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Review

The agri-food chain and antimicrobial resistance: A review

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ABSTRACT

Background: Antimicrobial resistance is becoming a major threat to public health and there is much current activity to ameliorate that threat. However, the relative contributions that potential sources of antimicrobial resistant (AMR) bacteria represent are not well established. Over-prescription of antimicrobials by clinicians is one source of selection for AMR bacteria/genes, but antimicrobials are used in greater quantities in food production. These bacteria/genes can then reach humans via food, the environment, or other means.

Scope and approach: Summarised in this review are potential transmission routes of AMR bacteria/genes from agricultural production to human infections. The situation is complicated, and it is difficult to compare studies because of different methodologies and definitions of resistance being used. Data and examples to illustrate each transmission route are provided where available.

Key findings and conclusions: Quantitative data for defined organism/phenotype/gene combinations for exposure assessment are rare. Another problem is the identification of indistinguishable AMR bacteria in foods and human cases, which is invariably taken to show that food consumption is a source of infections. However, these data do not show the direction in which the flow of the organism/gene occurred nor do they rule out another source(s), and such data are scant. Case control studies could identify food exposures associated with particular organism/gene infections. The construction of models representing potential transmission pathways may help to reveal their relative contributions. However, the data may not be available to support these models. The lack of coherent data hampers the development of effective policy.

1. Introduction

The discovery and introduction of antibiotics prior to the Second World War marked a pivotal point in the ability of humanity to combat bacterial infections. Formerly life-threatening infections became easily treatable, although the oft-quoted comment by a US surgeon general "it is time to close the book on infectious diseases, and declare the war against pestilence won" appears to be an urban myth (Spellberg & Taylor-Blake, 2013). However, ever since the discovery of antibiotics, the phenomenon of antimicrobial resistance (AMR) has been recognised (Davies & Davies, 2010) and in 1945 Sir Alexander Fleming warned of the potential for AMR to become a public health threat "then there is the danger that the ignorant man may easily under dose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant".[2] Of concern is the fact that AMR can readily be transmitted from bacterium to bacterium on segments of DNA by several means including phages, transposons and plasmids, so resulting in horizontal gene transfer (HGT) (Djordjevic, Stokes, & Chowdhury, 2013). The three predominant processes at play include "the emergence, invasion and occupation" (Baquero, Lanza, Cantón, & Coque, 2015) of environments, this process involving mobility in both bacteria and the genes themselves. HGT has been shown to occur in the environment, food (Jahan & Holley, 2016) and the gastrointestinal tract. These environments also act as reservoirs of AMR genes - the "resistome" (Forsberg et al., 2012). A previous

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[2] http://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-lecture.pdf.

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Table 1
A taxonomy of antimicrobial families.

Major group	Sub groups	Site of action	Examples
β-lactams	Penicillins	Cell wall synthesis	ampicillin, methicillin, penicillin G, amoxicillin
	Cephalosporins		1st generation: cefalothin, cefalonium 2nd generation: cefuroxime 3rd generation: cefotaxime, ceftriaxone, ceftiofur, ceftazidime 4th generation: cefquinome
	Monobactams		aztreonam
	Carbapenems		ertapenem, imipenem, meropenem
Aminoglycosides		Protein synthesis	kanamycin, streptomycin, tobramycin, gentamicin, neomycin, amikacin,
Sulphonamides		Folic acid synthesis	sulphonamide, sulfamethoxazole, sulfamethazine, sulfamerazine, sulfadimethoxine
Quinolones/ Fluoroquinolones		DNA synthesis	enrofloxacin, ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, nalidixic acid, flumequine, pefloxacin
Macrolides		Protein synthesis	azithromycin, clarithromycin, dirithromycin, erythromycin, azithromycin, clindamycin, tylosin, spiramycin, carbomycin, oleandomycin, kitsamycin, tiamulin
Polypeptides		Cell membranes	colistin, polymixin B, bacitracin
Other:			
Glycopeptides		Cell wall synthesis (Gram + ve)	avoparcin, vancomycin, teicoplanin, ardacin
Rifampin/Rifampicin		RNA synthesis	
Linezolid		Protein synthesis (Gram + ve)	Tetracycline, doxycycline, oxytetracycline, chlortetracycline
Tetracyclines		Protein synthesis	
Trimethoprim/ sulfamethoxacole		Folate synthesis	
Coccidiostats		Ionophore	Lasolacid, monensin, salinomycin, narasin. Not used in human medicine.
Streptograminins		Protein synthesis	virginiamycin, quinupristin, dalfopristin (last two combined = synercid)

