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REVIEW ARTICLE

ANTIBIOTIC RESISTANCE - AN EMERGING HEALTH PROBLEM: CAUSES, WORRIES, CHALLENGES AND SOLUTIONS – A REVIEW

[1]Ruchi Tiwari, [2]Sandip Chakraborty, [3,]*Kuldeep Dhama, [4]Rajagunalan, S. and [5]Shoor Vir Singh

[1]Department of Veterinary Microbiology and Immunology, Uttar Pradesh Pandit Deen Dayal Upadhayay Pashu Chikitsa Vigyan Vishwa Vidyalaya Evam Go-Anusandhan Sansthan (DUVASU), Mathura (U.P.) – 281001
[2]Animal Resources Development Department, Pt. Nehru Complex, Agartala, Pin – 799006
[3]Division of Pathology, [4]Division of Veterinary Public Health, Indian Veterinary Research Institute, Izatnagar, Bareilly (U.P.) – 243122
[5]Microbiology Laboratory, Animal Health Division, Central Institute for Research on Goats (CIRG), Makhdoom, PO-Farah, Dist. Mathura, Pin- 281122

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ABSTRACT

Untreatable bacterial infections become treatable due to the discovery of antibiotics in the previous century but their inappropriate and irrational uses ultimately led to emergence of resistant microbial population. Genes responsible for conferring resistance are transferred horizontally via conjugation; transduction or transformation. Tetracyclines and beta lactams represent 50% each of the total antibiotics used in feeds and global antibiotic consumption respectively. Due to development of antibiotic resistance there may be failure of the resistant bacteria to respond to the prescribed treatment; risk of infectious diseases becoming uncontrollable; financial burden; advanced therapeutic approaches may get jeopardized and ultimately resistant organisms may spread to distant countries and continents. Both intrinsic and acquired resistance mechanisms are involved in bacterial antibiotic resistance. Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Vancomycin-Resistant Enterococci (VRE) are among the most striking antibiotic resistant microbes in the recent years. Factors driving antibiotic resistance include: inadequate national commitment; improper surveillance; irrational use of drugs; poor disease prevention and insufficient diagnostics and therapeutics etc. Limiting infectious diseases; judicious uses of antibiotics; precise selection and completing the full course of antibiotics; and regular surveillance, monitoring and continuous vigilance are the steps to limit antibiotic resistance. The most common antibiotic-resistant organisms sourced from animals are some strains of *E. coli*; *Salmonella* etc., which can also infect humans. Disc diffusion method and Minimum inhibitory concentration (MIC) methods; gas chromatography (GC); High-performance liquid chromatography (HPLC) with UV mass spectrometry (MS) and nano quantity analyte detectors; microfluidic methods and electrochemical methods; European Union four-plate test (EU4pt); Frontier Post Test (FPT) are used to detect antibiotic residues. Use of penicillin or sulphonamides has raised public health and industrial issues. Prevention and control measures require involvement of various governmental agencies for accurate testing and screening; surveillance and monitoring. Along with this alternative therapeutic approaches viz. bacteriophages; virophage and mycophage; avian egg yolk antibody; cytokines and herbal; panchgavya and vaccine therapy; and diagnostics are the need of hours. The present review discusses all these aspects of antibiotic resistance and their solutions ultimately for social benefit with particular reference to emerging antibiotic resistance in animals and humans, its challenges, detection, antibiotic residues, prevention and control measures along with current and future scenario at International level, which would be helpful for formulating strategies for safeguarding health of animals as well as humans.

INTRODUCTION

The discovery of antibiotics being the wonderful amiable discovery of previous century had turned the untreatable era of bacterial infections into treatable conditions (Waksman, 1973). With the invention of antibiotic drug Penicillin in 1928, Sir Alexander Flemming draw the attention of scientist to look for the microbial products to counteract the pathogenic effects produced by the microorganism until 1940 when reports of penicillinase enzyme appeared. In modern medicine antibiotics were well thought-out as pillars of chemotherapy, however efficacy of these medicinal molecules against many pathogens is vulnerable and threatened owe to developing antibiotic resistance which affects all types/classes of natural, semi-synthetic, and/or completely synthetic antibiotics (Walsh, 2003). Before 1940, antibiotics were considered as the magical drugs for the treatment of various bacterial ailments. But now, increasingly, bacteria are able to resist the curative effects of these medications. These drugs are also being used as growth promoters because as these may also influence the growth rate because of thinning of mucous membrane of the gut, facilitating better absorption and assimilation and producing favorable conditions to beneficial microbes in the gut of animal by destroying harmful bacteria (Brotze-Oesterhelt and Brunner, 2008). The very frequent use of antibiotics in animals especially in cases of mastitis, febrile and inflammatory conditions, wounds and bacterial, and viral diseases to check secondary infections have widespread residual effects on products derived from animal origin viz., milk, eggs or meat and their by products. Antimicrobials are also used either directly or indirectly during the production processing, storage and transportation of these food products. Humans are the ultimate consumers of these products with antibiotic residues and thus the presence of these

Corresponding author: Kuldeep Dhama, Division of Pathology, Indian Veterinary Research Institute, Izatnagar, Bareilly (U.P.) - 243122

residues in routine diet may adversely affect the health. Antibiotics when used inappropriately and irrationally provide favorable conditions for development of resistant group of microbes that can spread very easily. The extraordinary genetic capacities of microbes have utilized the continuous survival pressure as a warning to their life. By expressing various resistance genes and all possible means of horizontal gene transmission in equilibrium with environmental microbiomes to support the rise of antibiotic resistance microorganisms are counteracting antimicrobial approaches, indeed (Sorensen *et al*., 2005; Walsh, 2006; Davies and Davies, 2010). Countless documents are available describing the genetics, origins, evolution, and mechanisms of antibiotic resistance. In the present review we will have a brief look on the underlying causes, genetic mechanisms including chromosomal or mobile genetic elements responsible for emerging resistance with relevant examples and steps to counteract the developing antibiotic resistance. Termination of the course of antibiotic without following prescribed format is a major cause of development of resistance worldwide. The socioeconomic factors at both individual as well as national level facilitate emergence and spread of antimicrobial resistance. Urban poor people exposed to inclement climate or due to their poor quality of living standard are more prone to develop resistance. The beta-lactam group of antibiotics is responsible for approximately 95% of all milk antibiotic contamination. In the developing countries nowadays multiple antibiotic resistance have been observed among important enteric pathogens viz., *Escerichia coli*; *Salmonella* and *Shigella*; *Klebsiella*; *Vibrio cholarae* which have increased the global worry (Calva *et al*., 1996; Murray and Lopez, 1997; Borroto *et al*., 2000; Aiello and Larson, 2003; Butaye *et al*., 2003; Byarugaba, 2004 and 2005; Soulsby, 2005; Aminov and Mackie, 2007; Aminov, 2009).

In these days, however, due to the advancement in the field of molecular biology and biotechnology to combat the antibiotic resistance arising due to the ever increasing threat of zoonotic diseases including food-borne zoonosis several new therapies have come into existence (Deb *et al*., 2013a; Dhama *et al*., 2013a,b,c; Tiwari *et al*., 2012; Mahima *et al.*, 2012).

- The term "antibiotic resistance" is defined as "a property of bacteria that confers the capacity to inactivate or exclude antibiotics, or a mechanism that blocks the inhibitory or killing effects of antibiotics to which it was previously sensitive, leading to survival despite exposure to antimicrobials" (Whyte *et al*., 2002).
- This is a consequence of the use, particularly misuse and indiscriminate use (Low or high doses, inappropriate use, casual use without prescription), of antimicrobial medicines and develop when a microorganism mutates or acquires a resistance (R) gene (Zhang *et al*., 2006).
- The antibiotic resistance may disseminate in the nature either by clonal spread of resistant clonal lineages or by horizontal gene transfer methods (Witte, 2004).
- Journey of antibiotic has seen various phases comprised of dark ages, preantibiotic era; primordial phase including advent of chemotherapy via the sulfonamides; golden years, the halcyon years and lean years chronologically.
- A wide array of biochemical and physiological mechanisms are responsible for development of resistance (Wright, 2007).
- Genes responsible for conferring resistance can be transferred horizontally between bacterial cells by conjugation, by involvement of bacteriophage through transduction or from environmental factors by transformation (Anderson, 1968; Hotchkiss and Gabor, 1970; Cirz *et al*., 2005; Mathew *et al*., 2007; Canton, 2009).
- Bacteria may acquire genes which encode for enzymes capable of destroying antibiotics hence nullifying the action of drug by being resistant (Abraham and Chain, 1940; Martinez *et al*., 2007).
- When a bacterium harbors many a resistance genes together, then it is called multidrug resistant (MDR), extremely drug-resistant (XDR) strains and/or totally drug resistant (TDR) strains as documented in cases of tuberculosis or informally, a superbug or super bacterium. Certain MDR pathogens may show resistance to second and even third-line antibiotics. They acquire them sequentially and such phenomenon is illustrated by *Staphylococcus aureus* when they pose a threat of nosocomial infection. *Pseudomonas aeruginosa* additionally is responsible for a greater degree of intrinsic resistance (Thomas *et al*., 1998; Girou *et al*., 2006; Wright, 2010).

- The resistant bacteria in animals can be transmitted to humans via three pathways:
  - Consumption of improper/undercooked contaminated meat, milk or eggs.
  - Close or direct contact with animals.
  - Through the environment (Hawkey and Jones, 2009).

- Unchecked/Uncontrolled and widespread application of antibiotics in both human and veterinary medicines is equally responsible for increase in prevalence of antibiotic-resistant bacterial infections, and emergence of new antimicrobial resistant pathogenic strains of various infectious agents (Hidron *et al*., 2008).
- A major source of antibiotic overuse is the extensive use of these drugs in livestock sector for promoting the growth and production of animals including poultry for getting more profitability to compensate unsanitary conditions present in livestock industry and agriculture (Toole *et al*., 1997; Richet *et al*., 2001).
- *Staphylococcus aureus* is amongst important and major resistant bacterial pathogens to the general population. Methicillin-resistant *Staphylococcus aureus* (MRSA) is nowadays frequent in hospital settings. MRSA has become a major community-acquired (CA) pathogen CA-MRSA, with enhanced virulence and transmission characteristics. In United States, resistance to penicillin; Methicillin; tetracycline and erythromycin groups of drugs have become more common. The emergence of glycopeptide intermediate *Staphylococcus aureus* (GISA) or vancomycin-intermediate *Staphylococcus aureus* (VISA) have made the situation more critical (Skurray and Firth, 1997; Chan *et al*., 2011; Xie *et al*., 2011).
- Tetracyclines being used since many a years in livestock and poultry sector represent almost 50% of the total antibiotics used in feeds.
- B-lactams group of antibiotic used for treating the infectious diseases in food animals, represents 50% of the global antibiotic consumption (Hirakata *et al*., 2005; Okeke *et al*., 2005).

Antibiotic resistance – An issue of global worry

- Antimicrobial resistance is an alarming public health threat worldwide which demands scrupulous investigations (Levy and Marshall, 2004; Zhang *et al*., 2006).
- Infections caused by resistant bacteria often fail to respond to the standard/prescribed treatment, which results into prolonged illness and greater mortality risk or death. Many pathogens have developed resistance over the years in different regions of the world including developing nations (Byarugaba, 2005; Islam, 2007).
- Antibiotic resistance reduces the effectiveness of treatment because animals/patients remain chronically ill, thus potentially spreading resistant microorganisms to others (Mitema *et al.*, 2001 and 2004).
- Many infectious diseases from becoming uncontrollable could overturn the progress made towards reaching the targets of the health-related Goals of United Nations Millennium Development (MDGs) set for 2015 (Pirmohamed *et al*., 2007).
- This gradual increase in antibiotic resistance may add to financial burden to the general public because of the inefficacy of first line medicines (Larsson *et al*., 2000).
- In absence of effective antimicrobials against infections, the success of treatments such as organ transplantation, cancer

chemotherapy and major surgery would be jeopardized (Radyowijati and Haak, 2002).

- With the continued emergence of multidrug resistant strains, the future may again be in hopeless conditions of pre-antibiotic era of untreatable infections (Boucher, *et al*., 2009; Rossolini and Thaller, 2010).
- In present scenario of globalization, resistant microorganisms may spread rapidly to distant countries and continents. Ever changing characteristics of microbes; selective pressures in the use of antibiotics along with social and technological changes all have acted as contributory factors (Aarestrup *et al*., 2001; Nugent *et al*., 2008).

