfer from animals to humans, along with other vectors such as wind, crops and flies (Heuer *et al.*, 2011). Thus, ABR in the natural environment varies depending on geographical location, species and ecosystems (Katakweba *et al.*, 2015). More specifically, the presence of nearby farms, human density and proximity, ABR levels carried by the livestock, and interaction with farm waste all influence the ABR seen in the nearby wild ungulates (Navarro-Gonzalez *et al.*, 2013).

The game meat industry in South Africa

Game meat refers to the flesh of wild ungulates from Africa that are suitable for human consumption and are utilized as food (Hoffman & Cawthorn, 2012). Examples of typical South African game meat are blesbok (*Damaliscus pygargus phillipsi*), blue wildebeest (*Connochaetes taurinus*), kudu (*Tragelaphus strepsiceros*), gemsbok (*Oryx gazelle*), and springbok (*Antidorcas marsupialis*) (Siegfried & Brown, 1992; Hoffman & Cawthorn, 2012). Hoffman & Bigalke (1999) view game meat as an organic product, because it is free of growth hormones and antibiotics, and originates from wild free-running animals. Also, game meat has a lower fat content and contains more minerals and protein than other mass-produced meat such as beef (Hoffman & Cawthorn, 2012). For all these reasons, game meat may be considered a healthier meat source alternative. It should therefore rightly be considered a luxury product.

There is growing demand for meat products, which has been indicated by a four- to fivefold increase in meat production in the last 50 years, owing to a rapidly increasing human population (Meissner *et al.*, 2013; Cawthorn & Hoffman, 2014; OECD, 2014). Additionally, there is high demand for organic and natural products, indicated by the rise in South Africa game meat exports, which are valued at between R60 million and R200 million (Magwedere *et al.*, 2012; Cloete, 2015; Sanchez, 2015). The National Agricultural Marketing Council (NAMC) (2006) estimates that game farming is increasing by 5% per annum in South Africa (Meissner *et al.*, 2013). As a result, game ranching could result in larger profits for farmers than livestock farming (Bekker *et al.*, 2011). The use of wild animals for meat products began in the 1800s, when eland and buffalo were domesticated in South Africa (Ntiamao-Baidu, 1997). Other sources of income from game ranching include sport and trophy hunting, live animal sales and tourism (Taylor *et al.*, 2015). The South African game meat industry is unique because of species diversity and abundance. It is also unique because utilization of game animals is largely a private industry, with twice the number of privately owned game ranches as public parks (Cloete, 2015).

Game ranching in Africa is practised predominantly in southern Africa, namely in South Africa, Zimbabwe and Namibia (Ntiamao-Baidu, 1997). Commercial wildlife ranches constitute 16.8% of the total agricultural land in South Africa, of which approximately 30% consists of mixed ranches (Dry, 2011; Otieno & Muchapondwa, 2016). Bekker *et al.* (2011) found that 85.7% of game on farms in South Africa were free roaming, and 14.3% were semi-extensive. In periods of drought, 90% of farmers provide supplemented feed to game.

The control of game meat throughout the supply chain is regulated by several national, provincial and local standards and regulations (Bekker *et al.*, 2011). The two national departments involved in the control of game meat are the Department of Health (DoH), which is responsible for the game meat after it leaves the abattoir, and the Department of Agriculture, Forestry and Fisheries (DAFF), which is responsible for the slaughter of animals and the import and export of game meat. Bekker *et al.* (2011) found that most environmental health practitioners that are trained in the meat inspection of domesticated animals are not properly trained in game meat inspection. Additionally, there is lack of disease surveillance and management in the South African game meat industry. Consequently, the recent outbreaks of swine flu and Rift Valley fever in animals from South Africa have led to concern by consumers over meat safety (Bekker *et al.*, 2011). Currently, it is thought that local legislation for game meat sales with regard to quality and production standards is inadequate. This holds true for ABR monitoring, as Magwedere *et al.* (2015) found that ABR tests were not taken routinely at all of the facilities they visited in Namibia during their research.

