The Importance of a One Health Approach to Preventing the Development and Spread of Antibiotic Resistance

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Abstract Antibiotic resistance is a continuing and growing problem. Antibiotic resistance causes increased deaths, complications, expenses and prolonged hospital stays. There are not likely to be many new classes of antibiotics becoming available in the next few decades. We need to take a "One Health" perspective to this problem. We need to preserve the usefulness of those antibiotics we currently have by decreasing their overall use in all sectors, and especially the use of broad spectrum agents. We also need to improve our ability to prevent infections and the spread of resistant bacteria wherever they arise or are found. This means improving our practices with infection control, hygiene and animal husbandry. We need to improve the development and the delivery of effective and safe vaccines to prevent infections. We need safe water supplies. Our failure to do this has already resulted in large numbers of people entering a "post-antibiotic era" for many common infections.

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1 Introduction

The ever increasing problem of antimicrobial resistance demonstrates why the concept of "One Health" is so vital. This concept helps us to better understand why the problem of antimicrobial resistance is currently so pervasive and then to understand how we should best intervene to improve the situation.

Antibiotic resistance is growing at an ever increasing rate in almost all bacterial species that cause disease in people and animals. There is also little prospect that any new class of effective drugs will be developed and become available to use in the next 10 years to treat serious infections caused by these resistant bacteria. We are now seeing more and more people die with common infections that were easily treatable with effective antibiotics 20 years ago. This is a growing pandemic (Carlet et al. 2011).

For many people around the world, particularly those in developing countries, they have already returned to the preantibiotic era because of rising resistance in some of the most common bacteria causing serious bacterial infections in people, e.g. *Escherichia coli*. An ever increasing proportion of these infections are now untreatable. For many infections caused by *E. coli* in countries such as India and China, there are no longer any readily available and effective oral therapies. Even when people are able to afford and access hospital care, no effective injectable antibiotics may be available. Unfortunately, there continues to be dramatic rises and spread of resistant bacteria—more recently Gram-negative strains resistant to broad spectrum cephalosporins and carbapenems (Kumarasamy et al. 2010; Walsh et al. 2011).

Antimicrobials are essential drugs. They are needed to maintain the health and welfare of people. In people, serious bacterial infections remain common and include bloodstream infections, meningitis, pneumonia and peritonitis. In the era before antibiotics, blood stream infections with *Staphylococcus aureus* and *Streptococcus pneumoniae* were associated with mortality rates of over 80 % (Finland et al. 1959). Antimicrobials are also important for animal health. Antimicrobial drugs are not effective against resistant bacteria.

The antibiotics last century was correctly hailed as "miracle drugs". Their development and use quickly led to dramatic decreases in the mortality and morbidity rates of common life-threatening bacterial infections. These dramatic observed affects, however, had a major downside—the continuing massive overuse of antibiotics in both people and in food animals. This overuse was also of poor efficacy. In people, most antibiotic use is mainly for conditions where the benefits are either nonexistent or marginal (e.g. viral infections, bronchitis, etc.). However, the majority of antibiotic volumes used in the world continue to be used in food animals. In contrast to people this antimicrobial use is not for the therapeutic use of individual sick animals. The vast majority of use of antimicrobials in food animals (when usage can be measured) continues to be for growth promotion and for mass prophylaxis.

Antibiotic resistance is harmful and associated with worse outcomes. Serious infections caused by resistant bacteria do not respond as well to therapy and are associated with higher mortalities and prolonged hospital stays (Carlet et al. 2011; Cosgrove et al. 2003; de Kraker et al. 2011; Klevens et al. 2007; Tumbarello et al. 2010; Wang and Chen 2005).

1.1 What are the Consequences of Antimicrobial Resistance?

For people infected with resistant bacteria there are many additional problems;

- Antibiotics need to be used are often much more expensive (e.g. linezolid compared to ampicillin to treat enterococcal infections).
- Antibiotics that need to be given intravenously instead of orally (e.g. for *E. coli*, meropenem instead of oral amoxycillin).
- Antibiotics with lower intrinsic activity need to be used (e.g. vancomycin compared to flucloxacillin to treat resistant *S. aureus* infections).
- There may be in the future no antibiotic available for them that is active against the bacteria causing their infection.

These factors result in

- increased deaths,
- increased complications,
- additional expenses,
- prolonged hospital stays,
- additional toxicity and
- the need to for intravenous therapy rather than oral therapy.

In food animals the consequences are similar (although the examples will be different).

1.2 One Health, the Environment and Antimicrobial Resistance

Wherever antibiotics are used, resistant bacteria eventually develop and spread. This occurs both with people and animals. These resistant bacteria spread from person to person, animals to animals, people to animals and animals to people. They contaminate waterways when excretions or waste from either people or animals enters these waterways. They also are found frequently in food produced from animals that have received antibiotics. Slaughter processes and distribution networks result in cross contamination of many food products with resistant bacteria.

The extensive use of antimicrobials in all sectors (human and agriculture) means these drugs are often also found in the environment, especially in waterways and soils where bacteria are then again exposed to these drugs, often in low concentrations. Antibiotics are commonly used in aquaculture and in horticulture (e.g. gentamicin and streptomycin to spray apples). This results in much easier ingress of residual antibiotics used into waterways (Diwan et al. 2010; Mayerhofer et al. 2009; Zhou et al. 2011).

People and animals often come in contact with or ingest resistant bacteria because exposure to them is so widespread. If water and/or foods have antibiotic residues in them, then people and animals also ingest these residues. Acquired resistant bacteria are frequently carried by people and animals. These bacteria are then often reexposed to more antibiotics. A positive and very harmful feedback loop then results that leads to very high rates of resistant bacteria being found in many people and animals (or their products e.g. foods).