Classical examples of antibacterial resistance

The development and distribution of antibiotic-resistant microbes in the biosphere is one of the good examples of the Darwinian theory of selection and survival of fittest. Reason behind this is anthropogenic due to misuse or overuse of such drugs superimposing selection pressure on the nature. The indiscriminate use of antimycotic agents and antibiotics to promote growth of farm animals and to prevent their infection rather than to cure infections most of times lead to drug resistance, emergence of antibiotic-resistant pathogenic microbes and development of "superbugs" and super-resistant strains, microbes harboring enhanced morbidity and mortality potentials due to multiple mutations endowing high levels of resistance against antibiotic drugs and thereby reduces the efficacy of the antimicrobials in the battle with various infections. (Meynell and Datta, 1967; Bryskier, 2005; Liu and Pop, 2009). Literature reveals more than 20,000 potential resistance genes (r genes) are existing in nature which are of nearly 400 different types among various species, fortunately they all have not been expressed yet (Depardieu *et al.*, 2007; Dantas *et al*., 2008). In real sense, antibiotic resistance is acting as a virulence factor which shore up the activity of pathogens (Couce and Blazquez, 2009).

Some of the common examples of MDR organisms are Methicillin-Resistant *Staphylococcus aureus* (MRSA), Vancomycin-Resistant Enterococci (VRE) among Gram positive bacteria, *Klebsiella pneumoniae* carbapenemase (KPC) producing Gram-negatives, Extended-spectrum β-lactamase (ESBLs) producing Gram-negative bacteria, Multidrug resistant *S. enteritica* serovar Typhimurium DT 104 (ACSSuT-phenotype), Imipenem-resistant or MDR Organisms *Acinetobacter baumannii, Acinetobacter baylyi, Pseudomonas aeruginosa, Bacteroides spp*., Clindamycin-resistant *Clostridium difficile*, Streptomycin-resistant *Thermus thermophilus, E. coli* resistant to multiple fluoroquinolone, resistance of *Mycobacterium tuberculosis* to isoniazid, rifampin, and multiple antifungal resistant *Scedosporium prolificans* infections (Gregory *et al*., 2001; Shoemaker *et al*., 2001; Trakulsomboon *et al*., 2001; Enright *et al.*, 2002; Bozdogan *et al*., 2003; Inoue *et al.*, 2004; Nandi *et al.*, 2004; Gomez and Neyfakh, 2006; World Health Organization, 2006; Perez *et al*., 2007; Reinert *et al*., 2007; Boucher and Corey, 2008; Maragakis and Perl, 2008; DeLeo and Chambers, 2009; Li *et al*., 2013). *E. coli* has developed low-level of resistance against fluoroquinolones and ciprofloxacin due to activity of qnrA1 and qnrS1 genes and because of mutation in gyrA gene respectively (Andersson, 2006; Allou *et al*., 2009). Similarly qnrB is quinolone-resistance determinant (Da Re *et al*., 2009). Rifamycin, broad-spectrum antibiotics target bacterial transcription by inhibition of RNA polymerase but mutational alteration of the drug target (ribosome) by ADP-ribosylation is the predominant mechanism initiating resistance and as an additive for the formation of rifampin resistome (Llano-Sotelo *et al*., 2002; Recht and Puglisi, 2001; Baysarowich *et al*., 2008). Actinomyces group of bacteria produces vast range of bioactive secondary metabolites/antibiotics which are strain specific rather than species–specific. To be specific they possess specific genotypes encoding for strain specific antibiotics out of which few have Aminoglycoside antibiotic (AG) inactivation enzymes (β-lactamases) while few strains of actinomycetes are AG producers showing multiple patterns of resistance (Benveniste and Davies, 1973; Ogawara *et al*., 1999). Sulfonamide and trimethoprim resistance in *Streptococcus agalactiae* has been observed due to presence of amplification of a naturally occurring gene (Brochet *et al*., 2008). Multilocus sequence typing has confirmed the antimicrobial resistance in *Streptococcus pneumoniae* isolates (Doern *et al*., 2001). Whole-genome sequencing is another approach for tracking the in vivo evolution of multidrug resistance in various bacteria, *Staphylococcus aureus* being a significant example (Mwangi *et al*., 2007).

Major mechanism of antifungal drug resistance is any change in the cell wall or plasma membrane, which leads to impaired drug uptake by the fungal cells and over expression of efflux pumps of the ABC (ATP binding cassette) transporter and MFS (major facilitator superfamily), drug transporters which belong to two different superfamilies (Mendez and Salas, 2001; Poole, 2005). These are multifunctional proteins, which mediate important physiological functions and are the most prominent contributors to phenomenon of Multiple Drug Resistance (MDR) in microorganisms. Hence, an alarming increase in bacterial resistance and increased proportion of MDR strains of bacteria has been documented. The macrolides and many related antibiotics act by binding with 50S ribosome subunit. Resistance can be acquired by modification of the RNA or protein components of the ribosome. A specific rRNA modification mechanism producing resistance to all antibiotics is spreading rapidly specifically against quinolones (Zengel *et al*., 1977; Yassin and Mankin, 2007; Roberts, 2008).

Mechanism of development of antibiotic resistance

Now sufficient documentary evidences are available specifying that antibiotic resistance is an ancient phenomenon and environmental microorganisms, including antibiotic producers, are source of such resistant determinants found in pathogenic microorganisms (Silver and Falkow, 1970; Kopecko and Punch, 1971; Bartoloni *et al*., 2009). Resistance to antibiotics may be either intrinsic (or natural) and acquired. Microbes lacking the target site are not affected by drugs that form the basis of the concept of intrinsic resistance (Fajardo *et al*., 2008). The differences in the chemical nature of the drugs and the membrane structure of the microbes are responsible for low permeability of drug under natural circumstances due to presence of inactivating microbial enzymes or alternative enzyme for the enzyme that may get inhibited by the antibiotic like the beta lactamases responsible for resistance against Beta lactam antibiotics and third generation cephalosporins (von Baum and Marre, 2005; Rossolini and Thaller, 2010). It may also be due to mutation in the target; post-transcriptional as well as post-translational modification of the drug target; reduced uptake and active efflux of the drug; chromosomally encoded multidrug resistance; R–factor; typical expression or suppression of genes *in vivo* that may be entirely different from the condition *in vitro* (Watanabe, 1971; Hall, 1997; Fluit *et al*., 2001; McKeegan *et al*., 2002; Poole, 2005; Piddock, 2006b; Torok *et al*., 2012). Gene deletion is also considered as a mechanism of development of antibiotic resistance as demonstrated in the case of *Burkholderia pseudomallei*, the bacterium has developed resistance against ceftazidime by deletion of Penicillin binding protein gene encoding (PBP 3) but this mechanism is extremely uncommon (Torok *et al*., 2012). The role of human intestinal microbial flora in the transfer of antibiotic resistance genes to pathogenic bacteria is also screened (Salyers *et al*., 2004; Sommer *et al.*, 2009). The hypothesis that the organism could acquire gene of resistance from soil/nature or aquatic environments is also investigated recently, as most of the antibiotics were obtained from soil borne organism and the soil is also suspected to be the source of resistance genes (Riesenfeld *et al*., 2004; D'Costa *et al*., 2006; D'Costa *et al*., 2007; Baquero, *et al*., 2008; Martinez, 2009; Szczepanowski *et al*., 2009; Allen *et al*., 2010; Walsh, 2013). The stress to which bacteria are exposed both within the host and also in the environment, results in development of adoptive mechanism like development of antibiotic resistance and formation of biofilms for their survival (Poole, 2012). Recently, development of rifampicin resistance among *E. coli* growing in an

antibiotic free environment at higher temperatures resulting from mutations of the *rpoB* gene was reported (Pallecchi *et al*., 2007; Pallecchi *et al*., 2008; Rodríguez-Verdugo *et al.*, 2013).

Non-chromosomal antibiotic resistance

Mobile genetic elements such as transposons, prophages, integrons, resistance islands (R factor), self replicating plasmids all carry resistance genes into sensitive microorganisms (Normark and Normark, 2002; Guerin *et al*., 2010). Plasmid-mediated quinolone resistance is emerging globally as a multifaceted threat (Rownd, 1969; Robicsek *et al*., 2006; Strahilevitz *et al*., 2009). Spread of plasmid is very rapid in between heterogeneous bacterial communities (Dionisio *et al*., 2002). Integrons are genetic elements associated with the resistance (r) genes related with transferable plasmid-mediated resistance (Gillings *et al*., 2008). OXA beta-lactamase genes responsible for resistance against Beta lactam antibiotics have been observed to be present on plasmids for several millions years (Davies, 1995; Barlow and Hall, 2002). Microarray technology involving gene signatures of microorganisms should be explored to elucidate and understand mechanisms of antibiotic action and developing resistance in more detail (Brazas and Hancock, 2005). Methylenomycin antibiotic is produced by two strains of Streptomyces where the genes for production and resistance both are located on the transferrable plasmids i.e. pSV1 and SCP1, mmr being the methylenomycin resistance gene (Chater and Bruton, 1985). Development of multiple resistance in microorganisms indicates molecular basis of new defense strategy of tiny super bugs (Alekshun and Levy, 2007). R-plasmid pTP10 of the *Corynebacterium xerosis* carries resistance genes for erythromycin chloramphenicol, kanamycin, and tetracycline antibiotics (Tauch *et al*., 1995).Genetic transformation of *Escherichia coli* and *Proteus mirabilis* explains the involvement of molecular nature of circular R-factors/plasmid DNA (Cohen and Miller, 1969; Cohen and Miller, 1970; Davies *et al*., 1971; Cohen *et al*., 1972). Conjugative plasmids are part of enterobacteria such as Plasmid F of *Escherichia coli* K-12, R-factor NR1 in *Proteus mirabilis* and other conjugative plasmids encoding antibiotic resistances in *Salmonella, Shigella, Klebsiella, Proteus*, and *Escherichia* (Watanabe *et al*., 1964; Rownd and Mickel, 1971; Silver and Cohen, 1972). They are considered as 'pre-antibiotic' plasmids means they were existing before the development of modern resistance encoded by modern R plasmids and it has been confirmed by incompatibility tests or Inc groups (Datta and Hughes, 1983; Nordmann and Poirel, 2005).

Microbial genetics explains existence of chromosomal and non-chromosomal r genes

A large number of bacteria and fungi acts as source of wonderful drugs. Antibiotics were produced as a means of self-defense by various bacteria and fungi as microbes are exposed to various organic, inorganic and industrial influents in the nature. To specify, antibiotic producing microorganisms harbor r-genes and R-factors in plasmids to confer their own protection from inhibitory or lethal actions of these secondary metabolites naturally. Currently due to excessive survival pressure microorganisms are either expressing these r-genes and R-factors or following various alternate approaches by episome mediated gene transfer or modifications in targets to overcome bactericidal activity of antibiotics for their prolonged survival in the nature (White *et al.*, 2005; Hopwood, 2007).

Reasons / Factors That Drive Antibiotic Resistance

- Inadequate national commitment to a comprehensive and coordinated response, ill-defined accountability and insufficient engagement of communities.
- Improper surveillance, tracking and monitoring systems.
- Lack of basic knowledge on the complexity of the processes that contribute to emergence and dissemination of resistance is one of the primary reasons of no significant accomplishment.
- Though steps have been taken at international, national, and local levels against this serious problem by proposing resolutions and a variety of recommendations have also been propounded but still the development of antibiotic resistance is relentless.
- Inappropriate and irrational use/dosing of drugs/medicines by humans and given even to their companion animals.
- Paucity of knowledge- Informations regarding natural biological functions of all the antibiotics is not completely known and understood.
- Poor disease prevention and control practices.
- Insufficient diagnostics, medicines, nosocomial transmission and vaccines (Finland, 1979).
- Consistent lack of skilled staff, deficit in training of R & D staffs persons and limited resources in order to enforce infection control practices to be followed.
- Inadequacy or less availability of proper guidelines for rational usage of antibiotics.
- Increased international trade and travel act as force for inter-continental spread.
- Reduction in the speed of development of new antimicrobials as laboratory and clinical trials take much time than the emergence of resistant genes (Baltz, 2006; Douthwaite, 2010; Rossolini and Thaller, 2010).

