Antimicrobial use, multidrug resistant enteric pathogen, methicillin-resistant Staphylococcus aureus, occupational risks

Introduction

The selection and movement of antimicrobial-resistant bacteria from animals to man has long been recognized. The first attempt to address this issue and produce recommendations was made over 40 years ago by the Joint Committee chaired by Professor M. M. Swann.1 The committee particularly addressed the issue of the then-widespread use of antimicrobials prescribed in human medicine as growth promoters and the public health implications of that use. Their recommendation was for the banning of the use of human therapeutic antibiotics as growth promoters for animals. Legislation followed to ban the use of certain antibiotics as growth promoters, but no restriction was placed on the use of such antibiotics for therapy or prophylaxis in animal use.

Prophylaxis is usually applied to food animals as mass medication (metaphylaxis). Examples are the use of medicated feed or water to prevent the emergence of infection in poultry, such as the vertical transmission of mycoplasmas through the egg to chicks, colibacillosis occurring during the post-weaning period in pigs, respiratory problems when young animals are regrouped and `shipping fever' following transport. Antimicrobials are also widely used on dairy farms for the prevention and treatment of infectious diseases, particularly of bovine mastitis,7 with systematic administration of antibiotics at different stages of the cow's productive cycle (for example, the dry period, 1–2 weeks before calving, and therapy of mastitis cases during lactation).8

In the UK, a total of 44.7 tonnes of antimicrobials were sold for animal use in 2010, of which 87% were purchased for prophylaxis and treatment of infections in food-producing animals.3 Fluoroquinolone and β-lactam antibiotics, including third-generation cephalosporins (3GCs), such as ceftiofur, are used increasingly, and these antibiotics are known both to cause co-selection and to select cross-resistance in bacteria common to man and animals. The strong selective pressure experienced by bacteria within the farm environment might facilitate the emergence of antibiotic resistance in livestock populations, with the potential for transfer to the human population and back to animals via different pathways (Figure 1).4

The emergence of methicillin-resistant Staphylococcus aureus (MRSA) in livestock, specifically in pigs5,6 and cattle,7 with potential for transmission to human populations, has raised concerns about the role played by animals in human MRSA carriage and infection, in particular in people in close contact with livestock, such as farmers and veterinarians. Although the extent of this
problem in the UK is considered to be limited, continuous surveillance and further investigations are required to enable a better understanding of the role of animal reservoirs and their impact on animal and human health.

The growing problem of resistant Gram-negative bacteria capable of producing extended-spectrum β-lactamases (ESBLs) has become a challenge in human medicine, not only for the effective treatment of healthcare-associated infections but also for the treatment of community-acquired infections, such as urinary tract infections (UTIs) caused by ESBL-producing Escherichia coli. The reports in recent years of the emergence of ESBL-producing E. coli in livestock9,10 have triggered alerts about the potential association between animal and human infections, and the likely selection for ESBLs due to the increased use of 3GCs in animal husbandry.

Concerns regarding antimicrobial resistance and infection control should not be limited to the human health sector, and collaborative initiatives with other professionals should be encouraged, particularly with veterinarians. In this context, veterinarians have a duty to control unnecessary chemotherapy and ensure appropriate use of antibiotics in animal husbandry. The UK Department of Health’s Advisory Committee on Antimicrobial Resistance and Healthcare-Associated Infection (ARHAI) considered it important to ensure that both the human and the veterinary health sectors worked together to address concerns around two main areas: MRSA and multidrug-resistant Gram-negative bacteria in humans and animals. The recommendations and guidance about these two topics, together with a review of the current knowledge, are presented in this paper, which exemplifies the importance of working across sectors to tackle global health problems.

**Methicillin-resistant Staphylococcus aureus**

**Background**

S. aureus is an important pathogen in humans that can produce a wide range of diseases, from minor skin infections to severe illnesses. Since the introduction of penicillin in the 1940s, the mortality due to infections caused by S. aureus and other Gram-positive bacteria has been considerably reduced. However, soon after the introduction of penicillin, the first reports of penicillinase-producing bacteria appeared, and by the late 1960s ≏80% of S. aureus recovered from hospitals and the community were penicillinase producers. In 1959, methicillin was introduced as an antibiotic resistant to the action of penicillinases, but only 2 years later, in 1961, the first MRSA was reported in the UK. In the last three decades MRSA in humans has become more widespread. In the UK, this is related primarily to exposure in healthcare settings, although community MRSA are increasing, and in some countries (the USA for instance) this is a cause of considerable concern. Although there has been a decrease in hospital-acquired MRSA in the UK as a result of the efforts and initiatives launched in recent years at national and
local level, MRSA control still remains a top priority for the health services in this country.