All sectors (people, animals and the environment) are directly and indirectly interconnected. A "One Health" approach to the problem of antimicrobial resistance means interventions will be better targeted against the complete and intertwined picture and not just, as occurs now, at subsections of this total picture.

1.3 Antibiotic Resistance is an Inevitable Consequence of Use

Genes encoding for antibiotic resistant are present naturally in the environment for most, if not all, antibiotics. This is because most antibiotics are derived from precursors that are "natural products" produced by fungi or higher order bacteria to help them survive against other microbial competitors (Davies and Davies 2010; Webb and Davies 1993). The organisms' that produce these antibiotics, however, usually need mechanisms to protect themselves against the effects of these toxic products they produce (after all antibiotics are designed to kill microorganisms). This means that often the microorganisms that produce antibiotics also have resistance genes and antibacterial products such as beta-lactamases etc. (Davies and Davies 2010; Webb and Davies 1993). This means whenever antibiotics are widely used, it is almost inevitable that resistance will develop as bacteria acquire resistance genes already present in the wider environment and these bacteria will then have a competitive advantage.

The greater the quantity of antibiotics used the more resistance will eventually develop. Resistant bacteria rapidly and easily move from site to site and from country to country. Because so much of this resistance is encoded by mobile genetic elements, the genes can move into other bacteria including quite different species. Thus the essential element to control antimicrobial resistance is to limit and decrease the amounts of antibiotics used in all sectors (i.e. human, agriculture, the environment). We need also to keep people and animals healthy so they do not need to receive antibiotics because they have less illness (good animal husbandry, immunisation etc.) and to stop the spread of resistant bacteria by better hygiene and infection control practices.

1.4 Resistant Bacteria and Genes Spread Easily

Resistant bacteria move readily from person to person, from hospital to hospital, from food animals to people and from country to country (Aarestrup et al. 2008b; Collignon et al. 2009; FAO 2003; Huijsdens et al. 2006; JETACAR 1999; Kennedy and Collignon 2010). Many spread through water and in foods. Foods (especially meats) also frequently contain bacteria that are multiresistant. Water is commonly contaminated with bacteria. When water is heavily contaminated with either human or animal faecal waste, then multiresistant bacteria can persist and even be distributed via chlorinated water supplies (e.g. in New Delhi with the MBL *E. coli* strains) (Walsh et al. 2011).

The bacterial genes that encode for antimicrobial resistance can also be readily transmitted between bacteria of the same species and also between bacteria of different species (Carlet et al. 2011; Kumarasamy et al. 2010; Walsh et al. 2011).

1.5 We Can Decrease the Spread of Resistant Bacteria and Prevent Them Causing Disease

Infection control interventions help. In the UK a national program decreased the number of MRSA bacteraemia episodes per year from 2003 to 2007 by over 40 % (from 3,955 to 2,376 episodes) (Health Protection Agency 2009).

Immunisations such as Hib were very effective in decreasing the amount of resistant Hib that was seen and was causing increasing problems 20 years ago (Collignon et al. 2008a, b). This is an example where immunisation has had a profound effect on decreasing the number of resistant bacteria causing disease. Similar effects have also been seen with Pneumococcus with a successful conjugated vaccine with much less disease now in children and therefore less antibiotics having to be used to treat children because they have less serious disease from this organism (Collignon et al. 2008a, b). In animals and fish, vaccines have been very

successful at preventing disease and through decreasing antimicrobial use (e.g. salmon and fluoroquinolone use in Norway) (Markestad and grave 1997).

Clean water is an essential component in controlling antimicrobial resistance. Water is likely to be the major vehicle, particularly in the developing world, where resistant bacteria spread from person to person. This means keeping contaminated animal waste and human waste out of water ways as much as is practicable and ensuring water is treated to such a standard that it minimises the risk that pathogens and commensal bacteria carrying resistant genes will be ingested by people or animals. Clean water considerably decreases the amount of GIT disease and transmission of *Salmonella*, *Campylobacter* and many other pathogens. This means less illness and thus less need for antibiotics.

We need to prevent multiresistant bacteria from being in our food supply. The best way to achieve this is to stop the use of "critically important" antibiotics in our food animals and better limit the use of all antibiotics in food animals. We can also decrease the number of organisms in food by better controls along the food chain such as the way animals are slaughtered so that there is less contamination of the carcass with bowel bacteria and find other ways to decrease the number of resistant bacteria in foods. At the other end of the food chain, after the food is produced, issues such as pasteurisation of milk and eggs or other heat treatment can considerably decrease the number of pathogens and therefore antibiotic resistant bacteria that are in the food that is subsequently distributed to consume. Obviously consumer education can also help stop cross contamination from uncooked foods and cooked foods but also to foods such as lettuce, tomatoes etc., which may not be cooked before they are ingested.

The use of animal and human manure to grow food is also an issue if it contains large numbers of pathogens including resistant bacteria that may not be inactivated or removed before the product reaches the market. This can have implication in the globalisation of food trade. A recent example was the Haemorrhagic *E. coli* outbreak in Germany. The bean sprouts involved came from bean seeds imported from Egypt. The seeds are presumed to have been contaminated by human or animal waste in Egypt. When germinated and grown in Germany, the *E. coli* already present, increased markedly in numbers. Then because these sprouts were not cooked before being ingested, large numbers of people became ill. This resulted in huge pressures on the hospitals and Intensive Care systems in Germany and was also associated with many deaths (CDC 2011).

1.6 Resistance to Antimicrobials Classified as "Critically Important" is Common

Increasing resistance is occurring in almost all medically important bacteria, including to antimicrobials classified as "critically important" or "last line" for human health (Collignon et al. 2009). This means when resistance is present there will be very limited or no antimicrobial therapy that will still be effective to treat

infections caused by these resistant bacteria. In hospitals we see increasing numbers of bacterial infections to which there are no effective antibiotics available. This includes infections caused by *E. coli*, *Acinetobacter* spp., *Serratia* spp. and *Enterobacter* spp. (Carlet et al. 2011; Fernando et al. 2010; Li et al. 2006; Walsh et al. 2011).