Steps to limit antibiotic resistance

- Limiting infectious diseases forms the fundamental step in reducing antimicrobial resistance. It is thus needed to give special attention to health transition from acute diseases in neonates towards chronic diseases in adults in order to limit the risk of indiscriminate spread of disease in various age groups.
- Importance to build and sustain a greater effort to reduce antibiotic resistance is provided by international commitment towards specific diseases including tuberculosis for which resistance is a major concern (Shah *et al*., 2007; Thiams *et al*., 2007; Velayati *et al*., 2009).
- Use antibiotics only in case of bacterial infections. In this regard, the introduction of fluoroquinolone group of antibiotics in the south-eastern Asian countries requires a special mention as it has illustrated a negative impact due to overuse. This proves that judicious use of antibiotics is the need of hour (Linton, 1977).
- Antibiotic therapy should be prescribed only after performing the antimicrobial sensitivity testing in the laboratories.
- Selection of such antibiotic should be promoted, which targets the infection causing microbe instead of broad-spectrum antibiotics. This will cause reduction in the development of early signs of antibiotic resistance provided there is feasibility of feedback intervention.
- Completion of full course of antibiotics should be followed. Any negligence in this regard ultimately encourages the pathogen to persist in the host.
- Virulence inhibitors should be used instead of antibiotics as this will check the occurrence and expression of disease.
- Stimulation of immune system of host, can also involve promoting gut microbiomes and commensals to enhance competitive colonization such as use of prebiotics and probiotics (Marshall *et al*., 2009; Dhama *et al*., 2011a).
- The burden imposed upon human health by antibiotic resistance especially in rural setting is huge but cannot be quantified with precision. For this reason regular surveillance, monitoring and continuous vigilance are of utmost importance.
- Strict hygienic practices and monitoring of antibiotic use in hospital settings to prevent spread of nosocomial spread of antibiotic resistance (Bergstrom *et al*., 2004).

(Duse, 1998; Newton *et al*., 2001; World Health Organization, 2001; Sirinavin and Dowell, 2002; von Baum and Marre, 2005; Falagas and Karveli, 2006; Zhang *et al*., 2006; Chetley *et al*., 2007; Iseman, 2007).

The antibiotic resistance in animals

Sometimes the bacterium causing disease to both humans and domestic animals may be common. The animals act as reservoir for these resistant strains because of indiscriminate use of antimicrobials (Wegener *et al.*, 1999). It is not surprising that antibiotics are widely used in agricultural and animal husbandry settings to treat the infections and to promote the growth and production of animals (Payne *et al.*, 2007). More than half of the total amount of antimicrobials consumed worldwide is reported to be as growth promoter (Wegener *et al*., 1999). The most common antibiotic-resistant organisms sourced from animals are some strains of *Salmonella, Campylobacter, Enterococci*, and *E. coli*, which could also infect humans as well. Although it is difficult to establish an obvious link, when animal pathogens/bacteria are exposed to an antibiotic used in animals which is related to an antibiotic used in humans, they may develop common resistances; the antibiotic resistant organisms in animals or their antibiotic resistant genes could spread to humans. As per World Health Organization (WHO), excessive and unnecessary use of antibiotics, particularly as growth promoters in livestock animals and poultry destined for human consumption, may lead to a growing risk to human health. In 1998, the European Union followed WHO recommendations and banned the use of antimicrobials in animals prescribed for the treatment of human infections as well as all antibiotic use for growth promotion in animals. An increase in international trade of animals and animal products is also a concern in the spread of antibiotic resistant clonal lineages. Use of fluoroquinolone drugs in veterinary medicine was reported to be associated with the development of resitance among S. enteritica DT 104 (Witte, 2004; Kahn and Line, 2005; Musgrove *et al*., 2006; Kikuvi *et al*., 2007; Luangtongkum *et al*., 2009; WHO, 2013).

Many countries have banned some specific drugs/antibiotics. DDT, diclofenac, paracitamol, aspirin, analgin, furazolidone, piperazine, nitrofurazone, penicillin as skin or eye ointment, tetracycline as liquid oral preparation of drug and many other drug combinations have been banned due to their side effects, residual toxicity and related food safety concerns but still they are sold in the markets in unauthorized manner (Chopra and Roberts, 2001). In USA, diclofenac has been completely banned after the detection of higher/toxic level of this drug in the viscera as well as the muscles of vultures which died owing to residual toxicity (Mbori-Ngacha, 1997; IMPACT, 2006; Newton *et al*., 2006; Hindler and Stelling, 2007).

Antibiotic resistance detection methods

Rising frequency of fungal infection as well as increased reports of resistance to antibacterial and antifungal agents indicates the importance of *in vitro* antibiotic and antifungal susceptibility testing. It reflects the necessity to assess drug sensitivity patterns before recommendation of any therapeutic agent. Different methods are available to assess the sensitivity of microbial agent against different concentrations of antibiotic and antifungal agents. For this Disc diffusion method and of Minimum inhibitory concentration (MIC) methods are used by observing the zone of inhibition and reduction of turbidity of broth culture, respectively. In disc diffusion methods, small discs containing antibiotics are placed over a plate upon which bacteria are growing. If the bacteria are sensitive to the antibiotic, a clear ring, or zone of inhibition, develops around the antibiotic disc. Sensitive drug produces large clear zone over the bacterial lawn as per the concentration of drug incorporated in the antibiotic/ antifungal discs, referred as zone of inhibition. Measurement of MIC of any drug is more sensitive technique comparatively, is used in R&D labs of different pharmaceuticals companies to set an appropriate dose/ concentration of drug after the assessment of sensitivity testing and before launching any medicine in the market. According to prescribed dosage medicines should be used to avoid the development of antibiotic resistance. Antibiotic susceptibility tests are used to determine the inhibitory activity of any antibacterial agent against bacteria, thereby suggesting for appropriate therapy. With the current increase in incidence of antibiotic resistant nosocomially acquired infection, it is also assuming greater clinical significance. Additionally, the sensitivity pattern of an organism may be important epidemiologically when used to identify certain strains within a given species (Oka, 1995; Joint FAO/ WHO Food Standards Programme, 2001; Danko *et al*., 2005).

Detection Methods for Antibiotic Residues

A number of methods have been defined for detection of antibiotic residues these include microbiological approaches, immunochemical techniques, gas chromatography (GC) methods, high-performance liquid chromatography (HPLC) with UV, mass spectrometry (MS) and nano quantity analyte detectors, microfluidic methods and electrochemical methods. The microbiological methods are preferred because of their convenience, low cost and broad-spectrum characteristics. Sarcina lutea kidney test is one of the first officially recognized microbiological method followed by Bacillus subtilis BGA test. The European Union four-plate test (EU4pt) comprising of three plates of agar medium inoculated with *Bacillus subtilis* at varying pH has found its application in detecting sulphonamide residues in meat. Recently Premi®Test has been certified by French Association for Normalization (AFNOR) validating the analytical effectiveness for a particular field of application commercially. To indicate whether antibiotic residues are present or not screening tests are valuable and are rapid and easy to use and at the same time reliable. They may be broad (detects beta-lactams and cephalosporins; aminoglycosides and tetracyclines; sulphonamides as well as macrolides) or narrow spectrum (covers only beta-lactams). Instead of the presence of commercial screening test methods non-commercial antibiotic residue screening test like *AS 1766.3.11* method is gaining much attention these days. Mass spectrometry (MS), a technique of chromatographic detection is indispensable for contaminant confirmation. At present, more than 80% of the analytical techniques for the determination of veterinary drugs are Liquid chromatography–mass spectrometry (LC-MS, or alternatively HPLC-MS) based, especially when detection is performed by multi-stage MS. Single-stage MS is still used for screening purposes and for quantification of maximum residue limits (MRLs) of substances; in fact, LC tandem MS is recommended for the detection of unauthorized and banned substances, whose detection capability (CCb) should be as low as reasonably achievable. Enzyme linked immunosorbent assay (ELISA) and fluorescence immunoassays (FIA) are excellent survey tools because of their high-throughput, user friendliness, and field portability. These assays are optimized to provide the greatest sensitivity at or near the regulatory safe/tolerance levels for the appropriate antibiotics. Frontier Post Test (FPT) can be performed to detect the day-today variation in the concentration of antibiotic residues in milk by using *Bacillus subtilis* starter culture (Andrews *et al*., 2000; CH 6.2. 2004; CH 12.16. 2004; Stead *et al*., 2004; Koréneková *et al*., 2007; Gaudin *et al.*, 2008 ; Pikkemaat *et al*., 2008; Pikkemaat, 2009 ; Plozza *et al*., 2011; www.dairysafevic. gov.au).

Residue Limits

Internationally recognized organizations such as World Health Organization (WHO), Food and Agriculture Organization (FAO), Veterinary Medicines Directorate (VMD) of the European Union as well as Food and Drug Administration (FDA) of the US, have set tolerance or maximum residue limits (MRLs), acceptable daily intakes for humans and withholding times for pharmacologically active substances including antimicrobial agents prior to marketing. Certain individuals develop tolerance to drugs and antibiotic-tolerant status of any individual may depend on physiological adaptations without direct connections to antibiotic target activity or to medicinal/drug uptake, efflux, or inactivation of drug inside the body of patient (Piddock, 2006a). FDA prohibits the extra label use of chloramphenicol, furazolidone, nitrofurazone, sulphonamide drugs, and flouroquinolones in lactating animals. The maximum residual

limit of antibiotic varies from country to country and with the antibiotics (Chee-Sanford *et al*., 2009). For example the MRL of different groups of antibiotics in milk are as betalactam antibiotics (4-100), aminoglycosides (100-1500) and macrolides (50-200) (Althaus *et al*., 2001; Ghidini *et al*., 2002; Pikkermaat, 2009; Sierra *et al*., 2009; Turnipseed *et al*., 2009).

Public health and Industrial aspects

The non-restrictive use of antibiotics in animal rearing may lead to problems due to presence of harmful residues in foods including meat, milk, eggs and raw materials of animal origin. The antibiotic resistant bacteria found among farm animals can enter the food chain and may affect humans. The presence of antibiotic residues in milk gives rise to high penalties. Human health problems importantly may result from intake of sub-chronic exposure like allergic reactions in sensitive persons, toxicity, carcinogenic effects, even though the legitimacy of some of these reactions is sometimes debated or under question (Doyle, 2006). Penicillins especially, as well as other ß-lactam antibiotics such as cephalosporins and carbapenems could cause allergies if high levels of residues persist in milk is consumed by penicillin-allergic persons. Tetracyclines residues have side effects of teeth staining of young children. Development and spread of antibiotic resistance represents a serious threat with potential public health implications and negative impacts. This is more likely in instances where the drug is fed continuously over a long period of time, when used at an extra label dose, beyond recommendations/prescriptions. Veterinary drug residues in food and food products of animal's sources are considered notorious public health hazards. Penicillin in chicken was reported to have caused severe anaphylactic reaction in a consumer. Skin allergies in persons hypersensitive to sulfonamides could occur following consumption of foods like eggs containing high concentrations of sulfonamide residues. Wrong doses and administration frequency even though generate resistant population of bacteria but the presence of residues in food products have got little effect on the selection of resistant population of bacteria in human. One interesting aspect is that essential role is played by lactic acid bacteria for acidification of milk as they allow protein precipitation along with flavour development and inhibition of undesirable flora. The antibiotic residues when present inhibit partially or totally the growth of such acidifying bacteria thereby causing serious problems including total fermentation failure (Sasanya *et al.*, 2005; Nisha, 2008; Abasi *et al*., 2009; Liliana Serna *et al*., 2011; Movassagh, 2011; Wachira *et al*., 2011).

Prevention and control strategies for antibiotic resistance

- Introducing the awareness programmes to make individuals and organizations aware of the problem through education by veterinary personnels, organizations, medical professionals, NGOs and governmental agencies.
- Record all treatment dates, medicines/drugs used, batch numbers together with the dosage administered, and the withdrawal periods for milk, meat and egg collection.
- Rapid testing and screening methodologies for the analysis of antibiotic residues and instant grading and prohibition of food containing antibiotics more than MRL.
- Adequate processing of milk will help in inactivation of antibiotics.
- Use of UV irradiation also helps in antibiotic inactivation.
- All milk from treated animals must be discarded.
- Irrational use of antibiotics in field veterinary practices should always be discouraged.
- Development of simple and economical field tests to identify drug residue in edible animal products.
- Fruitful life of antimicrobial drugs could be increased by adaptation of appropriate usage policies that discourage overuse and misuse, and encourage judicious usage practices.
- Improve diagnostic testing practices
- Transmission of infectious pathogens should be checked and intensive strategies for prevention and control of infection should be practiced.
- Regular vaccination programmes should be followed to avoid establishment and development of disease.
- There should be holistic approach and sound strategy to prevent and control emerging antibiotic resistance problems in human and veterinary medicine as well as agriculture.
- Development, improvement and execution of ideology for appropriate and judicious antimicrobial drug use in the production of food animals and plants for food-safety concerns and ultimate health benefits for both medico and veterinary perspectives i.e. safeguarding health issues of animals and humans both.
- Improved animal husbandry and food production practices to reduce the spread of infection and infectious pathogens.
- Regulatory bodies and frameworks need to address for appropriate antimicrobial drug use in agriculture and veterinary medicine while ensuring that such use does not pose a risk to human health.
- Several action items to strengthen; expand and coordinate prevailing national as well as international surveillance systems for resistant groups of microbes must form an integral part of the action plan. To address barriers to timely disseminate and update surveillance data and in order to gather information on the use of antibiotics additional action items are required.
- Surveillance system viz. National Healthcare Safety Network (NHSN) finds its appropriateness in preventing and restricting antibiotic resistance. It has shown its expansion in order to improve the capacity for collection and analysis of multidrug-resistant organisms (MDROs) and use of antibiotics. NHSN in collaboration with National Antimicrobial Resistance Monitoring System (NARMS); National Tuberculosis Surveillance System (NTSS) and United States Department of Agriculture (USDA) have undertaken initiatives in war footage to take care of such sensitive issues in developed nations of the world.

