REVIEW

Infection control in the UK: an antimicrobial resistance perspective

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Abstract

The spread of healthcare-associated infections has become a matter of global concern. These infections, which were once solely limited to hospital settings, have emerged in the community. Reduced infection control practices strengthen this rapid spread of infections, which has led to the increase in the occurrence of multi-drug resistant organisms. The state of infection control in the United Kingdom is of extreme importance because of several reported cases of infections caused by these organisms. In addition to antimicrobial usage in human medicine, antimicrobial agents used in agriculture must be considered as major factors in the prevalence of resistant organisms and the implications to the UK. However, this increased occurrence of antimicrobial resistant bacteria and their resulting infections could be reduced with the application of effective policies for antibiotic use in agricultural environments, stringent decontamination and sterilisation techniques and better regulations that encourage the search for, and development of, new and novel drugs.

Keywords: Infection control, healthcare associated infections, antimicrobial drug resistance, prophylaxis, health policy.

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Introduction

With a prevalence of 6.4%,[1] the spread of healthcare-associated infections (HCAIs) and their subsequent control has become an important issue in hospitals.[2] Historically, the hospital setting was subjected to daily rigorous sanitisation by dedicated cleaning staff, and all medical students and staff had to observe a stringent hygiene regimen.[3] Over time, there was a decrease in following these strict rules of hospital hygiene resulting in an increase in HCAIs. As a result, infection control practices, although not the primary cause of disease transmission, suffered great setbacks leading to the unintended spread of infectious diseases.[3]

Reduction in global infection control practices has led indirectly to the development of antimicrobial resistance (AMR), which is the evolution of pathogenic microorganisms to become resistant to anti-infective agents. Occurrence of these resistant microorganisms has increased worldwide,[4] spreading to the UK and increasing the risks of both patients and healthcare workers acquiring these infections in a healthcare setting as reported by the National Institute for Health and Care Excellence (NICE).[5] These infections, which were once mainly hospital-acquired, are now seen in the community and the issue of increasing resistance, as reported by WHO,[6] to antimicrobials has also become an issue beyond infection control in the hospital environment.

This paper focuses on the current state of infection control in the UK in terms of the major issues regarding anti microbial resistance. Consideration of antimicrobial usage in agriculture and human medicine will be reviewed, as well as their consequences relating to the major causes of AMR, the prevalence of global threat from this resistance and the implications to the UK. The need to develop new antibiotics as a consequence of this issue will be considered.

Methods

The methodology used for data collection was an internet search using keywords and phrases related to infection control in the UK and antibiotic use on UK farms and in UK human medicine. Other phrases used in the search were those involving causes and occurrences of AMR including the importance of new antimicrobial agents. The internet search engines used included ScienceDirect, Google Scholar, the Antimicrobial Resistance and Healthcare-associated Infections (AMRHAI) reference unit, the Department of Public Health (UK), Public Health England and the World Health Organisation (WHO).

Antibiotic use on UK farms

In a 2014 Review on Antimicrobial Resistance that was announced by the UK Prime Minister, several measures were identified to deal with the growing problem of AMR. One of these measures was a global commitment to monitor the use of antibiotic drugs by humans, in agriculture and in the environment.[7]

Although overlooked because of the restrictions placed on the class of antibiotics used, antimicrobial agents in livestock farming do contribute to AMR.[8] These drugs are used for various reasons such as for medicinal purposes, whether by mass medication (metaphylaxis) or preventative medication (prophylaxis), and to promote growth of the animals. Although the use of antibiotics as growth aids have been banned in Europe, they are still being used as prophylactics.[9]

In the United Kingdom, De Briyne *et al*.[10] reported that penicillins and tetracylines were the most commonly used antibiotics in cattle (32% and 10% respectively) and horses (24% and 11% respectively) to treat disorders such as mastitis and respiratory infections. In another study involving 88 UK farms, heifer calves with respiratory diseases, e.g., pneumonia, were treated with antibiotics (11.3% ±15.8%).[11] Despite the availability of guidelines on antibiotic use in agriculture, 50% of farmers appear to be unfamiliar with these guidelines leading to possible inefficient farming practices.[12]