Resistance rates in almost all types of bacteria are much higher in developing countries. For most people living in developing countries this problem is compounded by poor access to appropriate diagnostic facilities, less resources being available to help institute and maintain appropriate hygiene and infections control practises as well as difficulties in accessing adequate and affordable medical care.

Many classes of critically important antibiotics are also used in food production animals. The most important of these from a human health consequence perspective have been identified by the World Health Organisation (WHO) as fluoroquinolones, third- and fourth-generation cephalosporins and macrolides (Collignon et al. 2009; WHO 2009).

1.7 The Drug Pipeline is Empty

Most antimicrobial classes were discovered decades ago. There have been very few new classes of antibiotics developed in the last 30 years (fluoroquinolones, lipopeptides, oxazolidinones). There have been some developments in classes of antibiotics that have already existed that have led to agents with much improved activity (ketolides and tigecycline). However, these latter two agents are just variations of macrolides and tetracycline's respectively (Carlet et al. 2011; Collignon et al. 2009).

The problem we have is that antibiotic resistance is developing much faster than there are any new drugs or drug classes likely to be available in the near future. This is particularly a problem for Gram-negative bacteria where there does not even look that there are many promising drugs in any advanced research stage yet alone in the development pipeline. The financial rewards for pharmaceutical companies to research and then market completely new classes of antibiotics is relatively poor compared to the returns on drugs that need to be taken by a large percentage of the population continuously e.g. cholesterol-lowering drugs (Collignon et al. 2008a, b; Power 2006). Unfortunately this situation is not likely to change in the near future.

1.8 Surveillance is Essential

We need much better and timely surveillance of antimicrobial usage and of resistant bacteria—locally, nationally and internationally. The results need to be readily available so we can better see what is happening with resistance in different areas and needs to involve both the human and non-human sector. We need to

know the volumes and types of antimicrobials being used. This will allow not only the better choice of empiric antibiotic therapy but also help us better target problem areas with preventive interventions, improved antibiotic stewardship and other programs. This will then help to stop or slow resistance from getting worse in those targeted areas and hopefully even reverse some of the resistance levels seen.

2 What are the Most Important Bacteria We Need to Worry About?

Almost all bacteria that cause infections in people have higher rates of antimicrobial resistance present now compared to 10 or 20 years ago. Some infections, however, are more common and cause more serious infections in people. *E. coli*, *S. aureus, Enterococcus* spp. and *S. pneumoniae* are the most common bacteria causing serious infections in people (Beidenbach et al. 2004; Collignon et al. 2005; Collignon et al. 2011; Decousser et al. 2003; ECDC 2010; HPA 2009; Kennedy et al. 2008).

The more important examples of human infections are discussed below.

2.1 Escherichia coli

Escherichia coli is the commonest cause of serious bacterial infections in people. In the developed countries, bloodstream infections occur at rates between 30 and 60 episodes per 100,000 people each year (ECDC 2010; Kennedy et al. 2008) and are associated with substantial mortality and morbidity. There are likely over 2 million bloodstream infections per year worldwide. *E. coli* causes substantially more infections but which are not usually life-threatening e.g. urinary tract infections.

We are seeing rapidly increasing rates of antimicrobial resistance, including multiresistance. In many developing countries antimicrobial resistance is extensive and widespread and few or no agents may be available for therapy. Intravenous carbapenems e.g. meropenem can usually still be used to treat most infections. But even to these agents, resistance appears to be rapidly developing. These agents are usually only available in intravenous forms and are expensive. This effectively means that many people cannot access any antibiotics that are effective for these very common infections (Carlet et al. 2011).

The main reservoir for *E. coli* is the bowel and there is a large turnover every day of *E. coli* (Collignon and Angulo 2006; Corpet 1988; Johnson et al. 2006). While many *E. coli* strains are relatively specific in where they both live and multiply (e.g. some may be adapted for the pig gut), a large proportion of *E. coli* carried by people are acquired via foods and especially from poultry (Johnson et al. 2006). This is particularly the case for antibiotic resistant bacteria (Johnson et al. 2006). In many developed countries *E. coli* remains largely sensitive to third-

generation cephalosporins, fluoroquinolones and/or aminoglycosides and these agents can usually still be used to treat those with serious infections. However, this is not the case in countries especially developing countries (Walsh et al. 2011). Travellers from countries with low rates of resistance to critically important antimicrobials such as fluoroquinolones and third-generation cephalosporins, often acquire these bacteria when visiting countries with much higher endemic rates of infections—most likely via food and/or water. Carriage of these resistant bacteria can be over 50 % in travellers and persist after returning home for over 6 months (Kennedy and Collignon 2010; Tängdén et al. 2010).

We are seeing increasing levels of ESBL *E. coli* in developed countries including the US and Europe. These strains are resistant to all third- and fourth-generation cephalosporins, are often community acquired and foods are a source. In particular poultry has been found to be frequently contaminated with multiresistant *E. coli* (Brinas et al. 2003). In Hong Kong, ESBL rates in poultry *E. coli* isolates were 78 % (Ho et al. 2011). In people there is now a worldwide epidemic with resistant *E. coli* carrying encoding CTX-M and CMY ß-lactamases (Aarestrup et al. 2008a, b; Cavaco et al. 2008; Mesa et al. 2006; Zhao et al. 2001). In Europe there are 100,000's episodes per year and blood isolates in 2009 showed ranges in different countries of 4–29 % for ESBL's and 9–44 % for fluoroquinolone resistance. It is of note that ESBL bacteraemia in Europe is associated with a mortality of 32 % within 30 days of their sepsis (de Kraker et al. 2011).

