

REPORT OF THE STAKEHOLDER MEETING TO DISCUSS ANTIMICROBIAL RESISTANCE AND THE EXTENT THE FOOD CHAIN CONTRIBUTES TO THIS PROBLEM

**Conference Rooms A & B,
Food Standards Agency Headquarters
Aviation House
125 Kingsway
London WC2B 6NH**

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Delegate List

Annex B attached.

Abbreviations

Annex C attached.

Chair's introduction and welcome

1. The Chair, Professor Bill Reilly, welcomed everyone to the stakeholder meeting to discuss key issues concerning bacteria exhibiting antimicrobial resistance and the role the food chain may play in this phenomenon.
2. The Chair explained that the Food Standards Agency (FSA) arranged this meeting with interested parties to discuss these issues. He outlined the format for the meeting: in the morning there would be a series of presentations to provide background information and act as a stimulus for later discussion. Although there was time for a small number of questions after each presentation these were for clarification purposes only as the afternoon discussion session would provide the opportunity for more wide-ranging questions and comments.

Presentation 1: Antimicrobial resistance and the food chain – Dr Judith Hilton (Food Standards Agency)

3. The Chair invited Dr Judith Hilton to provide an overview of issues relating to antimicrobial resistance and the food chain.
4. An antimicrobial agent is a compound which, at low concentrations, exerts an action against microorganisms and exhibits selective toxicity towards them. Antibiotics are a particular type of antimicrobial agent – they are produced by, or derived from, a microorganism and selectively destroy, or inhibit the growth of, other microorganisms. Antimicrobial resistance is the ability of a microorganism to withstand an antimicrobial. Resistance to antimicrobial agents is often transferable and increases in

frequency in a bacterial population in response to selective pressure. The primary selective pressure that drives the emergence of antimicrobial-resistant bacteria is the use of antimicrobial drugs.

5. Bacteria that are resistant to antimicrobials used to treat disease in humans are a particular problem in modern medicine and the food chain may contribute to this problem. Disease-causing bacteria (pathogens) that are foodborne may be resistant to such antimicrobials. Other organisms which are found in foods but do not cause disease (commensals) can also be resistant to antimicrobials. Resistance from commensals can transfer to other bacteria, including pathogens under the right circumstances. The gastrointestinal (GI) tract may be colonised by commensal or pathogenic bacteria from food and the environment and as the GI tract is an important source of bacteria that cause endogenous infections, colonisation by antimicrobial resistant bacteria could have serious consequences.
6. Antimicrobials have a number of uses in animals. As in human medicine they may be used to treat disease. They are also used to prevent disease (prophylaxis) and this may be done on a large scale e.g. by treating a whole herd or flock (this is called metaphylaxis). Historically antimicrobials have also been given to animals in low doses to promote the growth of the animals (in which setting they are referred to as 'growth promoters').
7. There has been a longstanding concern over the use of antimicrobials in animals and the impact this may have on their use for treatment of human disease. A number of reports have been produced on the use of antimicrobials in animals, particularly those animals destined for the food chain. These include the Netherthorpe report (1962), the Swann report (1969), the Lamming report (1992) and the Advisory Committee on the Microbiological Safety of Food (ACMSF) report (1999). The Netherthorpe report (1962) recommended that there was no need to change animal husbandry practices but that this was an area that required monitoring. The Swann report (1969) identified the use of antimicrobials as growth promoters as a risk and the Lamming report (1992) suggested that prophylaxis may also be a risk.
8. The ACMSF report (1999) focused on therapeutic and prophylactic use of antimicrobials in animals (and farmed fish) as a risk factor for the emergence of organisms resistant to antimicrobials used in treatment of human infections. They also considered the role of imported food as a source of resistant organisms.
9. The ACMSF concluded that resistant bacteria in food animals have arisen as a consequence of the use of antimicrobials in the farm environment and current husbandry practice and that this is the origin of at least some of the resistant foodborne bacteria (such as *Salmonella* and *Campylobacter*) causing human infection. They suggested that some resistant bacteria will find their way to man through food chain exposure

pathways and recommended that we should aim to reduce exposure of farm animal bacterial populations to antimicrobial drugs. A very large series of recommendations, largely aimed at Government, were made in the report.

