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Review

Fate and Transport of Antibiotics and ARG's in the Agri-food System

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Antibiotics and agriculture are both essential for life. Antibiotics are used in humans, animals and plants for disease control and cure and agriculture provide food for the world. Antibiotics have long been used in agriculture for as long as they have been available to farmers. The use of antibiotics in agriculture has by several works of literature and research said to be counterproductive. The transport and fate of antibiotics in the food ecosystem poses a threat of induced antibiotic resistance genes and antibiotic-resistant bacteria which is a major environmental and health issue. This review article discusses the accumulation of findings that address aspects of fate and transport with emphasis on the Agri-food system.

Keywords: Antibiotics, Antibiotic resistant bacteria, Antibiotic resistant genes

INTRODUCTION

Antibiotics have been a wonder discovery to the world. An estimation of 100,000 to 200,000 tons of antibiotics are consumed yearly worldwide. In total, the antibiotic consumption within 2000 and 2010 increased over 30 percent from an estimation of 50 billion to about 70 billion standard units (Van Boeckel et al., 2015). Antibiotic consumption in 2010 was topped by India, China and the United States of America, consuming 13, 10 and 7 billion standard units respectively. Nevertheless, the United States led in terms of individual consumption same year (Van Boeckel et al., 2015), with 11 and 15 SU per individual more than India and China. Fleming after discovering penicillin was the first to caution the resistance of antibiotics if used too little or for a too short period of treatment (Aminov, 2010).

Bacteria resistance to antibiotics is a great threat to human health (WHO, 2014). An estimation of about 700,000 people die from antibiotic-resistant infections and further estimations suggest another 10 million will die each year by 2050 if no action is taken (Withnall, 2016). In the United States, there is an antibiotic-resistant bacteria infection of about 2 million according to the Center for Disease Control and Prevention (CDC) causing about 23,000 to die yearly (CDC, 2018). Microbial opposition to

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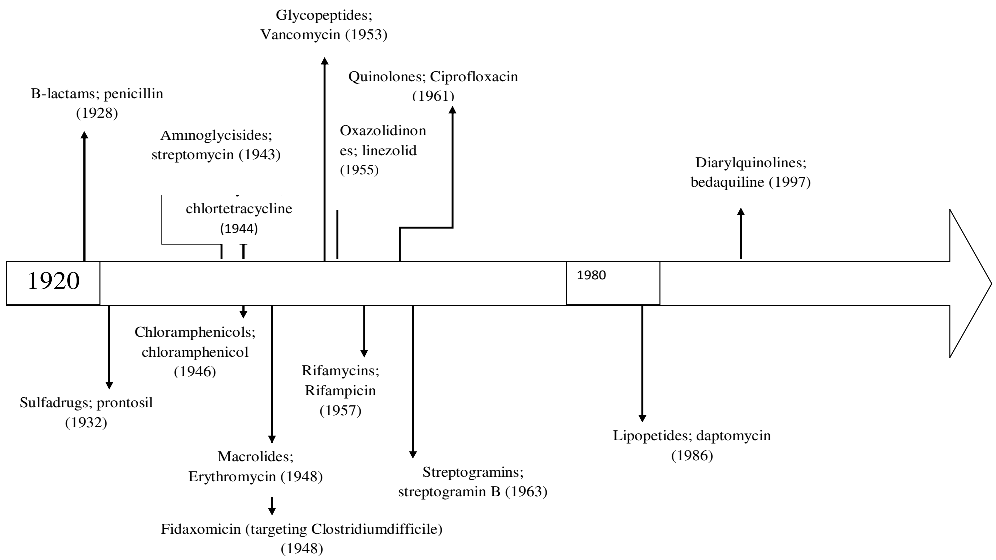

Figure 1. Diagram showing the timeline for antibiotics discovery

antibiotics is a global threat hence there is a need for a global strategy to combat its increase. According to Hicks et al., (2010), 258 million courses of antibiotics were prescribed in the United States at a frequency of 833 prescriptions per 1000 persons (Hicks et al., 2013). Meanwhile not all antibiotics fed to humans and animals are absorbed, most are passed out as waste (Chee-Sanford et al., 2009 and Pruden et al., 2006). Likewise, individuals flush unutilized antibiotics down toilets, wastes generated by health facilities are inappropriately discarded and septic spills deposits residuals of antibiotics into the soil, water bodies and groundwater contributing to antibiotics and ARG's build up in the environment.