2.2 *Staphylococcus aureus*

Staphylococcus aureus is commonly carried asymptomatically by people in the community, particularly in their noses and on skin. It is also present in many food animals such as poultry and pigs. In people it is one of the most common, virulent bacteria that cause infections especially healthcare associated infections (Beidenbach et al. 2004; Collignon et al. 2008a, b; Collignon et al. 2005; ECDC 2010; HPA 2009). Even now, when we have good medical support for patients in hospitals (including intensive care), if a person has *S. aureus* bacteraemia then their median mortality rate is 25 %. If they have an antibiotic resistant variety (e.g. MRSA), then their then with bacteraemia their median mortality rate is 35 % (Cosgrove et al. 2003).

Serious infections are very common. In Denmark the annual rate of all *S. aureus* bloodstream infections is about 28 per 100,000 inhabitants per year. In the USA *S. aureus* bloodstream infection rates may be as high as 50 per 100,000 per year (or about 150,000 episodes per year) (Collignon et al. 2005; ECDC 2010). In Australia it is about 30 per 100,000 populations (Collignon et al. 2005).

Rates of the more resistant varieties of *S. aureus* (i.e. MRSA) are very high. In the USA and in many European countries as many as half of all *S. aureus* isolates causing bloodstream infections are MRSA (ECDC 2010; Klevens et al. 2007). In hospital the percentage caused by MRSA are even higher. In the US it is estimated that there may be over 100,000 episodes of invasive MRSA infections per year, mainly bacteraemia (Klevens et al. 2007).

Recent developments have resulted in more agents that are effective against *S. aureus* and other Gram-positive bacteria becoming available. This has included newer antibiotics such as linezolid, tigecycline and daptomycin. However, resistance, associated toxicity and/or high cost have limited their use. These agents also do not appear to be more effective than vancomycin. Vancomycin is less active than beta-lactam antibiotics against methicillin sensitive strains of *S. aureus* (MSSA). Thus this also means that one other clinical cost of increasing resistance is the need to use drugs that are intrinsically less active in serious disease (Collignon et al. 2008a, b).

The increasing numbers of community MRSA strains that are not healthcare related is a major concern. These are now causing a large and increasing percentage of community acquired infections in the US, Europe and Australia and elsewhere. In some cities over 50 % of community *S. aureus* infections are now MRSA. This means that for very common infections, we now need to use antibiotics that are more expensive, more toxic and less effective than agents we could previously depend on.

MRSA strains also develop and spread in food animals. Similar factors drive this development and spread as happens in people—over use of antibiotic especially broad spectrum agents, crowding and poor housing, social disadvantage and less than optimal infections control and/or hygiene. Recently MRSA strains have been found that spread from pigs to human (e.g. in the Netherlands and Denmark) and cause infections in people (Aarestrup et al. 2008a, b; Khanna et al. 2008; Lewis et al. 2008).

2.3 *Streptococcus pneumoniae*

Streptococcus pneumoniae is spread from person to person. It is a common cause of pneumonia, meningitis, otitis media and bloodstream infections (Collignon and Turnidge 2000; Hsueh et al. 1999; Pallares et al. 1995). It does not have non-human reservoirs and thus all the resistance we likely results from antibiotic use in people and/or associated poor hygiene (that allows the spread of this bacteria from person to person).

Increasing levels of resistance are seen to all antibiotics, particularly to penicillins. One antibiotic that can still be relied on in all circumstances to treat serious pneumococcal disease (including meningitis) is vancomycin although its penetration into CSF is relatively poor and it is not absorbed when given orally. Other agents such as linezolid appear to be effective as resistance in pneumococcus is currently very low. Oral therapy is very important for the treatment of many infections other than meningitis. High dose oral amoxicillin appears to be effective when therapy is needed even if intermediate penicillin resistance is present. However, with other oral agents, unfortunately increasing numbers of pneumococci are developing resistance to tetracyclines, co-trimoxazole and macrolides, which limits therapeutic options such as the oral treatment of pneumonia and other conditions (Collignon and Turnidge 2000; Hsueh et al. 1999; Pallares et al. 1995).

2.4 Other Gram-Negative Bacilli

There are many Gram-negative bacteria that cause serious disease particularly in health care settings (Collignon et al. 2008a, b). Examples include *Enterobacter* spp., *Pseudomonas aeruginosa*, *Serratia, Klebsiella* and *Acinetobacter*. Some may be untreatable with any antibiotic including polymixins (Hujer et al. 2006); Fernando et al. 2010). Other examples include *P. aeruginosa* and *Burkeholderia* spp. where now frequently there are no effective antibiotics that can be used in those with serious infections such as acquired in intensive care units, patients with cystic fibrosis and complicated lung infections. An older and relatively toxic antibiotic (polymixin) is increasingly being used as IV therapy as no other option may often be available to treat these resistant bacteria (Li et al. 2006). Fosfomycin is also being increasing used to treat multiresistant Gram-negative infections.

2.5 Enterococcus

Enterococcus species in particular *Enterococcus faecium* are intrinsically resistant to large numbers of antimicrobials. In people most infections are caused by *Enterococcus faecalis* which remains normally sensitive to both ampicillin and vancomycin (Collignon et al. 2008a, b; Heuer et al. 2006; Moellering 2005). For some serious infections such as endocarditis, an aminoglycoside needs to be added to ampicillin to achieve bactericidal activity. If high-level resistance to aminoglycosides is present, then endocarditis (which in the preantibiotic era had 100 % mortality) will not usually be able to be cured.

Enterococci are intrinsically resistant to cephalosporins. This is likely an important reason why they are selected out and are increasing in numbers in environments such as hospitals where cephalosporins are frequently used. Enterococci are becoming increasingly important pathogens in hospital and cause many serious infections such as bloodstream infections. Of particular concern are vancomycin resistant Enterococci (VRE) as there are only limited options for therapy and it readily spreads within a hospital environment given its hardiness both to environmental stressors and also to disinfectants and cleaning. There is also the concern that the genes that encode for vancomycin resistance may spread to more virulent bacteria such as *S. aureus*. Fortunately compared to 10 years ago we now have more agents available to treat infections caused by VRE (e.g. linezolid).