(Food and Drug Administration, 2009; Interagency Task Force on Antimicrobial Resistance, 2012; Union of concerned scientists, 2012; www.usda.gov).

WHO has selected combating antimicrobial resistance as the theme for World Health Day, 2011 - wherein WHO issues an international/global call for concerted action to halt the spread of antimicrobial resistance and recommends a six-point policy package for governments and regulatory bodies (WHO, 2013) as mentioned below:

- develop and implement a comprehensive, financed national plan
- strengthen surveillance and laboratory capacity
- ensure uninterrupted access to essential medicines of assured quality
- regulate and promote rational use of medicines
- enhance prevention and control of infection
- foster innovation of research and development of new tools.

Alternative and complementary therapies

To overcome with hurdles of microbial resistance various alternative emerging novel therapies are coming into picture such as herbal medication, ethno-veterinary medicines, bacteriophage therapy, cytokine therapy, mycophage therapy, panchgavya therapies etc. which are opening new avenues to fight against these superbugs (Deb *et al*., 2013b; Dhama *et al*., 2013a,b,d,e).

Bacteriophage therapy

Bacteriophages are super-bugs which are considered as bacteria eaters, bacteriophages thrive over bacteria specifically, as they are viruses of bacteria. They enter their host bacterium through specific receptors and are unable to infect eukaryotic cells due to the absence

of receptors in them. Due to their lytic mode of life-cycle, endolysins and holin enzyme system phages can kill Gram+ve, Gram-ve, Acid-fast and many other bacteria as well. Oral administration or topical application of phages have been attempted for a wide range of bacterial infections, caused by wounds or surgical intervention like skin grafting (Mathur *et al.*, 2003; Tiwari *et al.*, 2011; Tiwari *et al*., 2012; Tiwari *et al*., 2013a; Ghannad and Mohammadi, 2012).

Virophages and Mycophages

These are viruses which act specifically against viruses and fungi, respectively. Virophage and Mycophage therapies are new emerging concepts, as antiviral drugs and antifungal drugs require long-term medications and may have many side effects. The mycophages and virophages can be modified and used in therapeutic preparations for the treatment of diseases against many pathogenic fungi and certain viruses and can thus reduce antifungal and anti-viral resistance to a certain extent (Ghabrial, 1980; Koonin, 2012; Tiwari *et al*., 2013b).

Cytokine therapy

These are intercellular regulatory proteins, which play a pivotal role in initiating, maintaining, and regulating immunologic homeostatic and inflammatory processes. Due to their multiple function, they are promising candidates for therapeutic interference in infectious and autoimmune diseases, in immunocompromised patients with AIDS. The immunoglobulin Fc fragment based cytokines provides superior therapeutic approach. Nevertheless, the development of new vaccines necessitates the development of new types of adjuvants to ensure an appropriate immune response (Antachopoulos and Roilides, 2005; Jazayeri and Carroll, 2008; Nicholls *et al*., 2010; Dhama *et al*., 2013d).

Avian egg antibodies therapy

Chicken are capable of producing antigen specific antibodies (IgY), which have function similar to IgG in response to antigen. It can be used to treat microbes, which do not respond to antibiotics. Treatment with these antibodies is safer, more efficient and less expensive in comparison to antibiotics. Specific IgY antibodies have been developed against different bacterial or viral pathogens viz., rotavirus, bovine respiratory syncitial virus, coronavirus, infectious bursal disease virus, *E. coli*, *Salmonella, Edwardsiella*, *Yersinia, Staphylococcus, Streptococcus* and *Pseudomonas* (Yegani and Korver, 2007; Shaban *et al*., 2007; Michael *et al*., 2010; Wilmar and Tambourgi, 2010; Dhama *et al*., 2011b; Ferella *et al*., 2012; Deb *et al*., 2013a).

Herbal therapy

Various herbs and their extract have been proved to have antimicrobial, antiviral or antifungal activities. For example neem, giloy, onion, garlic, mustard, red chili, turmeric, clove, cinnamon, saffron, curry leaf, fenugreek, ginger etc. Also these do not possess development of resistance like that of antibiotics, and are also comparatively safer and cost-effective. Globally many researches are going on exploring the role of plants and their extracts in enhancing the immunity of man and animals and thereby encouraging avoidance of antibiotics. Herbal therapy is also gaining much attention these days in the treatment of subclinical mastitis and uses of *Terminalia chebula* and *Terminalia belerica* in this regard are found to be significant (Hawari, and Fawzi A. 2008; Hashemi and Davoodi, 2012; Mahima *et al*., 2012; Vashney *et al*., 2012; Deb *et al*., 2013c; Mahima *et al*., 2013).

Panchgavya therapy

Nowadays, Panchgavya therapy is gaining much importance because cow urine (an important component of Panchgavya) is able to kill a number of bacteria that show antibiotic resistance. The antibiotic resistance germs of tuberculosis can be killed by cow dung and urine, particularly cow urine acts as a bioenhancer for anti-tuberculous drugs, for which it is gaining much importance in the international market as an anti-tubercular agent (Dhama *et al.*, 2005a,b; Jain and Mishra, 2011; Randhawa and Kullar, 2011; Dhama *et al*., 2013e).

Diagnostics

An interesting fact is that improvement in the field of diagnosis has also helped in the early detection of antibiotic resistance apart from alternative and complementary therapies. In this regard development of molecular beacon based polymerase chain reaction and DNA chips for detection of methicillin resistant *Staph. aureus* (MRSA); liquid culture systems and molecular line probe assays in the detection of drug-resistant tuberculosis needs a special mention (Fluit *et al*., 2001; Woodford and Sundsfjord, 2005; O'Grady *et al*., 2011; Wilson, 2011; Deb *et al*., 2013c).

Vaccines

Molecular biology has created an enormous impact on vaccine development, leading to development of DNA vaccines; Subunit vaccine; anti-idiotypic and virosome vaccine, virus-based nanoparticles and virus like particles, biotechnologically engineered vaccine. These do not have the problem of resistance because they enhance the body's natural defense system, while an antibiotic works differently. However, due to evolution of new strains that escape from immunity induced by particular vaccine may develop for example in case of influenza/flu viruses, so an update regarding vaccine strain is necessary annually. Plant based oral vaccine importantly have gained popularity in human medicine and has been found to be protective against diseases like Pneumonia, ***Cholera and*** Tetanus. Development of anti-staphylococcal and other more effective vaccines is under way (Mengeling *et al*., 1997; Mercenier *et al*., 2001; Dhama *et al*., 2008; Daniell *et al*., 2009; Dhama *et al*., 2013f).

Conclusion and Future Perspectives

Antibiotics have revolutionized medicine in many aspects; their discovery was a turning point in human history. With the growing development as well as emergence of antibiotic resistance microbes, it is vital that we no longer take the availability of effective antibiotics for granted. We must respond to this burning issue and growing problem, and our response needs to be holistic and thorough for an ultimate fruitful cause to have check on this precarious problem. There is a need of cost-effective, sustainable control program in animal husbandry practices viz., dairy, piggery, poultry industry etc. through the use of simple approaches. Implementation of an affordable preventions and control program at farm level may result in a reduction of antibiotic residues in food products of animal origin (milk, meat, and eggs), which would result in checking the residual and toxic effects to our forks (avoiding this menace from farm to forks). The regulatory policies are required to be put in place by the governmental authorities to address the problems of farmers. These alone cannot solve the inherent residue problems. Control strategies that focus on implementing on-farm measures to reduce the risk for contamination of animal products should be more sustainable. Identification of the factors and strategies promoting appropriate antimicrobial use or/and discouraging inappropriate use will facilitate the implementation strategies. Identify factors and strategies that promote appropriate antimicrobial use (i.e., best practices) or discourage inappropriate use in all types of healthcare settings, including in-patient and out-patient facilities, clinics and offices facilitate the implementation of these strategies. Advancement in identification of new sources of natural antibiotic products and their diversity, creative approaches to discover novel antibiotics and their controlled introduction to therapy, inhibitors of drug resistance, microbial virulence inhibitors, and alternative therapies like phage therapy, cytokine therapy, mycophage therapy, panchgavya therapy etc are some of the ways that can help us to tackle the challenges of antibiotic resistance in the 21st century. By building on our current efforts and thinking for future in right perspectives, we can extend the

life of current antibiotics and develop future antibiotic therapies to protect us from current and future drug resistant disease threats.

REFERENCES

Aarestrup, F.M., Seyfarth, A.M., Emborg, H.D., Pedersen, K., Hendriksen, R.S., and Bager, F. 2001. Effect of abolishment of the use of antimicrobial agents for growth promotion on occurrence of antimicrobial resistance in fecal enterococci from food animals in Denmark. Antimicrob. Agents Chemother., 45: 2054–2059.

Abasi, M.M., Rashidi, M.R., Javadi, A., Amirkhiz, M.B., Mirmahdavi, S. and Zabihi, M. 2009. Levels of tetracycline residues in cattle meat, liver, and kidney from a slaughterhouse in Tabriz, Iran. Turk. J. Vet. Anim. Sci., 33(4): 345-349.

Abraham, E.P. and Chain, E. 1940. An enzyme from bacteria able to destroy penicillin. Rev. Infect. Dis., 10**:** 677-678.

Aiello, A.E. and Larson, E.L. (2003). Antibacterial cleaning and hygiene products as emerging risk factor for antibiotic resistance in the community. Lancet Infect. Dis. 3: 501-506.

Alekshun, M.N. and Levy, S.B. 2007. Molecular mechanisms of antibacterial multidrug resistance. Cell. 128: 1037-1050.

Allen, H.K., Donato, J., Wang, H.H., Cloud-Hansen, K.A., Davies, J.E. and Handelsman, J. 2010. Call of the wild: antibiotic resistance genes in natural environments. Nat. Rev. Microbiol. 8**:** 251-259.

Allou, N., Cambau, E., Massias, L., Chau, F. and Fantin, B. 2009. Impact of low-level resistance to fluoroquinolones due to qnrA1 and qnrS1 genes or a gyrA mutation on ciprofloxacin bactericidal activity in a murine model of *Escherichia coli* urinary tract infection. Antimicrob. Agents Chemother., 53**:** 4292-4297.

Althaus, R.L., Molina, M.P., Rodriguez, M. and Fernandez, N. 2001. Detection limits of beta-lactam antibiotics in ewe milk by penzym enzymatic test. J. Food Prot., 64(11): 1844-1847.

Aminov, R.I. 2009. The role of antibiotics and antibiotic resistance in nature. Environ. Microbiol., 11:2970-2988.

Aminov, R.I. and Mackie, R.I. 2007. Evolution and ecology of antibiotic resistance genes. FEMS Microbiol. Lett.,271**:**147-161.

Anderson, E.S. 1968. The ecology of transferable drug resistance in the enterobacteria. Annu. Rev. Microbiol., 22:131–180.

Andersson, D. I. (2006). The biological cost of mutational antibiotic resistance: any practical conclusions? Curr. Opin. Microbiol. 9:461-465.

Andrews, A.H. 2000. Calf Health. *In:* The Health of Dairy Cattle. Andrews, A. H. ed. Blackwell Science, Oxford, UK. pp. 1–14.

Antachopoulos, C. and Roilides, E. 2005. Cytokines and fungal infections. Br. J. Haematol., 129: 583-596.

Baltz, R.H. 2006. Marcel Faber Roundtable: is our antibiotic pipeline unproductive because of starvation, constipation or lack of inspiration? J. Ind. Microbiol. Biotechnol., 33:507-513.