Agri-foods are foods obtained from agricultural sources. Food is any nutritious substance that individuals or animals eat so as to keep up life and development (Fao.org, 2003). Agriculture is the fundamental source of food for earth's population (Fao.org, 2003). Various opinion papers, reviews and reports have come up to address the conceivable connection between the use of antibiotics and the development of resistance in agri-foods and the world as a whole. This article amasses discoveries that address the current scenario regarding antibiotics, antibiotic resistance, antibiotic resistance genes (ARG's), sources of antibiotics in the environment, sources of antibiotics and ARG's in Agri-food, pathways of antibiotics and ARG 's in food, fate and implications of antibiotics and ARG 's, and suggestions to help with its remediation.

Antibiotics

They are substances produced either entirely or partly by microorganisms and are used "originally" for the treatment and or prevention of bacterial infections (Bouki et al., 2013; Ashbolt et al., 2013; Ding and He, 2010). Structurally they are classified into groups such as aminoglycosides, tetracyclines, β-lactams, sulfonamides. They have different modes of attacking bacteria but are mostly classified as being able to terminate (bactericidal) or slow the growth (bacteriostatic) of the target bacterial population provided they are optimally dosed (Roose-Amsaleg and Laverman, 2016). They can be attained from natural or unnatural sources. Apart from their use in the treatment of infections, antibiotics have been hugely integrated into livestock farming, example swine (Sus scrofa) production since the early 1950s (Cromwell, 2001) and as fodder additives and growth promoters (Cromwell, 2001; Bouki et al. 2013; Aminov, 2009). Although still practiced in most countries including the United States, the use of antibiotic as agents of development in animals has been discouraged by various international bodies including the European Union (Como et al., 2014).

Figure 1. Diagram showing the timeline for antibiotics discovery

Antibiotic Resistance

How antibiotics encode resistance mechanisms differ from one to the other. It is dependent on the modes of action, structures, and biochemical properties. Naturally some bacteria are resistant to certain types of antibiotics. When germs like bacteria and fungi are not killed by the drugs designed to kill them and continue to grow, antibiotic resistance is said to have occurred. Antibiotic resistance most commonly evolves in bacteria either through mutation of a target-site protein, through the acquisition of an antibiotic-resistance gene (ARG) that confers resistance through efflux or inactivation of the antibiotic, or through synthesis of a new target protein that is insensitive to the antibiotic (Emerald.tufts.edu, n.d.; Davies et al., 2010). Antibiotic resistances have been on a consistent increase and pose a great treat to the world as a whole. Reportedly, the increase in resistance is compounded by wrong use and improper disposal of antibiotics and antibiotic-containing wastes in the environment originating from human activity (Auerbach et al., 2007; Martinez, 2009; Pruden et al., 2012). Against mild coughs and the common cold antibiotics are typically ineffective hence adds to the growing global resistance to antibiotics (CDDEP, 2015). Contributing to the increase of ARG's in the environment is the global rise in population which has resulted in the intensification antibiotics use in the agri-food system such as food animals, crops and fruits. A typical example is avoparcin, a glycopeptide related to the human last line drug Vancomycin, is used in Australia as a growth promotion in pigs, chickens and feedlot cattle. (Abc.net.au, n.d.). This increase in usage also drives up antibiotic resistance. The prevalence of sepsis from 621,000 to 1,141,000 and number of deceased patients from 154,000 to 207,000 between the years 2000 and 2008 is another indication that global antibiotic resistance is on the rise (The Economist, 2016).

Antibiotic Resistance Genes (ARG's)

ARG's are internal or external segments of a DNA that encode enzymes and other proteins which moderate the opposition of antibiotics by bacteria. Roose-Amsaleg & Laverman (2016) summarized antibiotic resistance mechanisms in three categories: 1. Efflux of antibiotics; 2. Destruction of the active ingredient of the antibiotic and 3. Modification of the target structure via cell reprogramming. Genetically, antibiotic resistance spreads through bacteria populations both "vertically," and "horizontally," through conjugation; through viruses (Emerald.tufts.edu, n.d; Grenni et al., 2018; Aminov and Mackie, 2007; Baquero et al., 2008; Frost et al., 2005; Marti et al., 2014), bacteria locomotion, air, water and wind. Horizontal gene transfer can also occur between different bacterial species (Emerald.tufts.edu, n.d.) and horizontal gene transfer by conjugation is common in nature, or in technical systems, where the density of bacteria is high (Kalmbach et al., 1997 and Schwartz et al., 1998). Resistance can occur naturally, example Aeromona hydrophila is naturally resistant to ampicillin (Korzeniewska and Harnisz, 2012) and although resistance is widespread, not all bacteria are resistant to antibiotics. Additionally, resistance can be acquired from other resistant genes; it could also be as a result of aggregation of factors such as phenotypic responses (Como et al., 2014).