In most hospitals infection control practices try to limit the spread of these bacteria by isolating patients and requiring increased precautions to be taken by all medical and nursing staff looking after them e.g. gowns, gloves and isolation rooms. Thus the appearance of VRE is a concern particularly if also found in foods as was the case when avoparcin was used extensively as a growth promoter in the past. Other resistant enterococci can also spread via foods to people (Aarestrup et al. 2008a, b; Heuer et al. 2006).

2.6 Food-borne Pathogens (Salmonella and Campylobacter)

Antimicrobial resistance is increasing in many food-borne pathogens in particular S*almonella* and *Campylobacter*. Agents that were very effective in the past including ciprofloxacin are now ineffective. (Aarestrup et al. 2008a, b; Engberg et al. 2001; Iovine and Blaser 2004; Mead et al. 1999; Pegues et al. 2005; Unicomb et al. 2003). This fluoroquinolone resistance is clearly related to fluoroquinolone use in food animals.

Infections with non-typhi *Salmonella* strains are common in developed countries (and even more common in developing countries). In developed countries nearly all these strains are derived from food animals. Increasing antibiotic resistance is an issue in these bacteria as well and some have been impossible or very difficult to treat. Of particular concern is the development of ESBL as when this occurs there may be no therapy available to treat pregnant women or children if they develop serious infections (e.g. bacteraemia) as third-generation cephalosporins are the drug of choice in that circumstance. ESBL *Salmonella* strain can develop from the use of third-generation cephalosporins in poultry. In Canada a close association has been found between the use of third-generation cephalosporin (ceftiofur) ESBL *Salmonella* and ESBL *E. coli* (CIPARS 2007).

Salmonella typhi is a pathogen that spreads from person to person usually via contaminated food and water. It has no animal reservoir and thus all resistance is likely the result of what antibiotics given to people along with poor hygiene and poor water infrastructure. If improved water supply and sewage infrastructure were introduced this would also have a significant effect in decreasing numbers of these infections (including antibiotic resistant infections).

Campylobacter is the commonest cause of bacterial diarrhoea in developed countries. The main causative organism is *Campylobacter jejuni* and mainly derived from poultry as its initial source. Increasing resistance is seen in these strains to both fluoroquinolones and macrolides. For most cases, no antibiotic therapy is needed. However, with more severe disease, fluoroquinolones and macrolides are the agents of choice and thus this resistance is problematic. Wherever fluoroquinolones have been used in poultry resistance develops and spreads and can reach very high rates in countries such as in Spain (Aarestrup et al. 2008a, b; Collignon et al. 2008a, b). Even in the US, where only a small percentage of poultry were exposed to fluoroquinolones, ciprofloxacin resistance rates in *Campylobacter* where as high as 20 % in both poultry isolates and those isolates cultured from people.

2.7 When little or No Fluoroquinolone is Used in Food Animals There is Little Fluoroquinolone Resistance

In countries that have never allowed the use of fluoroquinolones in food animals e.g. Australia there is almost no resistance seen in *E. coli*, *Salmonella*, or *Campylobacter* in isolates derive from food animals or in foods produced from these animals

(Collignon et al. 2008a, b; Unicomb et al. 2003). It thus appears very likely that the major driving factor for resistance in most of these food borne pathogens that are derived from animals, is the use of antimicrobials and the types of the antimicrobials use in food animals.

In children and in pregnant women, fluoroquinolones are contraindicated and thus for invasive or serious disease with *Salmonella*, third generation cephalosporins are the agents of choice. Unfortunately increasing rates of resistance in *Salmonella* make this option difficult. This is particularly a problem in developing countries where invasive *Salmonella* infections are much more common. It, however, is also a problem for those living in developed countries as these infections can be acquired domestically and also by travellers when they have visited countries with much higher endemic rates of infections and/or resistance. In many countries (e.g. Denmark) imported foods have on them bacteria that are much more resistant than found on domestically produced foods (DANMAP 2009).

2.8 What Do We Need To Do?

We need to better control the development of resistant bacteria in people by considerably lowering the volumes of antibiotics we use. In most countries we need to reduce by at least 50 % or more, the total amount of antibiotics used in people as the majority is used for viral infections or is ineffectual. We also need to limit the spread of resistant bacteria by better hygiene and infection control. Otherwise resistance inevitably rises and rises.

However, even if we had both these optimally processes performed in people, this would not solve the problem. Resistant bacteria develop wherever antibiotics are used and two-thirds or more of all the antibiotics used in the world are used in food production animals. Aquaculture is also rapidly expanding and so it their use of antibiotics. Thus when resistant bacteria develop in these sectors they inevitably also spread to people. It profoundly complicates the issue of optimally managing antibiotic resistance if all the focus is just from a medical perspective in the human health sector.

This is where the concept of One Health is so important. We recognise that one sector impinges on the health of other sectors. It then follows that if we cannot only lower the usage of antibiotics in people but also better control and significantly lower the amounts of antibiotics used in food animals and aquaculture, this will then have a major flow-on effect to the human sector. We also need to also look at the water and waste from these animals and people, as this water will inevitably be contaminated with resistant bacteria and this water will be ingested by people and animals.

Interventions, particularly those targeting better infection control and improved antimicrobial use (decreasing use of broad spectrum antibiotics especially cephalosporins and fluoroquinolones) have made a difference. Antimicrobial stewardship (involving education plus restrictions on the types and quantities of antimicrobial used) is a major way that antibiotic usage can be improved. Attempts to implement this successfully are occurring. However, both implementation and sustainability are

difficult. It can also involve significant increased expenditure especially if electronic prescribing and data collection are part of the improved process.