Integrated livestock-game farming as a potential vector of antibiotic resistance transfer

The transfer of ABR can take place between neighbouring animals in nature by sharing pastures and water sources (Mercat *et al.*, 2016). For example, various studies have indicated that wild animals that live near livestock farms are more likely to carry antibiotic resistant microorganisms than those that are not exposed to food animals, because domestic animals are more frequently exposed to antibiotics. Furthermore, farms where wildlife species live in close proximity to livestock have increased risk of reciprocal disease transmission (Magwedere *et al.*, 2012).

Livestock production utilizes the largest land resources in the agricultural industry, accounting for approximately 70% of agricultural land in South Africa (Meissner *et al.*, 2013). Additionally, livestock farming is one of the fastest growing agricultural industries in developing countries (Thornton, 2010). But livestock production results in water pollution and depletion, and land degradation, and has a negative impact on biodiversity if farming practices are not managed correctly (Thornton, 2010; Meissner *et al.*, 2013).

Many farms in South Africa contain mixed species of livestock and wildlife for diversification and for economic reasons (Furstenburg, 2010). Otieno & Muchapondwa (2016) predicted that the performance of integrated farms would be higher than pure livestock farming. This approach helps to maintain biodiversity and conserve wildlife species and is less vulnerable to climate change (Ntiamoa-Baidu, 1997; Taylor *et al.*, 2015; Otieno & Muchapondwa, 2016). Game farming helps to conserve water, because wild animals can utilize semi-arid and arid environments more effectively than livestock (Ntiamoa-Baidu, 1997). The land is better conserved because game disperse over a larger land area (Ntiamoa-Baidu, 1997). Importantly for the farmer, integrated farming can have economic advantages (Taylor *et al.*, 2015). Farmers have better financial security as they have two income sources and do not have to rely on one income source because pure game farming is seasonal and pure livestock farming is affected by drought, which can occur frequently in South Africa (Taylor *et al.*, 2015).

Emergence of ABR in wildlife species would affect the South African game meat industry critically and potentially human health, while implicating the broader environment such as biodiversity and the further spread of ABR (Mercat *et al.*, 2016). An important factor that could affect ABR levels in wildlife species significantly is the transfer of antibiotic resistant bacteria from nearby livestock species via co-grazing and manure spreading. Other factors include leakage of antibiotic resistant bacteria from sewage, farm effluents and rivers and streams (Anon., 2006).

With regard to the effect of ABR transfer on co-grazing and co-habitation of livestock and wildlife species, a limited number of studies have been conducted, particularly in South Africa. Navarro-Gonzalez *et al.* (2013) studied ABR in *E. coli* isolates at a free-ranging livestock and wild ungulate interface in a national game reserve in Spain. Low ABR levels were detected in both the wild ungulates and in the free-ranging livestock, indicating that the free-ranging livestock were not an important source of ABR for wild ungulate ABR in that study. But perhaps higher resistance levels in the wild ungulates would have been seen if intensively reared livestock were studied instead of free range. The wild ungulates showed resistance to cephalosporin and fluoroquinolones, which are important antibiotics in human medicine, indicating that antibiotic resistant bacteria carried by wild ungulates are a concern to public health and that natural environments are not antibiotic resistant free (Navarro-Gonzalez *et al.*, 2013).

Mercat *et al.* (2016) investigated ABR in *E. coli* isolates at a cattle and wild ungulate interface in and around a national park in Zimbabwe. Higher ABR was shown in the ungulates at the interface than those that had no contact with cattle (Mercat *et al.*, 2016). This suggests that some ABR transfer had occurred across the interface of these animals. The cattle showed higher ABR than the ungulates, possibly owing to the administration of antibiotics to the cattle to treat infections (Mercat *et al.*, 2016). It was hypothesized that the resistant strains had spread across the interface and had emerged in the wild because the same ABR traits that were found in the ungulates were discovered in the cattle (Mercat *et al.*, 2016).