MRSA have been isolated from both healthy and diseased animals of many species, with MRSA infections having implications for animal health and welfare. The first reported animal MRSA isolate was recovered from milk from dairy cows in 1972 in Belgium,15 and since then it has been found in dogs, cats, horses, cows, pigs and poultry worldwide.16 Until recently, MRSA have been generally considered a human problem, with most efforts being devoted to controlling MRSA within the human population. However, reports of a porcine-associated MRSA strain causing infections in humans in close contact with pigs5 have highlighted the risk that animals, particularly food-producing animals, might pose to public health. In addition to this, the recent discovery of a novel bovine-associated MRSA strain infecting cattle and humans in England and Denmark7 has added to these concerns over livestock acting as a potential reservoir of resistant pathogens.

The multi-disciplinary working group of the Department of Health’s Advisory Committee on ARHAI considered it important to review the current knowledge about animal MRSA, as well as exploring and providing guidance on the occupational health issues for staff working in veterinary practice relating to animals infected or colonized with MRSA. Although such exposures are currently infrequent in England, MRSA was considered because it has a high public profile and there are fewer effective antibiotics to treat MRSA infections compared with those caused by methicillin-susceptible S. aureus (MSSA). However, many of the issues raised for MRSA apply equally to other organisms and veterinary practices. The group emphasized the general need to apply good standards of infection prevention and control and recognized that some veterinary practices had excellent infection control documents, which could be made available to others as examples of best practice.

MRSA in dogs and cats

MRSA have been isolated from healthy dogs and cats as well as from clinical cases, with the majority of isolates so far identified as common human-associated strains (e.g. EMRSA-15, and more rarely EMRSA-16 in the UK).17–19 This suggests a potential reverse zoonosis, which is facilitated by the close contact between pets and humans (e.g. in dogs and cats living in the home). Pets are thus colonized through contact with humans carrying MRSA and then they become a source of re-infection or re-colonization.16 In some cases, an infected human can be traced as a potential source of MRSA.20 Therapy animals (trained pets used as part of certain therapeutic schemes aiming to improve social, emotional and cognitive skills of people in nursing homes, hospitals or rehabilitation centres) can also become the reservoir or source of MRSA colonization and/or infections of humans in healthcare facilities and guidance is available relating to prevention and control of MRSA in these companion animals.21

Although there are few data on prevalence of MRSA in dogs and cats, a number of reports have described MRSA carriage rates within the animal hospital setting as ranging from 5% to 13%.17,18 This has led some to consider the possible issue of MRSA as an emerging problem in these species. However, a recent prevalence survey of healthy companion animals in the UK indicated that MRSA carriage in the community was low (overall prevalence of 1.5%), with a prevalence in dogs of 2.1% and in cats of 1.5%, suggesting that companion animals carrying MRSA probably pose a low risk for human health.22 Similarly, low prevalence rates in healthy animal populations have been reported in other countries,23,24 and no MRSA were isolated in a survey of 200 healthy dogs in Slovenia.25 Risk factors for MRSA infection in dogs and cats have been found to follow a similar pattern to those identified in MRSA infections in humans. A case–control study undertaken in the UK reported that the number of antimicrobial courses, the number of days admitted to a veterinary hospital, having surgical implants and having contact with humans who have been sick or admitted to hospital were significant risk factors for MRSA infection in dogs and cats.26 This study highlighted the importance of adherence to prescribed antimicrobial treatments and the need for responsible use of antimicrobials by clinicians within small-animal practices.26 Conversely, a recent study of risk factors for MRSA carriage in companion animals described surprising results in that risk factors that have been typically associated with human carriage (e.g. antimicrobial use and hospitalization), were not found to be significant in companion animals, which suggests that these animals might not be acting as an MRSA reservoir but instead behaving as a vector in transmission.22

MRSA in horses

MRSA is recognized increasingly as a cause of morbidity and mortality in horses, and has been isolated from both healthy and diseased animals. Most of these reports, however, have been from horses under veterinary care or in a veterinary hospital.27 Cases in veterinary hospitals appear to be sporadic, with minor outbreaks occurring. A low MRSA prevalence (0.67%) has been described in the UK general horse population,22 which coincides with findings from other countries, e.g. Slovenia, where no MRSA were identified from a survey of 300 healthy horses.25

The picture in equine MRSA, however, is very different from that in other companion animals, with the majority of horse MRSA strains not being associated with human infections.17,19,28–30 Such strains may have evolved separately in the equine population, which is of public health concern.