Sources of antibiotics in the environment

The use of antibiotics is increasing rapidly for initial treatment and as drugs of last resort in humans. Antibiotics use is the basic and major avenue of antibiotics in the environment. Various researches have shown after been taken as medication, most antibiotics are unused and released back into the environment as faeces and urine (Daghrir and Drogui 2013, Chee-Sanford et al., 2009 and Pruden et al., 2006). Research has shown high earning countries use more antibiotics per capita than middle and low income earning ones and even with proper use antibiotics still find their way into the environment. Crop fields are often fertilized by animal fertilizer prompting direct contamination of the environment and antibiotic buildup, Urban wastewater has been shown to contain antibiotic residues and antimicrobials can also be contributed to the environment via land application of municipal biosolids (Kumar et. al. 2005) or the direct use of wastewater irrigation (Shi et. al. 2013). Not all antibiotics break down upon entering the environment; some persist and have been found in the soils and rivers (Michael et al. 2013). The process and site for antibiotics production is also a factor contributing to the release of antibiotics into the environment. Residue from production sites can reach extreme high concentrations.

Sources of antibiotics and ARGS in Agri-food

Antibiotic resistance in food can be from either point source or non point source. Point sources are pollutions with a solitary distinguishable source (Armon and Starosvetsky, 2015) such as injection and feeding, non point source on the other hand refers to pollutions without a distinct source such as land runoff and septic tank seepage that disperse over wide areas. The exponential growth in population and prosperity pushes an increasing demand for food and to satisfy this need, farmers are transitioning to intensive agriculture and often use antibiotics to optimize production.

Antibiotics in meat

Antibiotics have been an integral part of food animal management for as long as they have been readily available to farmers. Antibiotics are used regularly in the livestock industry as growth promoters, for disease prevention, or as part of therapeutic treatment (Apley, 2012). Apart from being used as a prevention for diseases and prevention of infections, antibiotics are used as growth promoters and this has generated a lot of intense discussions regarding the high-use application of antibiotics. Worldwide consumption of antibiotics in 2010 by livestock according was at least 63,200 tons (Van Boeckel et al., 2015); this is bound to be same or more than all human utilization around the same time. A projection of 25,446 kg and 131,862 kg of antibiotics lincomycin and oxytetracycline are used by the swine industry in the United States of America per year (Apley, 2012), these alarming figures shed more light on how antibiotics and the meat industry are intertwined. Research has shown that not only is about 95 percent of antibiotics used by both humans and animals are excreted in an unaltered state. (Pruden et al., 2006) There are multiple microorganisms in the intestines of animals (Ferrer et al. 2017), which are likely to grow resistant to antibiotics when they are introduced frequently (Zhu et al., 2013) most of which can be transmitted between animals and humans (Aminov, 2009; Bouki et al., 2013; Liu et al., 2016; Witte, 2000; Mena et al., 2008; Diarrassouba et al., 2007). A 2013 study by Spoor et al showed that a bovine strain called CC97 had made two separate leaps to humans. There may be a lot more cross-species transmission than we anticipated.

Antibiotics in fish

Compared to the need for any other animal produce aquaculture produce is increasing faster (Fao.org, 2003). In 2010 State of World Fisheries and Aquaculture, the FAO said Aquaculture and fisheries was evaluated to have provided the world with around 110 million metric tons of food fish (FAO, State of World Fisheries and Aquaculture 2010). To meet this need the sector has turned to drastic methods which in turn has made antibiotics use in the sector a norm (Defoirdt et al., 2011) in spite of not having accurate information on dosage and use. The doses of antibiotics used in aquaculture cannot easily be known owing to the fact there are differences in how countries distribute and collate such information. Primarily antibiotics are used in aquaculture to nurse and or fend off diseases and the mode of application is either by direct injection or feed, they can also get into aquaculture systems by agriculture runoff. Treating a whole populace of fish regardless of whether just a couple is sick is a routine in aquaculture (Towers, 2014). With the explosive demand for farmed seafood the use of antibiotics in the fish industry is one that is still in its early stages. A study of fishes from 11 countries found residues of five antibiotics, some of which are also used to treat human diseases including residues of a kind of tetracycline (Oaklander, 2014). Fishes like animals do not make use of all antibiotics fed to it and excretes about 75 percent (Burridge et al., 2010) into its environment causing a possibility of leakage into ground water.