Baquero, F., Martinez, J.L. and Canton, R. 2008. Antibiotics and antibiotic resistance in water environments. Curr. Opin. Biotechnol., 19**:** 260-265.

Barlow, M. and Hall, B.G. 2002. Phylogenetic analysis shows that the OXA beta-lactamase genes have been on plasmids for millions of years. J. Mol. Evol., 55: 314-321.

Bartoloni, A., Pallecchi, L., Rodriguez, H., Fernandez, C., Mantella, A., Bartalesi, F., Strohmeyer, M., Kristiansson, C., Gotuzzo, E., Paradisi, F. and Rossolini, G.M. 2009. Antibiotic resistance in a very remote Amazonas community. Int. J. Antimicrob. Agents., 33**:** 125-129.

Baysarowich, J., Koteva, K., Hughes, D. W., Ejim, L., Griffiths, E., Zhang, K., Junop, M. and Wright, G.D. 2008. Rifamycin antibiotic resistance by ADP-ribosylation: structure and diversity of Arr. Proc. Natl. Acad. Sci., 105: 4886-4891.

Benveniste, R., and J. Davies, 1973. Aminoglycoside antibiotic-inactivation enzymes in actinomycetes similar to those present in clinical isolates of antibiotic-resistant bacteria. Proc. Natl. Acad. Sci., USA 172: 3628-3632.

Bergstrom, C.T., Lo, M. and Lipsitch, M. 2004. Ecological theory suggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals. Proc. Natl. Acad. Sci. U. S. A. 101**:** 13285-13290.

Borroto, R.J. and Martinez-Piedra, R. 2000. Geographical patterns of cholera in Mexico, 1991–1996. Int. J. Epidemiol., 29: 764–772.

Boucher, H.W. and Corey, G.R. 2008. Epidemiology of methicillin-resistant Staphylococcus aureus. Clin. Infect. Dis., 46 (Suppl 5): S344–S349.

Boucher, H.W., Talbot, G.H., Bradley, J.S., Edwards, J.E., Gilbert, D., Rice, L.B., Scheld, M., Spellberg, B. and Bartlett, J. 2009. Bad bugs, no drugs: no escape! An update from the Infectious Diseases Society of America. Clin. Infect. Dis., 48: 1-12.

Bozdogan, B.Ü., Esel, D., Whitener, C., Browne, F.A. and Appelbaum, P.C. 2003. Antibacterial susceptibility of a vancomycin-resistant *Staphylococcus aureus* strain isolated at the Hershey Medical Center. J. Antimicrob. Chemother., 52 (5): 864–868. doi:10.1093/jac/dkg457.

Brazas, M.D. and Hancock, R.E**.** 2005. Using microarray gene signatures to elucidate mechanisms of antibiotic action and resistance. Drug Discov. Today. 10**:** 1245-1252.

Brochet, M., Couve, E., Zouine, M., Poyart, C. and Glaser, P. 2008. A naturally occurring gene amplification leading to sulfonamide and trimethoprim resistance in *Streptococcus agalactiae*. J. Bacteriol., 190**:** 672-680.

Brotze-Oesterhelt, H. and Brunner, N.A. 2008. How many modes of action should an antibiotic have. Curr. Opin. Pharmacol., 8**:** 564-573.

Bryskier, A. (ed.). 2005. Antimicrobial agents: antibacterials and antifungals. ASM Press, Washington, DC.

Butaye, P., Cloeckaert, A. and Schwarz, S. 2003. Mobile genes coding for efflux-mediated antimicrobial resistance in Gram-positive and Gram-negative bacteria. Int. J. Antimicrob. Agents 22: 205–210.

Byarugaba, D.K. 2004. A view on antimicrobial resistance in developing countries and responsible risk factors. Int. J. Antimicrob. Agents 24: 105–110.

Byarugaba, D.K. 2005. Antimicrobial resistance and its containment in developing countries. *In:* Antibiotic Policies: Theory and Practice, ed. Gould, I. and Meer, V. pp. 617–646. New York: Springer.

Calva, J.J., Niebla-Pe´rez, A., Rodrı´guez-Lemoine, V., Santos, J.I. and Ama´ bile-Cuevas, C.F. 1996. Antibiotic usage and antibiotic resistance in Latin America. *In:* C.F. Ama´ bile-Cuevas (Ed.), Antibiotic resistance: from molecular basics to therapeutic options. R.G. Landes/ Chapman & Hall, Austin/New York, pp. 73–97.

Canton, R. 2009. Antibiotic resistance genes from the environment: a perspective through newly identified antibiotic resistance mechanisms in the clinical setting. Clin. Microbiol. Infect., 15(Suppl. 1)**:**20-25.

CH 12.16. 2004. Detection of the residues of inhibitory substances. The Four Plate Test (Bogaerts and Wolf, 1980). *In:* List of official methods for laboratory diagnostics of food and feed. Bullet. Ministry of Agriculture of the Slovak Republic. 36: 277–284

CH 6.2. 2004. Determination of sulphonamides by HPLC method. In: List of official methods for laboratory diagnostics of food and feed. Bullet. Ministry of Agriculture of the Slovak Republic. 36: 97–99.

Chan, C.X., Beiko, R.G. and Ragan, M.A. 2011. Lateral Transfer of Genes and Gene Fragments in *Staphylococcus* Extends beyond MobileElements. J.Bacteriol., 193(15):3964–3977.doi: 10.1128/ JB.01524-10.

Chater, K.F. and Bruton, C**.** 1985. Resistance, regulatory and production genes for the antibiotic methylenomycin are clustered. EMBO J. 4**:** 229-241.

Chee-Sanford, J.C., Mackie, R.I., Koike, S., Krapac, I.G., Lin, Y.F., Yannarell, A.C., Maxwell, S. and Aminov, R.I. 2009. Fate and transport of antibiotic residues and antibiotic resistance genes

following land application of manure waste. J. Environ. Qual., 38**:** 1086-1106.

Chetley, A., Hardon, A., Hodgkin, C. and Haaland, A. 2007. How to improve the use of medicines by consumers World Health Organization Geneva http://www.who.int/medicines/ publications/WHO_PSM_PAR_2007.2.pdf.

Chopra, I. and Roberts, M. 2001. Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiol. Mol. Biol. Rev., 65(2): 232-260.

Cirz, R.T., Chin, J.K., Andes, D.R., de Crécy-Lagard, V., Craig, W.A. and Romesberg, F.E. 2005. Inhibition of Mutation and Combating the Evolution of Antibiotic Resistance. PLoS Biol., 3 (6): e176. doi:10.1371/journal.pbio.0030176.

Cohen, S.N. and Miller, C.A. 1969. Multiple molecular species of circular R-factor DNA isolated from *Escherichia coli*. Nature. 224 (5226):1273–1277.

Cohen, S.N. and Miller, C.A. 1970. Non-chromosomal antibiotic resistance in bacteria. II. Molecular nature of R-factors isolated from *Proteus mirabilis* and *Escherichia coli*. J. Mol. Biol., 50(3): 671–687.

Cohen, S.N., Chang A.C.Y. and Hsu L. 1972. Nonchromosomal antibiotic resistance in bacteria: genetic transformation of *Escherichia coli* by R-Factor DNA. Proc. Natl. Acad. Sci., U.S.A. 69(8): 2110–2114.

Couce, A. and Blazquez, J. 2009. Side effects of antibiotics on genetic variability. FEMS Microbiol. Rev., 33**:** 531-538.

Da Re, S., Garnier, F., Guerin, E., Campoy, S., Denis, F. and Ploy, M.C. 2009. The SOS response promotes qnrB quinolone-resistance determinant expression. EMBO Rep., 10**:** 929-933.

Daniell, H., Singh, N.D., Mason, H. and Streatfield, S.J. 2009. Plant-made vaccine antigens and biopharmaceuticals. Trends Plant Sci., 14(12): 669–679.

Danko, J., Lešník, F. and Jenča, A. 2005. Xenobiotics and their relation to health. Košice: University of Veterinary Medicine, pp. 107.

Dantas, G., Sommer, M.O.A., Oluwasegun, R.D. and Church, G.M. 2008. Bacteria subsisting on antibiotics. Sci., 320**:**100-103.

Datta, N. and Hughes, V.M. 1983. Plasmids of the same Inc groups in enterobacteria before and after the medical use of antibiotics. Nature. 306**:**616-617.

Davies, J. 1995. Vicious circles: looking back on resistance plasmids. Genet. 139**:** 1465-1468.

Davies, J. and Davies, D. 2010. Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev., 74: 417–433.

Davies, J., Brzezinska, M. and Benveniste, R. 1971. The problems of drug-resistant pathogenic bacteria. R factors: biochemical mechanisms of resistance to aminoglycoside antibiotics. Ann. N Y Acad. Sci., U.S.A. 182: 226–233.

D'Costa, V.M., Griffiths, E. and Wright, G.D. 2007. Expanding the soil antibiotic resistome: exploring environmental diversity. Curr. Opin. Microbiol., 10:481-489.

D'Costa, V.M., McGrann, K.M., Hughes, D.W. and Wright, G.D. 2006. Sampling the antibiotic resistome. Sci., 311**:**374-377.

Deb, R., Chakraborty, S., Veeregowda, B.M., Verma, A.K., Tiwari, R. and Dhama, K. 2013a. Monoclonal Antibody and its use in the diagnosis of livestock diseases. Adv. Biosci. Biotechnol., 4: 50-62.

Deb, R., Kumar, A., Chakraborty, S., Verma, A.K., Tiwari, R., Dhama, K., Singh, U. and Kumar, S. 2013c. Trends in diagnosis and control of bovine mastitis: A review. Pak. J. Biol. Sci., 16(23): 1653-1661.

Deb, R., Mahima, Chakraborty, S., Verma, A.K., Tiwari, R. and Dhama, K. 2013b. Nutrigenomics and its role in male puberty of cattle - a mini review. Pak. J. Biol. Sci., (Available online). doi: 10.3923/ pjbs.2013.

DeLeo, F.R. and Chambers**,** H.F. 2009. Reemergence of antibiotic-resistant *Staphylococcus aureus* in the genomics era. J. Clin. Invest., 119: 2464-2474.

Depardieu, F., Podglajen, I., Leclercq, R., Collatz, E. and Courvalin, P. 2007. Modes and modulations of antibiotic resistance gene expression. Clin. Microbiol. Rev., 20**:** 79-114.

Dhama, K., Basaraddi, M.S., Tiwari, R. and Ananthakrshna L.R. 2011b. Egg yolk antibodies (EYA): applications in poultry. Poultry Technol., 6(4): 20-24.

Dhama, K., Chakraborty, S. and Tiwari, R. 2013e. Panchgavya therapy (Cowpathy) in safeguarding health of animals and humans – A review. Res. Opin. Anim. Vet. Sci., 3(6): 170-178.

Dhama, K., Chakraborty, S., Kapoor, S., Tiwari, R., Verma, A.K., Deb, R., Rajagunalan, S., Singh, R., Vora, K. and Natesan, S. 2013a. One world, one health - veterinary perspectives. Adv Anim Vet Sci., 1(1): 5-13.

Dhama, K., Chakraborty, S., Mahima, Wani, M.Y., Verma, A.K., Deb, R., Tiwari, R. and Kapoor, S. 2013b. Novel and emerging therapies safeguarding health of humans and their companion animals: A review. Pak. J. Bio. Sci., 16(3): 101-111. doi: 10.3923/pjbs.2013.101.111.

Dhama, K., Chakraborty, S., Wani, M.Y., Tiwari, R. and Barathidasan, R. 2013d. Cytokine therapy for combating animal and human diseases – A review. Res. Opin. Anim. Vet. Sci., 3(7): 195-208.

Dhama, K., Chauhan, R.S. and Singhal, L.K. 2005b. Anti-cancer activity of cow urine: current status and future directions. Int. J. Cow Sci., 1(2): 1-25.

Dhama, K., Mahendran, M., Gupta, P.K. and Rai, A. 2008. DNA Vaccines and their applications in Veterinary Practice: Current Perspectives. Vet. Res. Commun., 32: 341-56.

Dhama, K., Rajagunalan, S., Chakraborty, S., Verma, A.K., Kumar, A., Tiwari, R. and Kapoor, S. 2013c. Food-borne pathogens of Animal origin – Diagnosis, prevention and control and their zoonotic significance: A review. Pak. J. Biol. Sci, 16(20): 1076-1085.

Dhama, K., Rathore, R., Chauhan, R.S. and Tomar, S. 2005a. Panchgavya: an overview. Int. J. Cow Sci., 1(1): 1-15.