review, published in 2013, focused on the impact of food processing on the transfer of antimicrobial resistance to humans (Verraes et al., 2013). The current review has a broader focus as the entirety of the agri-food production chain is considered.

The emergence of AMR in clinically important bacteria has continued at the same time as the pipeline of new antibiotics has dwindled to the point where phrases such as "we are in the midst of an emerging crisis of antibiotic resistance for microbial pathogens in the United States and throughout the world" are appearing in the literature. There are claims that AMR infections have been increasing, for example for *Salmonella* (Su, Chiu, Chu, & Ou, 2004), but the data are patchy, complex and come from countries with different surveillance systems. A recent report from Canada indicates currently stable and, in some cases, decreasing incidences of AMR infections (Public Health Agency of Canada, 2016). In the UK the number of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia cases reduced by 81% from 2007/8 to 2012/13 but, in contrast, the number of isolates of carbapenemase-producing *Enterobacteriaceae* increased approximately ten fold between 2009 and 2014 (Department of Health antimicrobial resistance strategy analytical working group, 2016). This group of organisms is rated as "Priority 1: critical" for development of new antibiotics.[3] A similar increasing trend has been identified for *Klebsiella pneumoniae* in wider Europe, and resistance to third generation cephalosporins in *Escherichia coli* is also increasing (European Centre for Disease Prevention and Control, 2016). A comparison between the USA, Kuwait and China between 1994 and 2000 found a growth in AMR infections of 6, 17 and 22%, respectively, over the period. Looking to the future the "O'Neill report" predicts 10 million lives lost per year in 2050 because of AMR bacteria (O'Neill, 2016).

The term "antimicrobial" has a number of meanings, but in this review it is taken to mean antibiotics (small compounds produced by one organism that kills or inhibits another) and their chemical derivatives. There are many such chemicals and a categorization with some examples is provided in Table 1.

2. Development and transmission of AMR bacteria in agri-food settings

2.1. Use of antimicrobials in the agri-food chain

Antimicrobials are used for various purposes in animal production: 1) therapeutic treatment of diseased animals, 2) growth promotion, 3) treating a group of animals to combat disease in a proportion of them and to prevent disease from occurring in the rest (metaphylaxis) and, 4) use during periods of high susceptibility to infections (prophylaxis). Of these, the use of antimicrobial growth promoters (AGPs) has been banned in the EU since 2006 (http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32003R1831), and the cessation of AGP use is frequently suggested in the literature as a means of reducing or stabilising AMR bacteria. In the US medically important antimicrobials which are used in feed or water stopped being available over the counter at the end of 2016.[4] The benefits of using AGPs are not clear and might only be realised when sub-optimal hygiene conditions prevail (Rushton, 2015), or at early stages of production, although Hao et al. (2014) report data tending to show increased productivity with AGP use. An evaluation of the use of AGPs in less affluent countries concluded that there would be "negligible effects in these countries" at the national level on pork and chicken production if the use of AGPs were to be discontinued (Angulo, Collignon, Wegener, Braam, & Butler, 2005). The reasons for this included likely small decreases in production resulting from cessation of use of AGPs and the minor contribution that meat protein makes to the diet of the poor, although this is increasing in many low to middle income countries for those with increasing disposable income. A study of

[3] http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf.

[4] https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm507355.htm.