Commercially available antimicrobial agents, such as ivermectin, are also used on goat farms in the UK to treat ectoparasites such as lice and mange.[13] Extensive use of this macrocyclic lactone and other unnamed antibiotics by many goat farmers may have been ineffectively regulated and could have contributed to the increase in antibiotic resistance of infectious ectoparasites.[13]

A survey of UK broiler farms conducted by Hughes *et al*.[14] showed that 32% of poultry farmers used prescribed antibiotics such as amoxicillin for metaphylactic

purposes. On some participating farms, other antibiotics such as trimethoprim/sulfadiazine (16.8%) and tylosin tartrate (11.7%) were used as prophylactics.[14] Results of the 2008 study indicated that antibiotics were mainly used to prevent diseases in broilers rather than to treat them. Antibiotic management on broiler farms needs further investigation since antibiotic misuse is a potential factor in AMR.

United Kingdom pig farmers, like some European pig farmers,[15] seemed to focus more on their economic issues rather than infections in their animals[16] leading to overuse of antibiotics. As a consequence, it has been shown that there is a clear connection between the poor regulation of antibiotic use in UK farms and AMR in humans.[8]

Antibiotic use in UK human medicine

It is without doubt that antimicrobial agents have been effective against many human infectious diseases. The incidence of infectious diseases in the UK has not notably increased but the total usage of these agents have reportedly increased by 4.1% across the NHS Trusts in a five-year period (2008-2012).[17] While there has been a reduction in the use of fluoroquinolones, such as ciprofloxacin (-23.8%), within the same period, the 2014 study showed that there was an increase in the use of other drugs such as meropenem of the carbapenem class (94.8%), and penicillins such as piperacillin/tazobactam (142.3%). While the report provides expected and observed data on point-of-care antimicrobial usage, it does not show progressive usage, which is crucial in antimicrobial management.

Consequential spread of infectious diarrhoea caused by *Clostridium difficile* is reported to be a major concern in hospitals. In a 2015 study,[18] the mean number of patients suspected to be infected with these organisms was estimated to be 149.6 ± 173.6 in small hospitals, 75.0 ± 27.8 in medium hospitals and 43.78 ± 37.7 in large hospitals. In order to treat patients with diarrhoea that resulted from *Clostridum difficile* infection, metronidazole and fidaxomicin were the primary antimicrobial agents used while vancomycin was the secondary drug of choice.[18] One concern that emerged from the study was that with the increasing incidence there was the possible spread of infections due to poor infection control practices. Without

adequate infection control, the risk of the emergence of antimicrobial resistant *Clostridium difficile* increases. Since more first-line and second-line antibiotics are being used to treat infectious diarrhoea and a number of patients (mean = 10 ± 0.0) are re-admitted after an uncompleted course of treatment of the same drugs, there is the concern that AMR in *Clostridium difficile* could develop.

The concern of the spread of HCAIs was also noted in a 2009 study by Burnett *et al.*[19] Findings from the report that focused on patients with and without *Staphylococcus aureus* septicaemia identified critical issues of infection control that needed attention, such as communication, patient confidence in the NHS, and health and safety practices. Antibiotics are understandably used against HCAIs but there is the need to monitor the possible spread of resistant organisms with increased use in a closed environment found in healthcare settings. Another important concern is the use of antibiotics by persons outside of the hospital environment. Antimicrobial agents are also prescribed by general practitioners in the community. A review of databases such as the Clinical Practice Research Datalink (CPRD) by Shallcross and Davies[20] indicates that 80-90% of antibiotic prescriptions are given in primary care facilities. However, these programmes do not record actual use of antibiotics by patients. The possibility for the spread of resistant organisms between hospitals and community environments in conditions promoting the maintenance of resistance can be inferred.