A similar study was conducted by Katakweba *et al.* (2015), who researched ABR in *E. coli* and *Enterococci* at a wild ungulate and cattle interface in Tanzania. It was found that co-grazing between wild ungulates and cattle had not resulted in significant transfer of resistant bacteria or genes. Levels of ABR in the wildlife at the interface were not significantly higher than those of the isolated ungulates. It was noted in this study that these findings should be validated with a larger study and that drought might have caused some of the isolated wild ungulates to venture beyond the park boundaries to find water and come into contact with livestock and human environments and pick up ABR genes from those environments.

ABR transfer and development in natural environments is a complex occurrence with many influencing factors. More information is needed to obtain better understanding of the risks and influencing factors so that preventative measures can be employed to mitigate or minimize the distribution of ABR throughout the environment.

Antibiotic resistance situation in South Africa

Two acts regulate the use of antibiotics for animals in South Africa. The first is the Fertilisers, Farm Feeds, Agricultural Remedies and Stock Remedies Act (Act 36 of 1947), administered by DAFF. The second is the Medicines and Related Substances Control Act (Act 101 of 1965), administered by the DoH (Henton *et al.*, 2011).

Antibiotics that are available to the public and are sold over the counter are registered under Act 36, but records of use are not kept. Antibiotics available only via prescription by a veterinarian are registered under Act 101, which also controls human medicines (Henton *et al.*, 2011). Antibiotics registered in Act 36 are purchased and administered mainly by farmers. This is contrary to the WHO guidelines, which suggest that all antibiotics should be administered and used only by licenced professionals (Henton *et al.*, 2011).

Data on the sales and use of antibiotics in livestock production are scarce in South Africa. Therefore, it is difficult to identify trends and patterns of antibiotic consumption. Eagar *et al.* (2012) showed that several antibiotic classes are commonly used in the agricultural industry as in-feed growth promoters, which constitute about 68% of the total antimicrobial forms sold for food animals, as opposed to water medication, parenterals, topicals, and intramammarys.

The greatest volumes of antibiotics for food animals are used in intensively reared poultry and pigs, followed by feedlot cattle and dairy cows. Extensively farmed sheep, goats and cattle use the least amount of antibiotics of other food animals, as they have lower herd densities, feed mainly on grass, and are considered healthier (Henton *et al.*, 2011).

Environmental and clinical studies indicate that ABR rates in South Africa are high (Moyane *et al.*, 2013). Infections of greatest concern for South African health status are the human immunodeficiency virus and tuberculosis (TB), which dominate the healthcare sector (Eager *et al.*, 2012). A high burden of infection is accompanied by an equally high burden of antimicrobial use and, consequently, ABR, followed by the emergence of MDR bacteria (Mendelson & Matsoso, 2015). Outbreaks of MDR bacteria do exist, causing high morbidity and mortality rates. For example, WHO estimated that 8.5% of TB cases are from MDR-TB. Also, more than half of the cases of hospital-acquired *S. aureus* that were isolated from sick patients in public hospitals in 2010 were MRSA. In addition, up to 75% of *Klebsiella pneumoniae* isolated from hospitalized patients in 2010 and 2012 were ESBL-producing bacteria (Mendelson & Matsoso, 2015).

In developing countries such as South Africa, antibiotic use is poorly controlled, and antibiotics that are used in agriculture such as penicillins are often used for human therapy (Levy, 1998). In animal health, currently there is little published data on resistance rates in food animals. However, SANVAD highlighted high rates of resistance to tetracycline and sulphonamide, two commonly used growth promoters, in *E. coli*, *Salmonella* and *Enterococcus* species between 2002 and 2004 (Mendelson & Matsoso, 2015).

In response to the rise in outbreaks of MDR-bacterial infections in South Africa, various organisations have been established in an attempt to curb the ABR situation. For example, the South African Antibiotic Stewardship Programme (SAASP) consists of experts in various healthcare sectors who aim to promote the prescription of appropriate antibiotics and provide education on the matter (Mendelson & Matsoso, 2015).