MRSA in less-common species of pet animals

MRSA has also been isolated from rabbits, guinea pigs, a turtle, a bat and a parrot. The majority of such isolations have taken place from these animals while attending a veterinary surgeon.31

MRSA in food-producing animals

Food-producing animals pose a potential risk of infection to humans both through direct contact and through food products if not handled correctly and processed. Since 2003, with the first isolation of a novel pig-associated MRSA strain (ST398) in the Netherlands,32 much of the research effort on methicillin resistance in farm animals has focused on the study of this strain recovered from pigs and humans closely associated with pigs. The prevalence of ST398 MRSA among healthy pigs has been reported to be high in comparison with that in other animal species, with rates of up to 40% in the Netherlands.33,34 25%
in Canada35 and 49% in the USA.36 ST398 MRSA have also been isolated from animal species other than pigs, including dogs, horses, chickens and cows in the Netherlands and elsewhere.5,6,32–34,37–39

In dairy cows, S. aureus is a commonly isolated mastitis-causing pathogen.50–43 Antimicrobials are widely used in the dairy industry for the prevention and treatment of bovine mastitis and other infectious diseases.2 However, conventional MRSA isolates have been relatively rarely identified in bovine milk samples, with a few reports of MRSA detection from herds in Belgium,15 Korea,44,45 Hungary,46 Switzerland and Germany.37 The MRSA isolation rates described in these studies varied, ranging from 7.2% of MRSA causing subclinical mastitis on a farm in Hungary46 to lower recovery rates described in Korea (2.8% and 0.18% MRSA isolates detected in milk samples collected from 153 and 2555 farms, respectively).44,45

In the UK, there had been no reports of MRSA isolation from cows up to 2011, when a novel bovine-associated MRSA strain (LGA251), carrying a novel mecA gene, was discovered on dairy farms in this country.7 A previous large-scale prevalence survey, which was undertaken in England and Wales to determine the prevalence of MRSA isolated from dairy cattle,57 failed to identify this novel MRSA, using conventional molecular techniques, owing to the divergent nature of its mecA gene. The divergent mecA (named mecA_LGA251) was revealed using whole genome sequencing, and it appeared to be widely distributed in the UK, although in relatively low numbers (1.4% of S. aureus mastitis isolates carried the new gene, which was found in 2.8% of dairy farms).7

Food products of animal origin in Italy and Korea, including raw bovine milk, have also been found to be contaminated by MRSA isolates. However these isolates were found at a low prevalence, with 3%–3.75% of the S. aureus isolates tested being mecA-positive.48–50

**Animals in contact with humans at high risk of infection**

Animals belonging to owners infected with MRSA are at risk of also becoming infected. Subsequently, infected pets may act as a source of MRSA for their owners, creating a transmission cycle and potentially affecting the clearance of infection from their owners. As such, if measures are being taken to eliminate MRSA from humans, then treatment of in-contact animals may also be required.20,51,52

**Humans in contact with animals**

Where people are working with animals there is evidence to suggest that they are at higher risk of carrying MRSA. Since the discovery of ST398 in 2003, active screening of individuals in close contact with pigs and cattle has been carried out in the Netherlands, resulting in a large increase of reported MRSA, with carriage levels of the pig-associated MRSA strain rising from 0% pre-2003 to 33% of all reported MRSA cases in the human population during early 2007.7 In particular, ST398 MSSA and MRSA carriers have been identified among staff working in close contact with pigs and cattle, such as farmers.5,32,34–36,38,53,54 The contact with pigs has been described as a risk factor for humans to acquire MRSA isolates, with the risk being dependent on the frequency and the intensity of the contacts.54

Reports of ST398 MRSA causing infections in humans closely associated with pigs in the Netherlands raised concerns worldwide about farm animals being a potential reservoir of MRSA.5 ST398 community and hospital-acquired MRSA infections have been reported in other countries, including Denmark and Germany.6 The porcine-associated strain has not yet been encountered in the UK, other than a very few sporadic isolated cases, for which there were no apparent contacts with livestock animals.55 Interestingly, a recent study in the southern part of the Netherlands has shown no increased risk of MRSA carriage in human hospital staff in close contact with livestock outside their hospitals.56