The major action items needed are:

- Control and limit the amounts and types of antibiotic used in people.
- Control and limits the amounts and types of antibiotic used in non-human sectors. This is particularly in food animals and aquaculture but also in areas such as horticulture where heat stable compounds such as gentamicin and streptomycin can be used to spray apples.
- Better infection control and hygiene in people so that even if resistant bacteria develop, we better limit the spread to other people.
- Prevent infections by effective and safe vaccines.
- Clean water. Water in many countries, particularly in the developing world is a major vehicle that allows the spread of resistant bacteria from person to person, animal to animal and animal to people. We need to keep contaminated animal waste and human waste out of water ways as much as is practicable and ensuring water is treated to an appropriate standard.
- No multiantibiotic resistant bacteria in our foods. This will be best achieved by stopping the use of "critically important" antibiotics in our food animals and better limiting the use of all antibiotics in food animals. Globalisation of food can then spread these bacteria widely.
- Better controls on how animal and human faecal waste manure is used to help grow food. This waste will contain large numbers of pathogens including resistant bacteria that may not be inactivated or removed before the foods reach the market.
- Better surveillance of antimicrobial usage and of resistant bacteria—locally, nationally and internationally.

3 Conclusions

Antibiotic resistance causes increased deaths, complications, expenses, prolonged hospital stays, toxicity and difficulties in delivering therapy in the safest way to patients. Antibiotic resistance is a continuing and growing problem. There are not many likely new classes of antibiotics that will be available in the next few decades. Thus we need to preserve the usefulness of those antibiotics we currently have by decreasing their overall use, and especially the use of broad spectrum agents. We also need to improve our ability to prevent infections and the spread of resistant bacteria wherever they arise or are found. This means improving our practices with infection control, hygiene, animal husbandry and development and delivery of effective and safe vaccines. We need clean water to be available for people and for animals. Failure to do this will result in huge numbers of people entering a "post-antibiotic era" for too many common infections.

References

Aarestrup FM, Wegener HC, Collignon P (2008a) Resistance in bacteria of the food chain: epidemiology and control strategies. Expert Rev Anti Infect Ther 6:733–750

Aarestrup FM, McDermott PF, Wegener HC (2008b) Transmission of antimicrobial resistance from food animals to humans. In: Nachamkin I, 25, Szymanski C, Blaser M, (eds) *Campylobacter* 3rd edn. ASM Press, Washington DC, pp 645–665

Beidenbach DJ, Moet GJ, Jones RN (2004) Occurrence and antimicrobial resistance patterns comparisons among bloodstream infection isolates from the SENTRY antimicrobial surveillance programme (1997–2002). Diagn Microbiol Infect Dis 50:59–69

Brinas L, Moreno MA, Zarazaga M, Porrero C, Sáenz Y, García M, Dominguez L, Torres C (2003) Detection of CMY-2, CTX-M-14, and SHV-12 beta-lactamases in *Escherichia coli* fecal-sample isolates from healthy chickens. Antimicrob Ag Chemother 47:2056–2058

Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) (2007) *Salmonella* Heidelberg ceftiofur-related resistance in human and retail chicken isolates. Modified 16 Aug 2007. Available at www.phac-aspc.gc.ca/cipars-picra/heidelberg/heidelberg-eng.php

Carlet J, Collignon P, Goldmann D, Goossens H, Harbarth S, Jarlier V, Levy SB, N'Doye B, Pittet D, Richtmann R, Seto WH, van der Meer JW, Voss A (2011) Society's failure to protect a precious resource: antibiotics. Lancet 378:369–371

Cavaco LM, Abatih E, Aarestrup FM, Guardabassi L (2008) Selection and persistence of CTX-M-producing *Escherichia coli* in the intestinal flora of pigs treated with amoxicillin, ceftiofur or cefquinome. Antimicrob Ag Chemother 52:3612–3616

CDC Centers for Disease Control and Prevention (2011) Investigation update: outbreak of Shiga toxin-producing *E. coli* O104 (STEC O104:H4) infections associated with travel to Germany. Updated 8 July 2011 (FINAL Update), CDC, Atlanta. Department of Health and human services. Available at http://www.cdc.gov/ecoli/2011/ecolio104/

Collignon P, Courvalin P, Aidara-Kane A (2008a) Clinical importance of antimicrobial drugs to human health. Chapter 4. In: Guardabassi L, Jensen L, Kruse H (eds). Guide to antimicrobial use in animals, Blackwell, Oxford

Collignon P, Dreimanis D, Ferguson J (2008b) Bloodstream infections. In: Cruickshank M, Ferguson J (eds), Reducing harm to patients from health care associated infection: the role of surveillance: Australian Commission on Safety and Quality in Health Care, pp 53–89. Available at www.health.gov.au/internet/safety/publishing.nsf/Content/prog-HAI_Surveillance

Collignon P, Nimmo GR, Gottlieb T, Gosbell IB (2005) Australian Group on antimicrobial resistance. *Staphylococcus aureus* bacteremia, Australia. Emerg Infect Dis 11:554–561. Available at www.cdc.gov/ncidod/eid/vol11no04/pdfs/04-0772.pdf

Collignon PJ, Turnidge JD (2000) Antibiotic resistance in *Streptococcus pneumoniae*. Med J Aust 173(Suppl):S58–S64

Collignon P, Powers JH, Chiller TM, Aidara-Kane A, Aarestrup FM (2009) World Health Organization ranking of antimicrobials according to their importance in human medicine: a critical step for developing risk management strategies for the use of antimicrobials in food production animals. Clin Infect Dis 49(1):132–141, 1 July

Collignon P, Angulo FJ (2006) Fluoroquinolone-resistant *Escherichia coli*: food for thought. J Infect Dis 194(1):8–10