Antibiotic in plants

The use of antibiotics as growth promoters in animals (Como et al., 2014) and waste from intensive animal farming (Li et al., 2013; Martínez-Carballo et al., 2007; Motoyama et al., 2011) is a major source of antibiotics in the soil. In a 2002 paper Hamscher et. al. found soil remedied with liquid manure to have as high as 198.7 µg/kg tetracycline, further supporting the notion that antibiotics have the ability to retain in the environment.

Residual antibiotics in animals can create the avenue of ARGs to develop in the gastrointestinal tract and subsequently in the environment upon land application of manure (Chee-Sanford et al., 2009 and Heuer et al., 2011). The increasing use of recycled waste water for irrigation (Toze, 2006), together with close to 50 percent of biosolids been used as nutrients in fields (Kinney et. al. 2006) show how easy it is for planting fields and crops to be introduced to antibiotics and residual antibiotics. Also plants get introduced to antibiotics when they are spayed onto or injected into them, examples are the use of Oxytetracycline on peach, nectarine, pear and apple (McManus and Stockwell 2000) and the injecting of tetracyclines into the trunks of palm and elm (Agrios 1997). Furthermore, it is well researched that antibiotics and antibiotic resistant genes are used in genetic modification of plants and seeds as marker genes for the selection of transformed plant cells, a topic that has given rise to many concerns on if such practices lessen the treatment ability of antibiotics. The possible effects of reduction in the effectiveness of antibiotics have been the subject of many scientific and opinions papers, examples are Ramessar et al., (2007) and EFSA, (2009). The European Food Safety Authority (EFSA) issued opinions in 2004 and 2009 on using antibiotic resistance genes as marker genes in genetically modified plants saying a careful approach to the use of Antibiotic Resistance Marker Genes in GM plants should be looked into (EFSA. 2004, EFSA. 2009).

Pathways of antibiotics and ARG's in food

Pathway refers to how an antibiotics move from the source and enters into the agri-food environment. Detection of antibiotics in the environment has been well documented over the years by researchers. Antibiotics get into the agri-food environment through diverse pathways. A major pathway is the agricultural pathway where antibiotics used as part of farm management practices end up in food. Practices including feeding, nursing and or treating livestock with antibiotics, the use of liquid and solid waste as manure and the use of waste water for irrigation have all been researched to contribute majorly to how antibiotics get into the agri-food environment. Hamscher et al., (2002) found soil amended with liquid manure to have excessive amounts of tetracycline as high as 198.7 µg/kg tetracycline. The agricultural pathway also includes agricultural run offs, leakage in agricultural lagoons. Accumulation of antibiotics in agricultural wastewater, specifically in lagoon holding basins has been reported in concentrations at the mg/L level (Campagnolo et al., 2002, Zilles et al., 2005 and Bartelt-Hunt et al., 2011). Ionophore antibiotics have been detected in areas of Colorado representing pristine, urban, and agricultural environments. Ionophores are not approved for use in humans, thus highlighting the widespread contribution of the agricultural pathway (Kim et. al. 2006).