Dhama, K., Verma, V., Sawant, P.M., Tiwari, R., Vaid, R.K. and Chauhan, R.S. 2011a. Applications of Probiotics in Poultry: Enhancing Immunity and Beneficial Effects on Production Performances and Health - A Review. J. Immunol. Immunopathol., 13(1): 1-19.

Dhama, K., Wani, M.Y., Deb, R., Karthik, K., Tiwari, R., Barathidasan, R., Kumar, A., Mahima, Verma, A.K. and Singh, S.D. 2013f. Plant based oral vaccines for human and animal pathogens- A new era of prophylaxis: Current and future perspectives. J. Exp. Biol. Agri. Sci., 1(1): 1-12.

Dionisio, F., Matic, I., Radman, M., Rodrigues, O.R. and Taddei, F. 2002. Plasmids spread very fast in heterogeneous bacterial communities. Genet., 162**:** 1525.

Doern, G.V., Heilmann, K.P., Huynh, H.K., Rhomberg, P.R., Coffman, S.L. and Brueggemann, A.B. 2001. Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in the United States during 1999_2000, including a comparison of resistance rates since 1994-1995. Antimicrobial Agents and Chemother., 45(6): 1721-1729.

Douthwaite, S. 2010. Designer drugs for discerning bugs. Proc. Natl. Acad. Sci., U.S.A. 107(40): 17065-17066.

Doyle, M.P. 2006. Antimicrobial resistance: implications for the food system. Compr. Rev. Food Sci. Food Saf., 5**:** 71-137.

Duse, A.G. 1998. Antibiotic resistance in developing countries. *In:* Infection control practices, ed. A. Emerson, and M. Arrowsmith, pp. 38–44. Borken, Germany: 3MMedical Markets Laboratory.

Enright, M.C., Robinson, D.A., Randle, G., Feil, E.J., Grundmann, H. and Spratt, B.G. 2002. The evolutionary history of methicillin-resistant *Staphylococcus aureus* (MRSA). Proc. Natl. Acad. Sci., U.S.A. 99**:** 7687-7692.

Fajardo, A., Martinez-Martin, N., Mercadillo, M., Galan, J.C., Ghysels, B., Matthijs, S., Cornelis, P., Wiehlmann, L., Tummler, B., Baquero, F. and Martinez, J.L. 2008. The neglected intrinsic resistome of bacterial pathogens. PloS One 3**:** e1619.

Falagas, M.E. and Karveli, E.A. 2006. World Wide Web resources on antimicrobial resistance. Clin. Infect. Dis., 43: 630–633.

Ferella, A., Bellido, D., Chacana, P., Wigdorovitz, A., Dus Santos, M.J. and Mozgovoz, M.V. 2012. Chicken egg yolk antibodies against bovine respiratory syncitial virus neutralize the virus *in vitro*. Procedia Vaccinol., 6: 33-38.

Finland, M. 1979. Emergence of antibiotic resistance in hospitals, 1935-1975. Rev. Infect. Dis., 1**:**4-22.

Fluit, A.C., Visser, M.R. and Schmitz, F.J. 2001. Molecular detection of antimicrobial resistance. Clin. Microbiol. Rev., 14: 836–871.

Food and Drug Administration 2009. Grade 'A' pasteurized milk ordinance. U. S. department of health and human services. www.fda.gov.

Gaudin, V., Juhel-Gaugain, M., Morétain, J.P. and Sanders, P. 2008. AFNOR validation of Premi test, a microbiological based screening tube-test for the detection of antimicrobial residues in animal muscle tissue. Food Addit. Contam. Part A Chem. Anal. Control Expo. Risk Assess., 25(12): 1451-1464. doi: 10.1080/02652030802429088.

Ghabrial, S.A. 1980. Effects of Fungal Viruses on Their Hosts. Annu. Rev. Phytopathol., 18: 441-461.

Ghannad, M.S. and Mohammadi, A. 2012. Bacteriophage: time to re-evaluate the potential of phage therapy as a promising agent to control multidrug-resistant bacteria. Iran. J. Basic Med. Sci., 15: 693-701

Ghidini, S., Zanardi, E., Varisco, G. and Chizzolini, R. 2002. Prevalence of molecules of β-lactam antibiotics in bovine milk in Lombardia and Emilia Romagna (Italy). Ann. Fac. Medic. Vet. Di Parma., Vol. XXII, pp. 245-252.

Gillings, M., Boucher, Y., Labbate, M., Holmes, A., Krishnan, S.S., Holley, M. and Stokes, H.W. 2008. The evolution of class 1 integrons and the rise of antibiotic resistance. J. Bacteriol., 190**:** 5095-5100.

Girou, E., Legrand, P., Soing-Altrach, S., Astrid, L., Celine, P., Alexandra, A., Latifa, T. S. and Tam, C.S.H. 2006. Association between hand hygiene compliance and methicillin-resistant *Staphylococcus aureus* prevalence in a French rehabilitation hospital. Infect. Control Hosp. Epidemiol., 27(10): 1128–1130. doi:10.1086/507967.

Gomez, M.J., and Neyfakh, A.A. 2006. Genes involved in intrinsic antibiotic resistance of *Acinetobacter baylyi*.. Antimicrob. Agents Chemother., 50**:**3562-3567.

Gregory, S.T.**,** Cate, J.H. and Dahlberg, A.E. (2001). Streptomycin-resistant and streptomycin-dependent mutants of the extreme thermophile *Thermus thermophilus*. J. Mol. Biol., 309: 333-338.

Guerin, E., Cambray, G., Da Re, S., Mazel, D. and Ploy, M.C. 2010. The SOS response controls antibiotic resistance by regulating the integrase of integrons. Med. Sci., *(Paris*) 1**:** 28-30.

Hall, R.M. 1997. Mobile gene cassettes and integrons: moving antibiotic resistance genes in Gram-negative bacteria. Ciba Found. Symp., 207: 192–205.

Hashemi, S.R. and Davoodi, H. 2012. Herbal plants as new immuno-stimulator in poultry industry: A review. Asian J. Anim. Vet. Adv., 7: 105-116.

Hawari, A.D. and Fawzi, A. 2008. Prevalence and distribution of mastitis pathogens and their resistance against antimicrobial agents in dairy cows in Jordan. Am. J. Anim. Sci., 3: 36-39.

Hawkey, P.M. and Jones, A.M. 2009. The changing epidemiology of resistance. J. Antimicrobial Chemother., 64 (Suppl 1): i3–10. doi:10.1093/jac/dkp256.

Hidron, A.I., Edwards, J.R., Patel, J., Horan, T. C., Sievert, D.M., Pollock, D.A. and Fridkin, S. K. 2008. National Healthcare Safety Network Team *et al*. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. Infect. Control Hosp. Epidemiol., 29(11): 996–1011. doi:10.1086/591861.

Hindler, J. and Stelling, J. 2007. Medical microbiology: analysis and presentation of cumulative antibiograms: a new consensus guideline from the clinical and laboratory standards institute. Clin. Infect. Dis., 44(6): 867–873.

Hirakata, Y., Matsuda, J., Miyazaki, Y., Kamihira, S., Kawakami, S., Miyazawa, Y., Ono, Y., Nakazaki, N., Hirata, Y., Inoue, M., Turnidge, J.D., Bell, J.M., Jones, R.N. and Kohno S. 2005. SENTRY Asia-Pacific Participants. Regional variation in the prevalence of extended-spectrum beta-lactamase-producing clinical isolates in the Asia-Pacific region (SENTRY 1998–2002). Diagn. Microbiol. Infect. Dis., 52: 323–329.

Hopwood, D.A. 2007. How do antibiotic-producing bacteria ensure their self-resistance before antibiotic biosynthesis incapacitates them? Mol. Microbiol., 63**:** 937-940.

Hotchkiss, R.D. and Gabor, M. 1970. Bacterial transformation, with special reference to recombination process. Annu. Rev. Genet., 4:193–224.

IMPACT 2006. Counterfeit medicines: an update on estimates. Available at: www.who.int/medicines/services/counterfeit/impact/TheNewEstimatesCounterfeit.pdf.

Inoue, M., Lee, N.Y., Hong, S.W., Lee, K. and Felmingham, D. 2004. PROTEKT 1999–2000: a multicentre study of the antibiotic susceptibility of respiratory tract pathogens in Hong Kong, Japan and South Korea. Int. J. Antimicrob. Agents. 23: 44–51.

Interagency Task Force on Antimicrobial Resistance 2012. A public health action plan to combat antimicrobial resistance. pp. 3-36.

Iseman, M.D. 2007. Extensive drug-resistant Mycobacterium tuberculosis: Charles Darwin would understand. Clin. Infect. Dis., 45:1415–1416.

Islam, M., ed. 2007. Health Systems Assessment Approach: A How-To Manual. Arlington. Arlington, V. A: Management Sciences for Health.

Jazayeri, J.A. and Carroll, G.J. 2008. Fc-based cytokines: Prospects for engineering superior therapeutics. BioDrugs. 22: 11-26.

Joint FAO/WHO Food Standards Programme (2001). Control of Veterinary Drug Residues In Milk And Milk Products Codex Committee On Residues Of Veterinary Drugs In Foods, Thirteenth Session, Charleston, South Carolina, USA.

Kahn, C.M. and Line, S. 2005. Antimicrobial agents. In: The Merk Veterinary Manual, 9th ed., Whitehouse, NJ: Merck and Co. pp. 2056–2098.

Kikuvi, G.M., Schwarz, S., Ombui, J.N., Mitema, E.S. and Krehrenberg, K. 2007. Streptomycin and chloramphenicol resistance genes in Escherichia coli from cattle, pigs and chicken form Kenya. Microbial Drug Res., 13: 63–69.

Koonin, E.V. 2012. The wonder world of microbial viruses. Expert Rev. Anti-infective Therapy. 8(10): 1097-1099. doi: 10.1586/eri.10.96.

Kopecko, D.J. and Punch, J.D. 1971. The problems of drug-resistant pathogenic bacteria. Regulation of R-factor replication in *Proteus mirabilis*. Ann. N Y Acad. Sci., 182: 201–216.

Koréneková, B., Skalická, M., Nad, P. and Korének, M. 2007. Occurence of selected trace elements in cattle meat. Meso., 9: 328–331.

Larsson, M., Kronvall, G., Chuc, N.T., Karlsson, I., Lager, F., Hanh, H.D., Tomson, G. and Falkenberg, T. 2000. Antibiotic medication and bacterial resistance to antibiotics: A survey of children in a Vietnamese community. Trop. Med. Int. Health. 5: 711–721.

Levy, S.B. and Marshall, B. 2004. Antibacterial resistance worldwide: causes, challenges and responses. *Nat. Med*. 10(Suppl.)**:** S122-S129.

Li, W., Atkinson, G.C., Thakor, N.S., Allas, U., Lu, C.C., Chan, K.Y., Tenson, T., Schulten, K., Wilson, K.S., Hauryliuk, V. and Frank, J. 2013. Mechanism of tetracycline resistance by ribosomal protection protein Tet (O). Nature Commun., 4: 1477. doi: 10.1038/ncomms2470.

Liliana Serna, C., Leidy Johana, V.H. and Romulo Campos, G. 2011. Lactic acid bacteria with antimicrobial activity against pathogenic agent causing of bovine mastitis. Biotechnologia en. El. Sector Agropecuario y. Agroindustrial. 9(1): 97-104.

Linares, J. F., Gustafsson, I., Baquero, F. and Martinez. J.L. 2006. Antibiotics as intermicrobial signaling agents instead of weapons. Proc. Natl. Acad. Sci. U S A., 103(51). 19484-19489.

Linton, A. H. (1977). Antibiotic resistance: the present situation reviewed. Vet. Rec., 100: 354-360.

Liu, B. and Pop, M. 2009. ARDB—Antibiotic Resistance Genes Database. Nucleic Acids Res. 37**:** D443-D447.

Llano-Sotelo, B., Azucena, E.F., Kotra, L.P., Mobashery, S. and Chow, C.S. 2002. Aminoglycosides modified by resistance enzymes display diminished binding to the bacterial ribosomal aminoacyl-tRNA site. Chemistry Biol., 9: 455-463.

Luangtongkum, T., Jeon, B., Han, J., Plummer, P., Loque, C.M. and Zhang, Q. 2009. Antibiotic resistance in Campylobacter: emergence, transmission and persistence. Future Microbiol., 4(2): 189-200. doi: 10.2217/17460913.4.2.189.