Decousser JW, Pina P, Picot F et al. Delalande C, Pangon B, Courvalin P, Allouch P, ColBVH Study Group (2003). Frequency of isolation and antimicrobial susceptibility of bacterial pathogens isolated from patients with bloodstream infections: a French prospective national survey. J Antimicrob Chemother 51:1213–1222

Corpet DE (1988) Antibiotic resistance from food. New Engl J Med 318:1206–1207

Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y (2003) Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. Clinical Infect Dis 36:53–59

Danish Integrated Antimicrobial resistance Monitoring and Research Programme (DANMAP) (2009) Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark. Statens Serum Institut, Danish Veterinary and Food Administration, Danish Medicines Agency and Danish Institute for Food and Veterinary Research, Copenhagen, 2010. Available at www.danmap.org/pdfFiles/Danmap_2009.pdf

Davies J, Davies D (2010) Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev 74(3):417–433

de Kraker ME, Wolkewitz M, Davey PG, Koller W, Berger J, Nagler J, Icket C, Kalenic S, Horvatic J, Seifert H, Kaasch A, Paniara O, Argyropoulou A, Bompola M, Smyth E, Skally M, Raglio A, Dumpis U, Melbarde Kelmere A, Borg M, Xuereb D, Ghita MC, Noble M, Kolman J, Grabljevec S, Turner D, Lansbury L, Grundmann H (2011) Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to *Escherichia coli* resistant to third-generation cephalosporins. J Antimicrob Chemother 66:398–407

Diwan V, Tamhankar AJ, Khandal RK, Sen S, Aggarwal M, Marothi Y, Iyer RV, Sundblad-Tonderski K, Stålsby-Lundborg C (2010) Antibiotics and antibiotic-resistant bacteria in waters associated with a hospital in Ujjain, India. BMC Public Health 13(10):414

Engberg J, Aarestrup FM, Taylor DE, Gerner-Smidt P, Nachamkin I (2001) Quinolone and macrolide resistance in *Campylobacter jejuni* and *C. coli*: resistance mechanisms and trends in human isolates. Emerg Infect Dis 7:24–34

European Centre for Disease Prevention and Control (ECDC) (2010). Antimicrobial resistance surveillance in Europe 2009. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). ECDC, Stockholm. Available at www.ecdc.europa.eu/en/publications/Publications/1011_SUR_annual_EARS_Net_2009.pdf

Food and Agriculture Organization of the United Nations (FAO)/World Organisation for Animal Health (OIE)/World Health Organization (WHO) (2003) Joint expert workshop on non-human antimicrobial usage and antimicrobial resistance: scientific assessment. WHO, Geneva. Available at www.who.int/foodsafety/publications/micro/en/amr.pdf Accessed 1–5 Dec

Finland M, Jones WF Jr, Barnes MW (1959) Occurrence of serious bacterial infections since introduction of antibacterial agents. J Am Med Assoc 170:2188–2197

Fernando GA, Collignon PJ, Bell JM (2010) A risk for returned travellers: the "post-antibiotic era". Med J Aust. 10(193):59

Health Protection Agency (2009) Quarterly results from the mandatory surveillance of MRSA bacteraemia. MRSA bacteraemia, Health Protection agency, June. Available at www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1233906819629

Heuer OE, Hammerum AM, Collignon P, Wegener HC (2006) Human health hazard from antimicrobial-resistant enterococci in animals and food. Clin Infect Dis 43:911–916

Ho PL, Chow KH, Lai EL, Lo WU, Yeung MK, Chan J, Chan PY, Yuen KY (2011) Extensive dissemination of CTX-M-producing *Escherichia coli* with multidrug resistance to 'critically important' antibiotics among food animals in Hong Kong, 2008–2010. J Antimicrob Chemother 66(4):765–768

Hsueh P-R, Teng L-J, Lee L-N, Yang PC, Ho SW, Luh KT (1999) Dissemination of high-level penicillin-, extended-spectrum cephalosporin-, and erythromycin-resistant *Streptococcus pneumoniae* clones in Taiwan. J Clin Microbiol 37:221–224

Huijsdens XW, van Dijke BJ, Spalburg E, van Santen-Verheuvel MG, Heck ME, Pluister GN, Voss A, Wannet WJ, de Neeling AJ (2006) Community-acquired MRSA and pig-farming. Ann Clin Microbiol Antimicrob 5:26

Hujer KM, Hujer AM, Hulten EA, Bajaksouzian S, Adams JM, Donskey CJ, Ecker DJ, Massire C, Eshoo MW, Sampath R, Thomson JM, Rather PN, Craft DW, Fishbain JT, Ewell AJ, Jacobs MR, Paterson DL, Bonomo RA (2006) Analysis of antibiotic resistance genes in multidrug-resistant Acinetobacter sp. isolates from military and civilian patients treated at the Walter Reed Army Medical Center. Antimicrob Ag Chemother 50(12):4114–4123

Iovine NM, Blaser MJ (2004) Antibiotics in animal feed and spread of resistant *Campylobacter* from poultry to humans. Emerg Infect Dis 10:1158–1159

JETACAR (1999) The use of antibiotics in food-producing animals. Antibiotic-resistant bacteria in animals and humans 1999. Available at www.health.gov.au/internet/main/Publishing.nsf/Content/2A8435C711929352CA256F180057901E/$File/jetacar.pdf

Johnson JR, Kuskowski MA, Menard M, Gajewski A, Xercavins M, Garau J (2006) Similarity of human and chicken *Escherichia coli* isolates with relation to ciprofloxacin resistance status. J Infect Dis 2006(194):71–78

Kennedy KJ, Roberts JL, Collignon PJ (2008) *Escherichia coli* bacteraemia in Canberra: incidence and clinical features. Med J Aust 188:209–213

Kennedy K, Collignon P (2010) Colonisation with *Escherichia coli* resistant to "critically important" antibiotics: a high risk for international travellers. Eur J Clin Microbiol Infect Dis 29(12):1501–1506