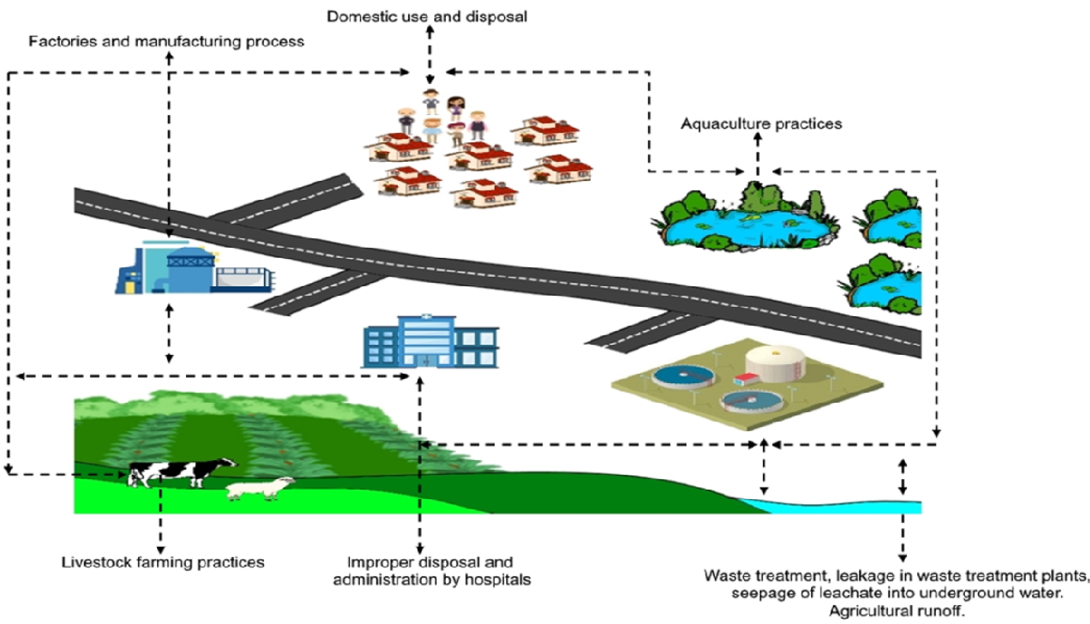

Figure 2. Various Sources of Antibiotics and ARGs in Agri-food

The anthropogenic pathway includes all human activities that result in the release of antibiotics and ARGs into the agri food eco system. These include poor handling of food and the improper disposal and use of antibiotics .Improper disposal is a prevalent way of how antibiotics end up in the agri food system. They end up in the soil or waste water which is primarily the need of agriculture. Verlicchi's paper of 2012 reported on a number of antibiotic compounds detected in wastewater treatment throughout the waste treatment process. In 2010 alone, 258 million courses were prescribed in the US at a frequency of 833 prescriptions per 1000 persons (Hicks et. al. 2013).

The industrial pathway

The process of making antibiotics also contributes to antibiotics in the agri-food ecosystem. The transport, disposal and treatment of waste emanating from such facilities can be made up of high concentrations of antibiotic residue (Kümmerer et al., 2000; Karthikeyan and Meyer, 2006). Several researches have touted industries as a source of antibiotic contamination of waterbodies and undergrounds waters. In Patancheru India Fick et al., reported ground water contaminations in low quantities (Fick et al., 2009). Likewise Larsson et al., identified a wastewater plant was offloading about 45 kg (99 lbs.) of antibiotics received from industries into rivers close by each day (Larsson et al. 2007). Even when treated, concentrations exceeding 1 mg/L have been detected in treated industrial effluents or recipient waters (Larsson et al., 2007 and Sim et al., 2011).

Figure 2. Various Sources of Antibiotics and ARGs in Agri-food

Fate and implications of antibiotics and ARG's

The greatest concern about antibiotics in the agri-food environment is their potential role in promoting resistance development in human and animal pathogens. Once in the environment antibiotics persist (Baquero et al., 2008; Berendonk et al., 2015; Vittecoq et al., 2016) and pose a detrimental treat to people and animals (Ashbolt et al., 2013). Treatment failure, prolonged illnesses, increased death rates and high monetary expenses to society are all implications of antibiotics and ARG's (Friedman et al., 2016). The therapeutic properties of antibiotics are a great resource to the world and one that should be kept pristine. Without global action, the implied economic cost of drug-resistant infections would be at least USD 100 trillion and could cut the annual world's GDP by 2 - 3.5% by 2050 (Kolb, 2017). Agriculture uses lakes ponds and ground water for animals and irrigation purposes. Humans likewise drink from streams and underground water sources. Both surface water (Murata et al., 2011; Ding et al., 2017) and underground water sources (Avisar et al., 2009; Yao et al. 2017; Araujo et al. 2017) have been identified in most areas to be contaminated by antibiotics and antibiotic resistant genes. Recent findings in the US and Germany found in excess 15 different types of antibiotics in streams receiving urban and industrial wastewaters and or runoff from agricultural practices (Ternes et al., 2002; Kolpin et al., 2002). In the event when such water is used for