The prevalence of antimicrobial resistance

Antimicrobial resistance is the development of reduced sensitivity to antimicrobial agents in microorganisms. Major antimicrobial resistant organisms as listed by Tang *et al.*[21] include meticillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), extended spectrum β-lactamase-producing (ESBL) *Enterobacteriaceae,* carbapenemase-producing *Enterobacteriaceae* (CPE) and carbapenem-resistant *Acinetobacter baumannii* (CRA). The main mechanisms of resistance in such organisms usually involve either the transmission of resistant genetic material from one bacterial cell to another or mutation/s in new genes. Antimicrobial resistance has become a global epidemic resulting in the generation of AMR policies

in many regions, including Europe. The European Centre for Disease Prevention and Control (ECDC) has acknowledged the threat of AMR and has identified the major causes of the rapid spread of AMR across Europe with a particular source being the use of antibiotics in agriculture.[22] A report from the B-Debate meeting with public health authorities across Europe stated that the unchecked use of antibiotics in farming practices led to selective pressure for resistant organisms, which could spread to humans.[22] These resistant organisms are spread through human consumption of inadequately prepared meat products[23] and dairy milk,[24] and human contact with animal waste.[25,26] Snow *et al.*[25] determined that 17 of 65 sampled dairy farms received animals with various strains of CTX-M *E. coli*, which is an ESBL-producing microorganism. Findings of the study outlined insufficient infection control practices, such as slurry containment, open herding and inadequate cleaning of feeding equipment used for calves.[25]

Mismanaged antimicrobial chemotherapy in relation to ineffective infection control strategies is also a source of the development of AMR in bacteria as well as the spread of AMR bacteria. The prevalence of CTX-M *Klebsiella pneumoniae*,[27] *Salmonella typhi* and *Salmonella paratyphi*,[28] and MRSA[29] has been documented in UK hospitals. Each study has identified poor infection control measures as a contributing factor to the spread of antimicrobial resistant microorganisms. While studies have found isolates of non-resistant *Pseudomonas aeruginosa* from water systems in UK hospital wards[30] as well as isolates of non-resistant *Staphylococcus spp* from various clinical instruments,[31] the risk of AMR evolution still exists. High standards in infection control are crucial, especially when staff are charged with the care of critically ill patients who are most susceptible to infections from antimicrobial resistant organisms.[32]

In the community setting, unchecked prescribing of antimicrobial agents has been identified as a contributing factor to the spread of antimicrobial resistant bacteria.[33] Due to misuse and abuse of antibiotics, the ECDC has recommended that antibiotic usage should be recorded as defined daily doses (DDD) over time.[22] Supplementary data such as the number of packages used per day and details about the package content enhances knowledge regarding the antibiotic

consumption.[22] Support for this recommendation was evidenced by a European study which showed that the average DDD per package increased between 0.04 and 0.31 per year.[34] This marked increase in antibiotic use is an indication of the potential risk of antimicrobial resistant bacteria transmission.[35]

Another aspect of inadequate infection control is the disposal of waste containing antibiotics. Samples of waste water and surface water from the UK environment were shown to contain multiple antibiotics such as amoxicillin, oxytetracycline and trimethoprim.[36] Emerging contaminants (EC) found in water sources at sites in Oxford along the Thames river and Boxford along the River Lambourn included pharmaceuticals.[37] ECs were also found in the Chalk aquifer, which provides potable water to parts of the UK.[38] The presence of antibiotics in water sources is an important factor in AMR since these compounds tend to be water-soluble and remain in the environment.[39,40] Improper waste disposal from farms and communities could contribute to the presence of antibiotics in UK water sources.[41] The constant exposure of non-resistant bacteria to antibiotics in water sources may encourage the evolution of antimicrobial resistant bacteria.

Another important consideration is the exposure of humans to water sources that are contaminated with antimicrobial resistant bacteria. A recent study showed that samples taken from coastal waters of England and Wales had a prevalence of 1.2% of 3rd generation cephalosporin-resistant *E. coli*.[42] This value may be low since only one strain of resistant *E. coli* was investigated. Persons taking part in recreational activities in these areas, such as water sports, swimming and diving, had an increased risk of infection from antimicrobial resistant bacteria due to ingestion of contaminated water.