Human and bovine S. aureus strain types are largely host-adapted.57–59 However, there is evidence suggesting that there has been transmission of MRSA between cows and humans.7,15,46 Moreover, the divergent mecA_LGA251 has been identified from both bovine7 and human MRSA strains recovered from clinical samples in the UK, Denmark and Ireland.7,60 and evidence suggests that cows might be acting as a potential reservoir from which novel MRSA strains are transmitted to humans.7 None of the human MRSA strains carrying the divergent mecA_LGA251 belonged to previously recognized human lineages, but were identified as cattle-associated or animal-associated clones. Further work is required to elucidate the precise direction of transmission. The risk of infection via ingestion of milk is non-existent in the UK, where milk is pasteurized, thus killing S. aureus. However, there might be a potential risk for infection and colonization with this new bovine MRSA strain in people in close contact with cattle.7

MRSA colonization has been identified as an occupational risk for veterinary professionals, with a reported prevalence of MRSA of 10% for equine veterinarians and 18% for small-animal hospital personnel.18,61 compared with up to 5% in the general population.61 The prevalence rates of MRSA in veterinarians and related staff most likely reflect transient carriage.42

When samples have been taken from veterinary and farming staff attending conferences, and therefore away from animal contact, higher rates than in the general population have also been found (British Small Animal Veterinary Association (BSAVA) 10%; British Equine Veterinary Association, 8%; Dairy Cattle Conference, 4%; American College of Veterinary Internal Medicine Forum, 6.5%; and Livestock Conference in the Netherlands, 4.6%).53–65 Whether or not such staff continue to be exposed by contaminated articles in their homes, clothing, cars or other fomites, as has been described in some human MRSA cases, is currently unknown.66

A number of groups have previously considered various aspects of MRSA and/or occupational health guidance for veterinary healthcare workers in the UK. The BSAVA produced a set of guidelines for the prevention and control of MRSA in companion animals,21,62 and the British Veterinary Association (BVA) has convened two groups: the BVA Member Services Group, which considered occupational health issues, and the BVA Policy Group, which produced a document on MRSA in all species.
Antimicrobial resistance in human and animals

ARHAI occupational health guidance for veterinary healthcare workers

Veterinary practitioners should consider and review MRSA infection rates in their own patients and set criteria as to when investigation of an increased number of cases is warranted. Multiple MRSA infections within a practice may indicate that MRSA has become an endemic problem and prospective surveillance may be necessary.

Screening of veterinary staff for MRSA

Screening, as in healthcare-associated human outbreaks, is never a substitute for rigorous infection prevention and control measures, particularly hand hygiene, isolation and appropriate decontamination procedures. It is important to realize that routine screening of staff and the environment is not necessary in most circumstances, but when undertaken it is essential to differentiate transient MRSA carriage from colonization and persistent carriage. Transient carriage is more common, and accounts for the majority of MRSA cross-infection. It is controlled most effectively by hand decontamination and other hygiene measures.62,67 Screening of staff, extrapolating from human hospitals, when indicated, should not be performed during or within 12 h (and ideally 24 h) of a period of duty in contact with MRSA-positive animals, as it is very likely to detect transient or short-term MRSA contamination rather than genuine colonization.67 Any resident animals (the practice cat for instance) should also be screened. Staff should be reminded (not just for MRSA-related issues) that they should self-examine regularly for hand and other skin infections and problems with eczema and dermatitis, and report these through locally agreed occupational health arrangements.

Staff screening should be considered in discussion with veterinary occupational health and infection control staff if the epidemiology suggests staff-to-animal transmissions of MRSA that have not been prevented by infection prevention and control measures. The occupational health services, with the consent of the staff member, should liaise and communicate with his/her general practitioner when decolonization treatment is given, or if treatment of any skin condition is required. The ARHAI sub-group proposed that the use of an occupational health service will usually be the most effective way to address staff-related issues. One source of advice and local (charged for) support to veterinary practices can be found at www.NHSplus.com.

Veterinary workers admitted to hospital for treatment

If admitted to hospital, veterinary workers treating MRSA-affected pets will now be amongst those screened as part of the mandatory universal screening of patients admitted for elective and emergency surgery. Such veterinary workers should remind NHS doctors that they have been in contact with MRSA-affected animals. They should not be screened within ~12 h (and ideally 24 h) of contact with such animals as they may be labelled incorrectly as MRSA carriers.

Conclusions

Currently, livestock-associated MRSA and companion animal MRSA are not affecting significant numbers of animals in England, but this needs to be kept under review, particularly after the discovery of a novel cattle-associated MRSA strain causing clinical disease in cows and humans,7 which has highlighted the potential of strains to emerge and transmit to the human population from cattle reservoirs.