Table 1. Timeline for various antibiotic resistant genes

Antibiotic Class	Example	Class Discovered	Resistance Identified	Mechanism of Action	Notes	Reference
Penicillins	Penicillin Cephalosporin Carbapenem monobactam	1928	1940	Inhibit cell wall synthesis	First antibiotic, discovered by Alexander Fleming.	Abraham et al., 1940
Aminoglycosides	Gentamicin Amikacin Tobramycin Netilmicin streptomycin	1943	1946	Inhibit protein synthesis	Streptomycin was the subject of the first ever randomized medical trial, run by the MRC.	Encyclopedia Britannica Online, 2018
Cephalosporins	Cefalexin	1945	1956	Inhibit cell wall synthesis	Most cephalosporins are excreted primarily in urine, so their doses must be adjusted in patients with renal insufficiency.	Werth, 2018
Tetracyclines and Glycylcyclines	Tetracycline Tigecycline Doxycycline Minocycline	1948	1953	Inhibit protein synthesis	Human cells do not allow tetracycline's to be transported hence are spared the effects of tetracycline on protein synthesis	Encyclopedia Britannica Online., 2018
Macrolides	Azithromycin Telithromycin Erythromycin clarithromycin	1948	1956	Inhibit protein synthesis	Macrolides are not to be used on non-ruminant herbivores, such rabbits. They rapidly produce a reaction causing fatal digestive disturbance.	Giguere et al., 2006
Fluoroquinolone	Ciprofloxacin Norfloxacin Levofloxacin moxifloxacin	1978	1985	Inhibit DNA gyrase	In 2018, the U.S. FDA stated Concerns regarding low blood sugar and mental health problems	U.S FDA, 2018
Glycopeptides	Vancomycin Teichoplanin Telavancin	1953	1986	Inhibit cell wall synthesis	Glycans on cell surface attached to membrane proteins and those bound to proteins play a critical role in inflammation	Maverakis et al., 2015

irrigation antibiotics are introduced to fruits and crops and further transferred into humans and animals when they feed on such fruits and crops. A safer approach will be to use treated water. Meanwhile Verlicchi et al. (2012) found antibiotic compounds in wastewater treatment throughout the waste treatment process implying a possibility that some antibiotics may survive the treatment and make it to various homes and agricultural sites. Animals exposed to antibiotics develop resistant genes to antibiotics over time, the resistant bacteria subsequently proliferate the animal Resistant genes are carried on to others animals as the animals interact, further colonizing the animal thriving well in the intestines and muscles (www1.udel.edu, n.d.). Using such animals for food by other animals or humans makes them susceptible to a host of diseases with the potential of lives been lost. Sepsis majorly is due to antibiotic resistant bacteria (Antibiotic Research UK, n.d.)and is responsible for one out of five deaths in newborns in India, Pakistan, Afghanistan, Nepal, Bangladesh (Bhutta Z. n.d), accounts for more deaths than lung cancer (35,000) and bowel cancer (16,000) (Antibiotic Research UK, n.d.). Antibiotic resistant bacteria each year cause more than 23,000 deaths in the USA, 38,000 deaths in Thailand, and over 25,000 deaths in the European Union (Phumart et al. 2012, CDC 2013 and ECDC/EMEA 2009). Studies from Tanzania and Mozambique indicate that resistant infections result in increased mortality in neonates and children under five (Kayange et al. 2010; Roca et al. 2008). The W.H.O and the Infectious Disease Society of America (IDSA) in their report stated older antibiotics are fast becoming less effective as a result of antibiotic resistance and some bacteria already been resistant to all available antibiotics (WHO 2018 and Boucher 2013). According to the W.H.O fifty-one new therapeutic entities antibiotics (including combinations), are in phase 1-3 clinical trials as of May 2017 (WHO, 2017), but the bigger question is how long are they going to hold their therapeutic properties.

CONCLUSION AND SUGGESTIONS

Antibiotics though useful, when accumulated in the environment gives rise to ARG's and have detrimental effects. Researches indicate antibiotics accumulate in Agri foods which are later consumed by humans and animals and these have serious social and health implications. Antibiotics use cannot be stopped outright. However, strategies such as reducing the need for antibiotics through improved water, sanitation, and immunization; Pharmaceutical companies directing their effort and funding equally to antibiotics as to chronic illnesses; regulating practices which introduce sub-optimal concentrations of antibiotics in various agricultural and environmental systems; researching into vaccine developments to lessen farmers dependency on antibiotics and lastly, giving more education on the uses dosage and administration of antibiotics will go a long way to help curtail the situation.

Conflict of interest

The authors of this work solely declared no conflict of interest.

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