Mahima, A.K., Rahal, A., Deb, R., Latheef, S.K. and Samad, H.A., Tiwari, R., Verma, A.K., Kumar, A. and Dhama, K. 2012. Immunomodulatory and therauptic potential of herbal, traditional/indigenous and ethanoveterinary medicine. Pak. J. Biol. Sci., 15: 754-774.

Mahima, Verma, A.K., Tiwari, R., Karthik, K., Chakraborty, S., Deb, R. and Dhama, K. 2013. Neutraceuticals from fruit and vegetables at a glance: a review. J. Biol. Sci., 13(2): 38-47.

Maragakis, L.L. and Perl, T.M. 2008. *Acinetobacter baumannii*: epidemiology, antimicrobial resistance, and treatment options. Clin. Infect. Dis., 46:1254–63.

Marshall, B.M., Ochieng, D.J. and Levy, S.B. 2009. Commensals: unappreciated reservoir of antibiotic resistance. Microbe 4**:** 231-238.

Martinez, J.L. 2009. The role of natural environments in the evolution of resistance traits in pathogenic bacteria. Proc. Biol. Sci., 276**:**2521-2530.

Martinez, J.L., Baquero, F. and Andersson, D. (2007). Predicting antibiotic resistance. Nat. Rev. Microbiol., 5**:** 958-965.

Mathew, A.G., Cissell, R. and Liamthong, S. 2007. Antibiotic resistance in bacteria associated with food animals: a United States perspective of livestock production. Foodborne Pathog. Dis., 4(2): 115–133. doi:10.1089/fpd.2006.0066.

Mathur, M.D., Vidhani, S. and Mehndiratta, P.L. 2003. Bacteriophage therapy: An alternative to conventional antibiotics. J. Assoc. Physicians India. 51: 593-596.

Mbori-Ngacha, D.N. 1997. Rational approach to limiting emergence of antimicrobial drug resistance. East Afr. Med. J., 74: 187–189.

McKeegan, K.S., Borges-Walmsley, M.I. and Walmsley, A.R. 2002. Microbial and viral drug resistance mechanisms. Trends Microbiol., 10 (Suppl.): S8- S14.

Mendez, C., and Salas, J. 2001. The role of ABC transporters in antibiotic-producing organisms: drug secretion and resistance mechanisms. Res. Microbiol., 152**:** 341-350.

Mengeling, W.L., Brockmeier, S.L., Lager, K.M. and Vorwald, A.C. 1997. The role of biotechnologically engineered vaccines and diagnostics in pseudorabies (Aujeszky's disease) eradication strategies. Vet. Microbiol., 55: 49-60.

Mercenier, A., Wiedermann, U. and Breiteneder, H. 2001. Edible genetically modified microorganisms and plants for improved health. Curr. Opin. Biotechnol., 12: 510-515.

Meynell, E. and Datta, N. 1967. Mutant drug resistant factors of high transmissibility. Nature., 214 (5091): 885–887.

Michael, A., Meenatchisundaram, S., Parameswari, G., Subbraj, T., Selvakumaran, R. and Ramalingam, S. 2010. Chicken egg yolk antibodies (IgY) as an alternative to mammalian antibodies. Ind. J. Sci. Technol., 3(4): 468-474.

Mitema, E.S. and Kikuvi, G. 2004. Surveillance of overall use of antimicrobial drugs in humans over a five-year period (1997–2001) in Kenya. J. Antimicob. Chemother., 54: 966-967.

Mitema, E.S., Kikuvi, G.M., Stohr, K. and Wegener, H. 2001. An assessment of antimicrobial consumption in food producing animals in Kenya. J. Vet. Pharmacol. Ther., 24: 385–390.

Movassagh, M.H. 2011. Detection of beta lactam antibiotics residues in Iranian ultra high temperature milk by Beta star test. Annals Biol. Res., 2(2): 95-98.

Murray, C.J. and Lopez, A. D. 1997. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet. 349: 1269–1276.

Musgrove, M.T., Jones, D.R., Northcutt, J.K., Cox, N.A., Harrison, M.A., Fedorka-Cray, K.J. and Ladely, S.R. (2006). Antimicrobial resistance in *Salmonella* and *Escherichia coli* isolated from commercial shell eggs. Poult. Sci., 85(9): 1665-1669.

Mwangi, M.M., Wu, S.W., Zhou, Y., Sieradzki, K., de Lencastre, H., Richardson, P., Bruce, D., Rubin, E., Myers, E. , Siggia, E.D. and Tomasz, A. 2007. Tracking the in vivo evolution of multidrug resistance in *Staphylococcus aureus* by whole-genome sequencing. Proc. Natl. Acad. Sci. U. S. A. 104: 9451-9456.

Nandi, S., Maurer, J.J., Hofacre, C. and Summers, A.O. 2004. Gram-positive bacteria are a major reservoir of class 1 antibiotic resistance integrons in poultry litter. Proc. Natl. Acad. Sci. U. S. A. 101**:** 7118-7122.

Newton, P., Proux, S., Green, M., Smithuis, F., Rozendaal, J., Prakongpan, S., Chotivanich, K., Mayxay, M., Looareesuwan, S., Farrar, J., Nosten, F. and White, N.J. 2001. Fake artesunate in Southeast Asia. Lancet. 357: 1948–1950.

Newton, P.N., Green, M.D., Ferna´ ndez, F.M., Day, N.P.J. and White, N.J. 2006. Counterfeit anti-infective medicines. Lancet. Inf. Dis., 6: 602–613.

Nicholls, E.F., Madera, L. and Hancock, R.E. 2010. Immunomodulators as adjuvants for vaccines and antimicrobial therapy. Ann. Acad. Sci., 12: 46-61.

Nisha, A.R. 2008. Antibiotic residues – a global health hazard. 1(12): 375-377.

Nordmann, P., and Poirel, L. 2005. Emergence of plasmid-mediated resistance to quinolones in Enterobacteriaceae. J. Antimicrob. Chemother. 56**:** 463-469.

Normark, B.H. and Normark, S. 2002. Evolution and spread of antibiotic resistance. J. Internal Med., 252: 91–106.

Nugent, R., Pickett, J. and Back, E. 2008. Drug Resistance as a Global Health Policy Priority. Drug Resistance Working Group Background Paper. Center for Global Development. Source: http://www.cgdev.org/doc/ghprn/Concept%20Paper.pdf.

O'grady, J., Maeurer, M., Mwaba, P., Kapata, N., Bates, M., Hoelscher, M. and Zumla, A. 2011. New and improved diagnostics for detection of drug-resistant pulmonary tuberculosis. Curr. Opin. Pulm. Med., 17(3): 134-141.

Ogawara, H., Kawamura, N., Kudo, T., Suzuki, K.I. and Nakase, T. 1999. Distribution of β-lactamases in actinomycetes. Antimicrob. Agents Chemother., 43**:** 3014-3017.

Oka, H. 1995. Regulation and Current Residue Detection Methods of Antibiotics Used in the European Union. *In:* Chemical Analysis for Antibiotics Used in Agriculture. Eds. Oka, H., Nazakawa. H., Harada, K. and Macneil, J. D. AOAC International.

Okeke, I.N., Klugman, K.P., Bhutta, Z.A., Duse, A.G., Jenkins, P., O'Brien, T.F., Pablos- Mendez, A. and Laxminarayan, R. 2005. Antimicrobial resistance in developing countries. Part II: strategies for containment. Lancet. Infect. Dis., 5: 568–580.

Pallecchi, L., Bartoloni, A., Paradisi, F. and Rossolini, G.M. 2008. Antibiotic resistance in the absence of antimicrobial use: mechanisms and implications. Expert Rev. Anti Infect. Ther. 6**:** 725-732.

Pallecchi, L., Lucchetti, C., Bartoloni, A., Bartalesi, F., Mantella, A., Gamboa, H., Carattoli, A., Paradisi, F. and Rossolini, G.M. 2007. Population structure and resistance genes in antibiotic-resistant bacteria from a remote community with minimal antibiotic exposure. Antimicrob. Agents Chemother., 51**:** 1179-1184.

Payne, D.J. Gwynn, M.N., Holmes, D.J. and Pompliano, D.L. 2007. Drugs for bad bugs: confronting the challenges of antibacterial discovery. Nat. Rev. Drug Discov., 6**:** 29-40.

Perez, F., Hujer, A.M., Hujer, K.M., Decker, B.K., Rather, P.N. and Bonomo. R.A. 2007. Global challenge of multidrug-resistant *Acinetobacter baumannii*. Antimicrob. Agents Chemother., 51**:** 3471-3484.

Piddock, L.J. 2006. Clinically relevant chromosomally encoded multidrug resistance efflux pumps in bacteria. Clin. Microbiol. Rev., 19**:** 382-402.

Piddock, L.J. 2006. Multidrug-resistance efflux pumps—not just for resistance. Nat. Rev. Microbiol., 4**:** 629-636.

Pikkemaat, M.G. 2009. Microbial screening methods for detection of antibiotic residues in slaughter house. Anal. Bioanal. Chem., 395(4): 893-905. doi: 10.1007/s00216-009-2841-6.

Pikkemaat, M.G., Oostra-van Dijk, S., Schouten, J., Rappaline, M. and Van Egmond, H.J. 2008. A new microbiological screening method for the detection of antimicrobial residues in slaughter animals: the Nouws antibiotic test (NAT-screening). Food Control. 19: 781–789.

Pirmohamed, M., Atuah, K.N., Dodoo, A.N. and Winstanley, P. 2007. Pharmacovigilance in developing countries. BMJ., 335: 462.

Plozza, T., Trenerry, V.C., Zeglinski, P., Nguyen, H. and Johnstone, P. 2011. The confirmation and quantification of selected aminoglycoside residues in animal tissue and bovine milk by liquid chromatography tandem mass spectrometry. Int. Food Res. J., 18(3): 1077-1084.

Poole, K. 2005. Efflux-mediated antimicrobial resistance. J. Antimicrob. Chemother., 56**:** 20-51.

Poole, K. 2012. Stress responses as determinants of antimicrobial resistance in Gram-negative bacteria. Trends Microbiol., 20: 227-234.

Radyowijati, A. and Haak, H. 2002. Determinants of Antimicrobial Use in the Developing World. Child Health Research Project, Special Report 4: 1.

Recht, M.I. and Puglisi, J.D. 2001. Aminoglycoside resistance with homogeneous and heterogeneous populations of antibiotic-resistant ribosomes. Antimicrobial Agents Chemother., 45(9): 2414-2419.

Reinert, R.R., Low, D.E., Rossi, F., Zhang, X., Wattal, C. and Dowzicky, M.J. 2007. Antimicrobial susceptibility among organisms from the Asia/Pacific Rim, Europe and Latin and North America collected as part of TEST and the *in vitro* activity of tigecycline. J. Antimicrob. Chemother., 60: 1018–1029.

Richet, H.M., Mohammed, J., McDonald, L.C. and Jarvis, W.R. 2001. Building communication networks: international network for the study and prevention of emerging antimicrobial resistance. Emerg. Infect. Dis., 7: 319–322.

Riesenfeld, C.S., Goodman, R.M. and Handelsman, J. 2004. Uncultured soil bacteria are a reservoir of new antibiotic resistance genes. Environ. Microbiol., 6**:** 981-989.

Roberts, M.C. 2008. Update on macrolide-lincosamide-streptogramin, ketolide, and oxazolidinone resistance genes. FEMS Microbiol. Lett., 282**:**147-159.

Robicsek, A., Jacoby, G.A. and Hooper, D.C. 2006. The worldwide emergence of plasmid-mediated quinolone resistance. Lancet Infect. Dis., 6**:** 629-640.

Rodríguez-Verdugo, A., Gaut, B.S. and Tenaillon, O. 2013. Evolution of *Escherichia coli* rifampicin resistance in an antibiotic-free environment during thermal stress. BMC Evol. Biol., 13: 50

Rossolini, G.M. and Thaller M.C. 2010. Coping with antibiotic resistance: contributions from genomics. Genome Med., 2:15.

Rownd, R. 1969. Replication of a bacterial episome under relaxed control. J Mol Biol., 44(3): 387–402.

Rownd, R. and Mickel, S. 1971. Dissociation and reassociation of RTF and r-determinants of the R-factor NR1 in *Proteus mirabilis*. Nat. New Biol., 234(45): 40–43.

Salyers, A.A., Gupta, A. and Wang, Y. 2004. Human intestinal bacteria as reservoirs for antibiotic resistance genes. TRENDS in Microbiol. 12: 412-416.