Occupational health physicians may recommend staff screening when clusters of animals with MRSA infections and associated on-going transmission occurs. The working group confirmed that some veterinary workers exposed to MRSA-affected animals were not currently able to access occupational health advice. It was proposed that such advice, where not available locally, should be sought from www.NHSplus.com. Staff must have had at least 12 h and preferably 24 h off-duty before being screened for MRSA.

Multidrug-resistant Gram-negative enteric pathogens

Background

The development of antibiotic resistance in Enterobacteriaceae has very much been a history of the introduction of a novel antibiotic and the relatively rapid appearance of resistance. This was seen when ampicillin, the first non-toxic effective agent with activity against Enterobacteriaceae, was introduced in 1961. In 1968, the resistance rate to ampicillin in pre-admission surgical patients at the Hammersmith Hospital (London, UK) was 17%, most of which could be transferred to E. coli K12.48 A similar scenario occurred with the aminoglycoside gentamicin in the 1970s. In particular, the spectre of Klebsiella pneumoniae strains resistant to all but colistin causing major outbreaks of cross-infection in hospitals spurred the development of 3GCs, such as cefotaxime, ceftazidime and ceftriaxone, and their introduction in 1981–82. These are highly active agents, which were designed to be invulnerable to hydrolysis by the prevalent β-lactamases carried by Gram-negative bacteria (GNB)—namely TEM and SHV. Their performance was impressive, but the harbinger of doom appeared rapidly, albeit initially rarely. The first plasmid-encoded β-lactamase hydrolysing cefotaxime was detected in Germany in 1983,65 being a single amino acid variant of the Klebsiella chromosomal β-lactamase SHV-1. It was designated SHV-2, and was the first ESBL, a term later coined by Philippon and colleagues.70 This first review described the French TEM-3 and subsequent variants evolving in different parts of the world, TEM-3 being the first ESBL derived by mutation from the very common TEM-1/2 enzymes that 3GCs were designed to circumvent. Their rapid emergence and dissemination were due to the fact that the ESBL genes were on mobile elements (transposons) located on promiscuous plasmids, leading to spread amongst different species of GNB. Antibiotic resistance in Enterobacteriaceae is particularly difficult to control as large numbers of bacteria occur in the gut with easy dissemination to other individuals, but also, more importantly, to the wider environment through sewage, water and soil to animals and humans and back into the gut flora of previously non-colonized individuals. Most antibiotics active against GNB have

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ESBLs in humans and animals in the UK

During the 1990s ESBLs were rare in the UK, where a national survey only identified some TEM/SHV ESBLs at a rate below 1.9% in Enterobacteriaceae. The first CTX-M outbreak involved the novel CTX-M-26 gene in Birmingham caused by a clone of K. pneumoniae. In 2003–04, increasing reports of ESBLs to the HPA Antibiotic Resistance Monitoring and Reference Laboratory (ARMLR) heralded the upsurge in largely CTX-M-15-producing E. coli and Klebsiella spp. More recently CTX-M-14 has been identified as the second most common genotype, but at a much lower frequency compared with CTX-M-15.

ESBL-producing E. coli have been slightly later to appear in veterinary medicine, but it is clear that both CTX-M-15 and CTX-M-14 are established in dairy herds, with reports from other food animals, including poultry. The first outbreak in cattle caused by CTX-M-14 was recorded in 2004 in North Wales and for CTX-M-15 was in southern England in 2006. It seems most probable that food animals have acquired the CTX-M ESBL genes from human-derived strains. The growing use of 3GCs (particularly ceftriaxone) in the treatment of food-producing animals is concerning and may well be selecting for ESBLs.

ESBLs and the environment and food

Enterobacteriaceae contaminate meat products at slaughter and ESBLs have been demonstrated in a number of studies. One such study of chicken breast meat found very low levels in UK- and Irish-produced meat (1/64 samples had CTX-M-1) but high rates in Brazilian chicken (5/10 samples had CTX-M-2), suggesting this could be a source of human colonization. A detailed study of a town in the Netherlands has linked the rise in human infections caused by CTX-M-1, a genotype previously uncommon there, to high rates in Dutch-produced chicken and asymptomatic carriage in healthy adults in the town.

Both human and animal faeces contain large numbers of ESBL-producing coliforms (ESBLPCs), which can cause cross-colonization to other individuals. This route is obviously very important in food-producing animals and extensive rapid spread through whole herds of animals has been seen. Spread amongst humans in hospitals is well documented not just for Klebsiella spp., but also for E. coli and also in care homes for the elderly. In the ‘true’ community amongst family groups, ESBLPCs have been shown to spread from patients with community-acquired UTI to 16.7% of their family contacts.