South Africa has been part of the Global Antibiotic Resistance Partnership (GARP) since 2010. Its aim is to address and recommend solutions for the ABR situation in South Africa, together with the other three participating countries, namely India, Vietnam, and Kenya (Moyane *et al.*, 2013).

In addition, the DoH has developed an implementation plan for the ABR strategy framework in South Africa from 2014 to 2019. Its three main objectives are i) to better control infections, predominantly through vaccinations, and to prevent infection through for example improved water sanitation, ii) to enhance antimicrobial surveillance and documenting, and iii) to implement antimicrobial stewardship (Mendelson & Matsoso, 2015).

With regard to antimicrobial surveillance in the animal health industry, Eagar *et al.* (2012) compared antimicrobial surveillance systems for veterinary practice from other countries, and concluded that a

combination of the Australian and United Kingdom systems would be the best approach to apply to the animal health industry in South Africa, because the national ABR surveillance programme of antibiotic usage and ABR on food-producing animals in South Africa has not been established. This type of surveillance system would include the volumes of veterinary antimicrobials that are consumed, with a veterinary ABR surveillance and monitoring programme (Eager *et al.*, 2012; Moyane *et al.*, 2013).

The lack of an efficient ABR surveillance system in South Africa makes it difficult to obtain data on the quantities of antimicrobials that are sold by veterinary pharmaceutical companies, indicating that a good surveillance programme needs to be established that would aid in administering and tracking antimicrobials throughout the country. Eager *et al.* (2012) noted that resistant *S. aureus* mastitis is a current problem in the South African farming industry, followed by increased resistant *E. coli* and *Enterococcus* species to tetracyclines, fluoroquinolones, sulphonamides, amoxicillin, and trimethoprim-sulpha combinations. In addition, high resistance in *S. aureus*, *Campylobacter jejuni*, and some *Listeria* and *Salmonella* species has been reported for tetracycline from a poultry abattoir. High resistance was also reported in *S. aureus* isolates for penicillin and amoxicillin in cattle that had mastitis (Henton *et al.*, 2011).

Additionally, it was found that antibiotic usage in the agriculture industry has been increasing. Growth promoters that are currently being used in South Africa are banned in other countries (Moyane *et al.*, 2013). Consequently, South Africa has recently been considered a major contributor to the increase in antibiotic use worldwide (Mendelson & Matsoso, 2015).

Conclusion

The misuse and overuse of antibiotics in agriculture promote the development of antibiotic resistant bacteria, which are most commonly transmitted to humans via the food chain. A possibly overlooked transmission vector of antibiotic resistant bacteria in the food chain is wildlife, a sector that is becoming a public health concern owing to increased involvement between humans and wildlife. There are opportunities for growth in the South African game meat industry, which are likely to be accompanied by an increase in exports as more people realise the health benefits of game meat, as well as the growing consumer trend for organic and natural products. However, there is not much control over the production of game meat in South Africa. Currently, it is thought that local legislation for game meat sales with regard to quality and production standards and ABR monitoring is inadequate. The growth of the game meat industry highlights the importance of developing regulations and surveillance programmes to monitor ABR levels and to research ABR and transfer, as well as the possible transfer vectors among game species. This is critical owing to the possible uptake of antibiotic resistant microorganisms from nearby animals and the environment, as well as the intrinsic resistance of microorganisms harboured by wild species which can enter the food chain.

Acknowledgements

This research was supported by the South African Research Chairs Initiative (SARChI) and was funded by the South African Department of Science and Technology, as administered by the National Research Foundation (NRF) of South Africa and Stellenbosch University. The financial assistance of the NRF towards this research is acknowledged. Opinions expressed and conclusions arrived at are those of the authors, and are not necessarily to be attributed to the NRF.

Authors' Contributions

MvdH formulated and executed this review article as part of her MSc research thesis. PG and LCH were responsible for the supervision, editing and development of the article.

Conflict of Interest Declaration

None of the authors has any conflict of interest.

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