Sasanya, J.J., Okeng, J.W.O., Ejobi, F. and Muganwa, M. 2005. Use of sulphonamides in layers in Kampala district, Uganda and sulphonamide residues in commercial eggs. Afr. Health Sci., 5(1): 33-39.

Shaban R., Ehsan S., Seyed A.G., Jesse L.G., Mohammad, A. and Torshizi, K. 2007. The effect of egg-derived antibody on prevention of avian Influenza subtype H9N2 in layer chicken. Int. J. Poul. Sci., 6(3): 207-210.

Shah, N.S., Wright, A., Bai, G.H., Barrera, L., Boulahbal, F., Martin-Casabona, N., Drobniewski, F., Gilpin, C., Havelkova, M., Lepe, R., Lumb, R., Metchock, B., Portaels, F., Rodrigues, M. F., Rusch-Gerdes, S., Deun, A.V., Vincent, V., Laserson, K., Wells, C. and Cegielski, J.P. 2007. Worldwide emergence of extensively drug-resistant tuberculosis. Emerg. Infect. Dis., 13**:** 380-387.

Shoemaker, N.B., Vlamakis, H., Hayes, K. and Salyers, A.A. 2001. Evidence for extensive resistance gene transfer among Bacteroides spp. and among Bacteroides and other genera in the human colon. Appl. Environ. Microbiol., 67**:** 561-568.

Sierra, D., Contreras, A., Sánchez, A., Luengo, C., Corrales, J.C., Morales, C.T., de la Fe, C., Guirao, I. and Gonzalo, C. 2009. Short communication: detection limits of non-beta-lactam antibiotics in goat's milk by microbiological residues screening tests. J. Dairy Sci., 92(9): 4200-4206.

Silver, R.P. and Cohen, S.N. 1972. Nonchromosomal antibiotic resistance in bacteria. V. Isolation and characterization of R factor mutants exhibiting temperature-sensitive repression of fertility. J. Bacteriol., 110(3):1082–1088.

Silver, R.P. and Falkow, S. 1970. Specific labeling and physical characterization of R-factor deoxyribonucleic acid in *Escherichia coli*. J Bacteriol., 104 (1):331–339.

Sirinavin, S. and Dowell, S.F. 2002. Antimicrobial resistance in countries with limited resources: Unique challenges and limited alternatives. Semin. Pediatr. Infect. Dis., 15: 94–98.

Skurray, R.A. and Firth, N. 1997. Molecular evolution of multiple-antibiotic-resistant staphylococci, p. 167-191. *In:* D.J. Chadwick (ed.), Antibiotic resistance: origins, evolution, selection and spread. Wiley, Chichester, United Kingdom.

Sommer, M.O. Dantas, A.G. and Church, G.M. 2009. Functional characterization of the antibiotic resistance reservoir in the human microflora. Sci., 325**:**1128-1131.

Sorensen, S.J., Bailey, M., Hansen, L.H., Kroer, N. and Wuertz, S. 2005. Studying plasmid horizontal transfer in situ: a critical review. Nat. Rev. Microbiol., 3**:** 700-710.

Soulsby, E.J. 2005. Resistance to antimicrobials in humans and animals: Overusing antibiotics is not the only cause and reducing use is not the only solution. BMJ., 331 (7527): 1219–1220. doi:10.1136/bmj.331.7527.1219.

Stead, S., Sharman, J.A., Tarbin, J.A., Gibson, E., Richmond, S., Stark, J. and Geijp, E. 2004. Meeting maximum residue limits: an improved screening technique for rapid detection of antimicrobial residues in animal food products. Food Additives and Contaminants. 21: 216–221.

Strahilevitz, J., Jacoby, G.A., Hooper, D.C. and Robicsek. A. 2009. Plasmid-mediated quinolone resistance: a multifaceted threat. Clin. Microbiol. Rev., 22**:** 664-689.

Szczepanowski, R., Linke, B. , Krahn, I., Gartemann, K.H., Gützkow, T. , Eichler, W., Pühler, A. and Schlüter, A. 2009. Detection of 140 clinically relevant antibiotic-resistance genes in the plasmid metagenome of wastewater treatment plant bacteria showing reduced susceptibility to selected antibiotics. Microbiol., 155**:** 2306-2319.

Tauch, A., Kassing. F., Kalinowski. J. and Puhler, A. 1995. The erythromycin resistance gene of the *Corynebacterium xerosis* R-plasmid pTP10 also carrying chloramphenicol, kanamycin, and tetracycline resistances is capable of transposition in *Corynebacterium glutamicum*. Plasmid., 33(3): 168-179.

Thiam, S., LeFevre, A.M., Hane, F., Ndiaye, A., Ba, F., Fielding, K.L., Ndir, M. and Lienhardt, C. 2007. Effectiveness of a strategy to improve adherence to tuberculosis treatment in a resource-poor setting: a cluster randomized controlled trial. JAMA. 297: 380–386.

Thomas, J.K., Forrest, A., Bhavnani, S.M., Hyatt, J.M., Cheng, A., Ballow, C.H. and Schentag, J.J. (1998). Pharmacodynamic Evaluation of Factors Associated with the Development of Bacterial Resistance in Acutely Ill Patients during Therapy. .Antimicrob. Agents Chemother., 42(3): 521–527.

Tiwari, R., Chakraborty, S., Dhama, K., Wani, M.Y., Kumar, A. and Kapoor, S. 2013b. Wonder world of phages: Potential biocontrol agents safeguarding biosphere and health of animals and humans – Current scenario and perspectives. Pak. J. Biol. Sci., (Available online).

Tiwari, R., Dhama, K., Chakraborty, S., Kumar, A., Rahal, A. and Kapoor, S. 2013a. Bacteriophage therapy for safeguarding animal and human health: A review. Pak. J. Biol. Sci., (Available online). doi: 10.3923/pjbs.2013.

Tiwari, R., Dhama, K., Wani, M. Y., Verma, V., Vaid, R.K. and Chauhan, R.S. 2011. Bacteriophage therapy - a novel tool for combating bacterial diseases of poultry – a review. J. Immunol. Immunopathol., 13(2): 55-66.

Tiwari, R., Hirpurkar, S.D. and Dhama, K. 2012. Therapeutic Potential of Bacteriophages against Pathogenic Bacteria. LAP LAMBERT Academic Publishing, AV Akademikerverlag GmbH & Co. KG, Germany, pp: 1-108.

Toole, M.J. and Waldman, R.J. 1997. The public health aspects of complex emergencies and refugee situations. Annu. Rev. Pub. Health 18: 283–312.

Török, M.E., Chantratita, N. and Peacock, S.J. 2012. Bacterial gene loss as a mechanism for gain of antimicrobial resistance. Curr. Opin. Microbiol., 15: 583-587.

Trakulsomboon, S., Danchaivijitr, S., Rongrungruang, Y., Dhiraputra, C., Susaemgrat, W., Ito, T. and Hiramatsu, K. 2001. First report of methicillin-resistant *Staphylococcus aureus* with reduced susceptibility to vancomycin in Thailand. J. Clin. Microbiol., 39: 591–595.

Turnipseed, S.B., Clark, S.B., Karbiwnyk, C.M., Andersen, W.C., Miller, K.E. and Madson, M. R. 2009. Analysis of aminoglycoside residues in bovine milk by liquid chromatography electrospray ion trap mass spectrometry after derivatization with phenyl isocyanate. J. Chromatography B: Analytical Technol. Biomed. Life Sci., 877(14-15): 1487-1493.

Union of Concerned Scientists 2012. www.ucsusa.org.

Vashney, S., Vashney, P., Dash, S.K., Gupta, M.K., Kumar, A., Singh, B. and Sharma, A. 2012. Antibacterial activity of fruits of *Terminelia chebula* and *Terminalia belerica* against mastitis field isolates. Medicinal Plants. 4(3): 167-169.

Velayati, A.A., Masjedi, M.R., Farnia, P., Tabarsi, P., Ghanavi, J., ZiaZarifi, A.H. and Hoffner, S.E. 2009. Emergence of new forms of totally drug-resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran. Chest. 136**:** 420-425.

von Baum, H. and Marre, R. 2005. Antimicrobial resistance of Escherichia coli and therapeutic implications. Int. J. Med. Microbiol., 295: 503-511

Wachira, W.M., Shitandi, A. and Ngure, R. 2011. Determination of the limit of detection of penicillin G residues in poultry meat using a low cost microbiological method. Int. Food Res. J., 18(3): 1203-1208.

Waksman, S.A. 1973. History of the word 'antibiotic.' J. Hist. Med. Allied Sci., 28**:**284-286.

Walsh, C. 2003. Antibiotics: actions, origins, resistance. ASM Press, Washington, DC.

Walsh, F. 2013. Investigating antibiotic resistance in non-clinical environments. Front Microbiol., 4: 19.

Walsh, T.R. 2006. Combinatorial genetic evolution of multiresistance. Curr. Opin. Microbiol., 9**:** 476-482.

Watanabe, T. 1971. The problems of drug-resistant pathogenic bacteria. The origin of R factors. Ann. N Y Acad. Sci., 182**:** 126–140.

Watanabe, T., Ogata, C. and Sato, S. 1964. Episome-mediated transfer of drug resistance in Enterobacteriaceae 8. Six-drug-resistance R factor. J. Bacteriol., 88: 922–928.

Wegener, H.C., Aarestrup, F.M., Jensen, L.B., Hammerum, A.M. and Bager, F. 1999. Use of antimicrobial growth promoters in food animals and Enterococcus faecium resistance to therapeutic antimicrobial drugs in Europe. Emerg Infect Dis., 5: 329-335.

White, D.G., Alekshun, M.N. and McDermott P.F. (ed.). 2005. Frontiers in antimicrobial resistance: a tribute to Stuart B. Levy. ASM Press, Washington, DC.

WHO 2001. WHO Global strategy for containment of antimicrobial resistance. Geneva, Switzerland: World Health Organization.

WHO 2013. Antimicrobial resistance. www.who.int.

Whyte, S.R., Geest, S.V.D. and Hardon, A. 2002. Social lives of medicines. Cambridge: Cambridge University Press.

Wilmar, D.S. and Tambourgi, D.V. 2010. IgY: A promising antibody for use in immunodiagnostic and in Immunotherapy. Vet. Immunol. Immunopathol., 135: 173–180.

Wilson, M.L. 2011. Recent advances in the laboratory detection of *Mycobacterium tuberculosis* complex and drug resistance. Clin. Infect. Dis., 52(11): 1350-1355.

Witte, W. 2004. International dissemination of antibiotic resistant strains of bacterial pathogens. Infect. Genet. Evol. 4: 187-191.

Woodford, N. and Sundsfjord, A. 2005. Molecular detection of antibiotic resistance: when and where? J. Antimicrob. Chemother., 56(2): 259-261.

World Health Organization 2006. Global tuberculosis control: WHO report. Geneva: the Organization; WHO/HTM/TB/2006.362.

Wright, G. D. 2010. Antibiotic resistance in the environment: a link to the clinic? Curr. Opin. Microbiol., 13(5): 589–594.

Wright, G.D. 2007. The antibiotic resistome: the nexus of chemical and genetic diversity. Nat. Rev. Microbiol., 5**:** 175-186.

www.dairysafevic.gov.au.

www.usda.gov.

Xie, P., Joshua, G., James, R.C., Akinori, O. and Boger, D.L. 2011. A Redesigned Vancomycin Engineered for Dual d-Ala-d-Ala and d-Ala-d-Lac Binding Exhibits Potent Antimicrobial Activity against Vancomycin-Resistant Bacteria. J. Am. Chem. Soc., 133(35): 13946–13949.

Yassin, A. and Mankin, A.S. 2007. Potential new antibiotic sites in the ribosome revealed by deleterious mutations in RNA of the large ribosomal subunit. J. Biol. Chem., 282**:** 24329-24342.

Yegani, M. and Korver, D.R. 2007. Application of egg yolk antibodies as replacement for antibiotics in poultry. World Poultry. 23(5): 22-25.

Yeh, P.J., Hegreness, M.J., Aiden, A.P. and Kishony, R. 2009. Drug interactions and the evolution of antibiotic resistance. Nat. Rev. Microbiol., 7: 460-466.

Zengel, J.M., Young, R., Dennis, P.P. and Nomura, M. 1977. Role of ribosomal protein S12 in peptide chain elongation: analysis of pleiotropic, streptomycin-resistant mutants of *Escherichia coli*. J. Bacteriol., 129: 1320-1329.

Zhang, R., Eggleston, K., Rotimi, V. and Zeckhauser, R.J. 2006. Antibiotic resistance as a global threat: evidence from China, Kuwait and the United States. Global Health. 2: 6.

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