Direct contamination of water courses can occur via animals in fields and spreading of manure on land. It has been estimated that ~70 million tons of animal manure are spread onto agricultural land per annum in the UK. Multidrug-resistant bacteria have been detected in subsurface water flow several months after pig slurry was applied to agricultural soils, illustrating persistence and dissemination to water catchments. The extent to which ESBLPCs or their antibiotic resistance genes in the environment flow back into man is not understood, as large-scale integrated studies have not been undertaken in the UK. It is reasonable to assume in countries in South Asia, where sewage and water treatment are variable and there is extensive use of antibiotics, that flow is significant and is a major driver of the high levels of antibiotic resistance in Enterobacteriaceae seen in those countries.

Carbapenem resistance in Enterobacteriaceae

The global distribution and increasing prevalence of CTX-M-producing Enterobacteriaceae has caused an accelerating change in prescribing in human medicine away from 3GCs and quinolones to carbapenems, such as meropenem, imipenem and ertapenem, and formulations including a β-lactamase-inhibitor or antibiotic combinations (e.g. co-amoxiclav and piperacillin/tazobactam). There has been particular concern over
carbapenem-resistant Enterobacteriaceae and Pseudomonas spp., which are endemic in the USA, Israel, Greece, parts of South America and China. The rapid appearance and then spread from South Asia of the New Delhi metallo-β-lactamase (NDM-1) has caused considerable alarm because of the almost pan-resistance of isolates in which it is found and the rapidly mobile genetic elements on which it is located. The spread was initially linked with ‘medical tourism’, mainly from the UK, but spread to the Middle East and Balkans has occurred. In India, environmental dissemination seems to be extensive, with detection in wastewater seepage and tap water. In China NDM-1 has now been found in Acinetobacter baumannii, but most clinically significant carbapenem-resistant isolates across the country carry KPC-2 or IMP-4. IMP-4 was originally described in Citrobacter youngae in China in 1998.

These carbapenemases are spreading rapidly and are increasingly seen in E. coli. It seems likely they could follow the same epidemiological model as CTX-M ESBLs, making the further study of these bacteria, which have already dispersed, a paradigm for the recognition and control of carbapenemases.

**Scope and purpose of the report of The Joint Working Group of DEFRA Antimicrobial Resistance Co-ordination (DARC) and ARHAI 2012**

The first attempt to carefully consider the impact of the veterinary use of antibiotics in food production was the Swann report in 1969. This joint committee was appointed by both the Health and Agriculture Ministers. It recommended that only antibiotics that ‘have little or no application as therapeutic agents in man and animals and will not impair the efficacy of a prescribed therapeutic drug or drugs through the development of resistant strains of organisms’ should be used for growth promotion. Tetrazyclines, penicillins, tylosin and sulphonamides were all identified as unsuitable for use in animals and the government largely accepted their findings. The later report from the House of Lords Science and Technology Committee further emphasized the importance of considering the impact of animal and human use of antibiotics together. It was against this historical background and the rapid rise of ESBLPCs in both humans and animals in the UK that a joint working group of ARHAI and DARC was established under the chairmanship of Professor Peter Hawkey. The report they produced (The Joint Working Group of DARC and ARHAI 2012) addressed the following issues: (i) the current state of knowledge with regard to the occurrence, distribution, identification and ecology of ESBLPCs; (ii) the causation and development of the problem; (iii) the impact on human and animal health; and (iv) identification of the areas in which collaborative working and research could lead to a greater understanding, a reduction or a slowing of the rate of increase in the occurrence of ESBLPCs. The report provides a range of recommendations for public health and animal health.

**Findings and recommendations**

The committee decided to consider both animal and human issues together in sections in which a particular theme was addressed. The recommendations arising from each theme are shown in Figure 2 and the research gaps identified are listed in Figure 3. The full discussion and recommendations have been published. A brief synopsis of the contents of each theme discussion is given below.

**Characterization**

The importance of both clinical and veterinary laboratories being able to reliably identify ESBLPCs, plasmidic AmpC producers and carbapenemase-producing GNB was recognized. The need to employ methods appropriate for the level of characterization needed (i.e. DNA sequencing to identify a specific genotype is inappropriate for a routine diagnostic sample in which an E. coli is thought to be significant). A high level of characterization is important in an epidemiological study.