Antimicrobial resistance to colistin
Colistin, also known as polymixin E, has been considered as a critical agent against some common multidrug-resistant Gram-negative aerobic bacilli, including CPEs. The mechanism of action of colistin is to damage the integrity of the outer envelope of Gram-negative bacilli by causing instability of membrane-bound lipopolysaccharides.[43] This damage allows cellular contents to escape, which results in

apoptosis. Because of its toxic effects on the human kidney, colistin use in antimicrobial therapy was halted.[44] However, the rapid emergence of CPEs had prompted the return of the usage of this drug. Overuse of colistin has now resulted in infections caused by colistin-resistant CPEs. Initially, resistance was thought to result from chromosomal mutations. Recent reports on colistin resistance in Europe, including a study published by the ECDC,[45] revealed that resistance can now be mediated by the transfer of plasmids containing the colistin-resistant gene known as *MCR-1*.[46–50]

Infection control strategies to curb the spread of antimicrobial resistant bacteria

Effective infection control strategies are important in reducing the spread of antimicrobial resistant bacteria. One strategy is the implementation of policies and guidelines. The Department of Health has issued a 5-year plan that involves policies to lessen the impact of AMR on both humans and animals. The paper identifies seven important actions needed to achieve this goal, which includes the revision of infection control practices in agriculture and human settings.[51]

Adherence to proper and effective animal husbandry was recommended as a way of protecting animals from infectious antimicrobial resistant bacteria.[9,51] In terms of antimicrobial therapy, farmers and agricultural authorities should maintain accurate information regarding health and safety practices and antibiotic use.[9] Other recommendations include a total ban of antibiotic use in prophylaxis, a ban on unregulated antibiotics in animals and discontinuation of cephalosporins and fluoroquinolones in animal antimicrobial chemotherapy.[8]

The 2013 edition of the NICE clinical guidelines has defined clear rules that govern infection control practices in both hospital and non-hospital environments. These include proper training of all staff, availability of items needed to carry out their duties (gloves, antiseptic agents, etc.), effective sterilisation and disinfection techniques and proper waste disposal management.[52] These measures should be at the forefront of infection control since there has been an increase in public interest in CPEs in the UK.[53] Decontamination, disinfection and sterilisation have been identified as excellent methods of the elimination

and extermination of infectious agents.[54] Another method of reducing the spread of infectious organisms is the proper use of gloves.[55]

A key action of the UK five-year plan is to encourage research and development in new antibiotic drug therapies.[51] Due to the overuse of antibiotics in humans and animals, which was first reported by the Swann Committee (1969) and the increase of the "major public health threat" of AMR as highlighted in House of Lords' report (1998), there is an immediate need for new antibiotic drugs.[56] The progress of novel drug discovery is limited by factors such as financial gain and strict regulations regarding drug trials and manufacture.[57] Authorities have altered such regulations, which has revitalised the interest of large pharmaceutical companies into resuming the search for new and more effective drugs against antimicrobial resistant bacteria.[58] This endeavour could also be strengthened with synergistic studies that show the mechanism(s) of combinatorial therapies.[59] Researchers are also encouraged to investigate natural-based and semi-synthetic compounds as viable alternatives. Some medicinal scientists have identified chalcones,[60] which are plant-based intermediates of flavonoids, and their ferrocenyl derivatives as potential drugs since these exhibit potent antimicrobial activity.[61–64]

Conclusion

Infection control practices and appropriate prescribing of antibiotics are essential tools against AMR. With the overuse of antibiotics on farms and in human medicine across the UK, it is evident that AMR continues to spread. However, this increase in the prevalence of antimicrobial resistant bacteria and their resulting infections could be slowed with the implementation of effective policies for antibiotic use in animals and farms, strict decontamination and sterilisation techniques and better regulations that encourage the search for new and novel drugs.

Conflicts of Interest

The authors whose names are listed in this article certify that they have NO affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript. No sources of funding were required for this review.

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