Khanna T, Friendship R, Dewey C, Weese JS (2008) Methicillin resistant *Staphylococcus aureus* colonization in pigs and pig farmers. Vet Microbiol 128:298–303

Klevens RM, Morrison MA, Nadle J, Petit S, Gershman K, Ray S, Harrison LH, Lynfield R, Dumyati G, Townes JM, Craig AS, Zell ER, Fosheim GE, McDougal LK, Carey RB, Fridkin SK (2007) Active bacterial core surveillance (ABCs) MRSA investigators. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. J Am Med Assoc 298:1763–1771

Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, Chaudhary U, Doumith M, Giske CG, Irfan S, Krishnan P, Kumar AV, Maharjan S, Mushtaq S, Noorie T, Paterson DL, Pearson A, Perry C, Pike R, Rao B, Ray U, Sarma JB, Sharma M, Sheridan E, Thirunarayan MA, Turton J, Upadhyay S, Warner M, Welfare W, Livermore DM, Woodford N (2010) Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect Dis 2010(9):597–602

Lewis HC, Mølbak K, Reese C, Aarestrup FM, Selchau M, Sørum M, Skov RL (2008) Pigs as Source of methicillin-resistant *Staphylococcus aureus* CC398 infections in humans. Den Emerg Infect Dis 14:1383–1388

Li J, Nation RL, Turnidge JD, Milne RW, Coulthard K, Rayner CR, Paterson DL (2006) Colistin: the re-emerging antibiotic for multidrug-resistant gram-negative bacterial infections. Lancet Infect Dis 6:589–601

Mayerhofer G, Schwaiger-Nemirova I, Kuhn T, Girsch L, Allerberger F (2009) Detecting streptomycin in apples from orchards treated for fire blight. J Antimicrob Chemother 63(5):1076–1077

Markestad A, Grave K (1997) Reduction of antibacterial drug use in Norwegian fish farming due to vaccination. Dev Biol Stand 90:365–369

Mead PS, Slutsker L, Dietz V, McCaig LF, Bresee JS, Shapiro C, Griffin PM, Tauxe RV (1999) Food-related illness and death in the United States. Emerg Infect Dis 5:607–625

Mesa RJ, Blanc V, Blanch AR, Cortés P, González JJ, Lavilla S, Miró E, Muniesa M, Saco M, Tórtola MT, Mirelis B, Coll P, Llagostera M, Prats G, Navarro F (2006) Extended-spectrum beta-lactamase-producing Enterobacteriaceae in different environments (humans, food, animal farms and sewage). J Antimicrob Chemother 58:211–215

Moellering R (2005) *Enterococcus* species, *Streptococcus bovis* and *Leuconostoc* species. In: Mandell, GL, Bennett JE, Dolin R (eds) Principles and practice of infectious diseases 6th edn. Elsevier Churchill Livingstone, Philadelphia pp 2411–2422

Pallares R, Liñares J, Vadillo M, Cabellos C, Manresa F, Viladrich PF, Martin R, Gudiol F (1995) Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. New Engl J Med 333:474–480

Pegues D, Ohl M, Miller S (2005) *Salmonella* species including *Salmonella typhi*. In: Mandell, GL, Bennett JE, Dolin R (eds) Principles and practice of infectious diseases 6th edn. Elsevier Churchill Livingstone, Philadelphia pp 2636–2654

Power E (2006) Impact of antibiotic restrictions: the pharmaceutical perspective. Clin Microbiol Infect 12(Suppl 5):25–34

Tängdén T, Cars O, Melhus A, Löwdin E (2010) Foreign travel is a major risk factor for colonization with *Escherichia coli* producing CTX-M-type extended-spectrum beta-lactamases: a prospective study with Swedish volunteers. Antimicrob Ag Chemother 54:3564–3568

Tumbarello M, Spanu T, Di Bidino R, Marchetti M, Ruggeri M, Trecarichi EM, De Pascale G, Proli EM, Cauda R, Cicchetti A, Fadda G (2010) Costs of bloodstream infections caused by

Escherichia coli and influence of extended-spectrum-beta-lactamase production and inadequate initial antibiotic therapy. Antimicrob Ag Chemother 54:4085–4091

Unicomb L, Ferguson j, Riley TV, Collignon P (2003) Fluoroquinolone resistance in *Campylobacter* absent from isolates, Australia. Emerg Infect Dis 2003(9):1482–1483

Walsh TR, Weeks J, Livermore DM, Toleman MA (2011) Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. Lancet Infect Dis 11:355–362

Wang H, Chen M (2005) China Nosocomial Pathogens Resistance Surveillance Study Group. Surveillance for antimicrobial resistance among clinical isolates of gram-negative bacteria from intensive care unit patients in China, 1996 to 2002. Diagn Microbiol Infect Dis 51:201–208

Webb V, Davies J (1993) Antibiotic preparations contain DNA: a source of drug resistance genes? Antimicobiol Ag Chemother 37:2379–2384

World Health Organization (WHO) (2009). WHO list of Critically Important Antimicrobials (CIA). 2nd Rev. WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR), Copenhagen, 2009. Available at www.who.int/foodborne_disease/resistance/cia/en/index.html

Zhao S, White DG, McDermott PF, Friedman S, English L, Ayers S, Meng J, Maurer JJ, Holland R, Walker RD (2001) Identification and expression of cephamycinase bla(CMY) genes in *Escherichia coli* and *Salmonella* isolates from food animals and ground meat. Antimicrob Ag Chemother 45:3647–3650

Zhou LJ, Ying GG, Zhao JL, Yang JF, Wang L, Yang B, Liu S (2011) Trends in the occurrence of human and veterinary antibiotics in the sediments of the Yellow River, Hai River and Liao River in northern China. Environ Pollut 159(7):1877–1885

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