A review of the currently used screening tests was undertaken and optimum breakpoints were presented, together with an algorithm for phenotypic testing. All of the current phenotypic and molecular confirmatory tests are described with advice on the selection of the most appropriate tests. A special sub-section considered the peculiarities of identifying and characterizing carbapenemase producers.

**Transfer pathways**

The complex inter-relationships of different sources of ESBLPCs and their routes of transfer between man, animals and different environmental compartments were considered. This is best summarized diagrammatically and is reproduced from the report in Figure 1. The major drivers for selection and transfer were identified, the single most important being antimicrobial use. The likely impact of changes in use of antibiotics such as 3GCs and fluoroquinolones was examined, particularly in relation to evidence for direct versus co-selection. The possible significance of antibiotic residues and quaternary ammonium compounds in selecting for Class 1 integrons, on which many ESBL and carbapenemase genes are carried, was also examined. The pathways of transmission, whilst appearing to be straightforward, are more complex, as ESBLPCs have a significant reservoir in individuals in the community and there is a lack of data. The influence of travel to and from areas of the world with a high incidence of ESBLPCs was recognized as important, but again data on the degree of ‘escape’ and persistence of such strains is lacking. The knowledge of transmission in the healthcare setting is more comprehensive and the evidence base to inform control more robust. In the food animal setting, local spread has been documented, with presumed spread through manure contamination. The factors resulting in persistence are not very clear but antibiotic use plays some part, as it does in the human setting. Data on likely risks of transmission from animals via food are largely lacking, but studies published after the report indicate this can be a route of human gut colonization. In turn, the ultimate fate of ESBLPCs arising from animals and man in the wider environment is not entirely clear. Many bacteria will die in the course of handling and spreading manure and the processing of human sewage; however, a significant number will probably survive. Limited data reviewed by the group suggested that the opportunity for transfer back into water and food sources, particularly for animals, does exist. These transfers are poorly studied and no reliable estimate of the size of the resistance gene flow can be made.
Characterization

1. All clinical laboratories should identify coliforms to species level and use reliable tests for detection of ESBLPCs adhering to EUCAST breakpoints whilst testing all presumptive ESBL-producing isolates for the presence of ESBLs.

2. All clinical laboratories should report overall prevalence of ESBL phenotypes on coliforms and they should increase the usage of rapid ESBL tests to ensure patients are given optimal treatment.

3. Protocols for appropriate use of reference laboratories should be in place. These should include any Enterobacteriaceae isolate suspected of being carbapenem-resistant must be sent to the HPA reference laboratory for confirmation and typing. All reference laboratories should be capable of providing genotyping of both ESBL genes (e.g. CTX-M) and producer strains to elucidate epidemiology and support surveillance for new successful clones.

Transfer pathways

1. Further work should be carried out to understand what happens to bacteria with antimicrobial resistance genes in human and animal waste during storage and associated processes before it is applied to land.

2. The carriage rate of ESBLPCs in the healthy human population and in travellers to high prevalence areas should be determined as denominator data from which to compare rates of ESBLPCs in patients with exposure to healthcare facilities.

3. The prevalence of ESBL-carrying organisms or resistance determinants in retail food samples, environmental samples and all categories of food handlers should be determined to elucidate the resistance gene cycle.

Surveillance

1. Standardized data should be collected and published on the use of antimicrobials in hospital and community settings, as well as in veterinary practice.

2. Medical and veterinary laboratories should provide prevalence data of ESBLPCs which should include the capacity to identify both epidemic and emergent bacterial clones carrying ESBLs as well as epidemic promiscuous plasmids bearing ESBLs and any increases in prevalence. Data should be provided to clinical teams and to the local HPU along with details of agreed actions to be taken following a significant rise in cases.

3. Local data on rates of infection caused by ESBLPCs should be used for risk assessment and should include targeted prevalence surveys in critical areas e.g. intensive care, renal and other specialized units. Data should be collected and disseminated through the CCDC and DIPCs to relevant clinicians with appropriate advice and guidance for action to reduce rates of infection.

Therapy

1. Appropriate national guidelines on antimicrobial prescribing, and good antibiotic stewardship should be followed and should include education and training of staff. Critically important agents used for treating human infections (e.g. carbapenems) should not be licensed for use in animals. Agents such as carbapenems, glycolcyclines and polymyxins should be used extremely judiciously. Susceptibility tests should be undertaken whenever possible with proper medical assessment before these agents are used.

2. Professional bodies (e.g. BVA and BSAC) should actively inform practising clinicians and veterinarians about the problem of ESBLs, via sharing of information in appropriate journals.

3. Local and national point prevalence surveys on combination therapies or treatment options which have been tried in outbreak and/or difficult cases, should be published to provide information for others to consider. The efficacy of the various treatment regimens for ESBL-associated UTI needs analysis, or better, prospective clinical trials.

Control options

1. All organizations should consider developing clear guidance on good infection control practices to include recognition and management of an outbreak of multi-resistant Gram-negative bacterial infections (including ESBL infections). The guidance should be based on national guidance and be appropriate for their settings and should include education and training of staff and appropriate written information for patients and the public.

Figure 2. Summary of recommendations made by the advisory committee.
The historical emergence of ESBLPCs and carbapenemase producers was documented in both animals and man. The adequacy of regional and national surveillance was reviewed and recommendations were made.

Therapy

The importance of identifying patients with ESBLPCs and ensuring rapid treatment was recognized by the group. The importance of risk-based empirical regimens was emphasized, as was the early use of carbapenems in those with clear features of sepsicaemia. A useful and comprehensive table of agents available to treat infections in humans caused by ESBLPCs and carbapenemase producers was prepared.

Control options

The interventions needed to control the spread of ESBLPCs in the healthcare setting were worked out more than 30 years ago with outbreaks of gentamicin-resistant Klebsiella. They were reviewed

Figure 2.

Continued.

Research gaps

1. A wider surveillance of gut carriage of ESBLPCs in humans should be incorporated into Infectious Intestinal Disease (IID) programmes.

2. Carriage of ESBLPCs in domestic and imported foods warrants further investigation.

3. ‘Point of care’ testing or other rapid detection methods for ESBLPCs should be explored.

4. The effectiveness of selective gut decontamination needs to be reviewed.

5. Further research into novel therapies (e.g. gamma irradiation of food and the use of vaccines) should be undertaken.

6. Further research into routes of transmission and human–animal cycling should be carried out and if appropriate, further research into methodologies to minimize such transmission. The possibility of reducing ESBLPCs in human and animal waste prior to release into the environment should be evaluated as a control option.

7. Research on the carriage patterns of resistant bacteria in animals compared with humans and the influence of the usage of various antimicrobials would be useful.

Figure 3. Summary of research gaps in understanding ESBLPCs identified by the advisory committee.

Surveillance

The historical emergence of ESBLPCs and carbapenemase producers was documented in both animals and man. The adequacy of regional and national surveillance was reviewed and recommendations were made.

Therapy

The importance of identifying patients with ESBLPCs and ensuring rapid treatment was recognized by the group. The importance of risk-based empirical regimens was emphasized, as was the early use of carbapenems in those with clear features of sepsicaemia. A useful and comprehensive table of agents available to treat infections in humans caused by ESBLPCs and carbapenemase producers was prepared.

Control options

The interventions needed to control the spread of ESBLPCs in the healthcare setting were worked out more than 30 years ago with outbreaks of gentamicin-resistant Klebsiella. They were reviewed
by the group and updated and refined. The position for control of ESBLPCs in the community is much more difficult. A better understanding of the contribution of different drivers to maintaining high levels of faecal colonization in the community is needed before definitive recommendations can be made. Spread from food and the environment in the UK would appear to be modest, but continued exposure to even low levels of ESBLPCs could drive the problem. Again there is a lack of data on the influence of different environmental compartments.

Control in the veterinary arena is potentially difficult but rests heavily on limiting antimicrobial use to avoid selection, changing husbandry and improving biosecurity. The problems associated with ESBL genes moving into zoonotic pathogens such as Salmonella enterica will require special efforts if they become more common in the UK.

Outcome measures
The group has made recommendations for the institution of better structured evidence-based outcome measures against which the effect of interventions can be judged.

Conclusions
ESBLPCs have extremely complex interactions with their human and animal hosts, selection by antibiotics and the varied environments in which they can survive and be transmitted. The working group has attempted to identify areas where we have enough data to formulate practical interventions and have brought these forward for use by society. Some areas are unclear due to lack of data and a series of recommendations for future research (Figure 3) have been presented. ESBLPCs, unlike the small-pox and polio viruses are a microbial threat that can never be eliminated, merely ameliorated. It is likely that the most significant changes in selection and transmission of ESBLPCs can only be brought about by large-scale changes in the ways we use antibiotics, produce our food, dispose of sewage and produce drinking water. This report provides pointers for those changes and promulgates practical advice based on our current state of knowledge, domestic and industrial infrastructure and practice.

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