10. The recommendations from the ACMSF report (1999) were taken forward through the Defra Antimicrobial Resistance Co-ordination (DARC) Group. A final report on these recommendations was made to the ACMSF in September 2007. However since the ACMSF report was written in 1999 newly emerging antimicrobial resistance issues in both human and animal medicine have arisen and require consideration.
11. Following Dr Hilton's presentation clarification of the meeting purpose was requested from the floor. Dr Hilton explained that the FSA is considering formulating a new strategy on antimicrobial resistance. This meeting was an opportunity for the Agency's stakeholders to share their views on antimicrobial resistance and the direction the Agency should be heading towards. The Chair added that the open discussion session later in the meeting would also help to determine the role of the Agency in tackling antimicrobial resistance and should identify areas of particular concern. Comments gathered during the meeting would be fed into the consultation process of a new strategy for antimicrobial resistance.

Presentation 2: Antimicrobial resistance in foodborne zoonotic pathogens in England and Wales, 2001 - 2006 – Professor John Threlfall (Health Protection Agency)

12. The Chair invited Professor John Threlfall to provide an overview of the available information relating to antimicrobial resistance in foodborne pathogens and commensals in England and Wales.
13. Prof Threlfall explained that there was little information available on antimicrobial resistance in commensal bacteria because these were not usually sought in formal surveys. However there was considerable data available for foodborne pathogens and he would concentrate on resistance in *Salmonella enterica*, *Campylobacter* spp. and *Escherichia coli* O157.
14. *Salmonella enterica* from two serovars, Enteritidis and Typhimurium, account for the majority of isolates of *Salmonella* received by the Health Protection Agency (HPA). Since peaking in the mid-1990s the levels of *S. Enteritidis* had generally declined. This appeared largely due to a large decrease in isolates of *S. Enteritidis* PT4 following vaccination of poultry flocks in the late 1990s. Antimicrobial resistance in *S. Enteritidis* between 2000 and 2006 had risen slightly from 19% of isolates to 26% but the percentage of multi-drug resistant organisms had remained low, peaking at 3% of isolates in 2004. Particularly notable during this time was an increase in resistance to fluoroquinolones from approximately 10% to 20%. Much of this was believed to be due to *S. Enteritidis* PT1 isolates linked to non-UK eggs and/or foreign travel. During this time drug

resistance among *S. Typhimurium* decreased from a peak of 90% of isolates in 2002 to 62% in 2006. The percentage of multi-drug resistant isolates in this serovar is much higher than for *S. Enteritidis* with a peak level of 76% in 2002 decreasing to 44% of isolates in 2006. The decrease was believed to be due to a decrease in a particular type of multi-drug resistant *S. Typhimurium*, DT104. Unlike *S. Enteritidis* resistance to fluoroquinolones has remained relatively constant at approximately 10% over this period of time. Mapping antimicrobial sales to resistance levels in *S. Enteritidis* and *S. Typhimurium* did not show a positive correlation i.e. decreased sales did not result in decreased levels of resistance.

15. Resistance to fluoroquinolones is particularly concerning as this is an important class of drugs for treatment of human infections. Between 2000 and 2005, 14% of 130,000 *Salmonella* isolates from 10 European countries exhibited fluoroquinolone resistance via a variety of mechanisms. The majority of these were due to mutational change but a new mechanism of transferable fluoroquinolone resistance has also been described recently in *Salmonella*. The presence of another relatively newly described antibiotic resistance mechanism, the CTX-M type extended spectrum beta-lactamases (ESBLs), which confer resistance to beta-lactam antibiotics in *Salmonella* was also highlighted.
16. In *Campylobacter* resistance to two important antimicrobials, ciprofloxacin and erythromycin, shows marked differences in resistance rates between the two main disease causing species, *C. jejuni* and *C. coli*. *C. coli* is generally more resistant to these drugs than *C. jejuni*. Resistance to ciprofloxacin peaked at approx 45% of isolates for *C. coli* and around 30% of *C. jejuni* isolates in 2005. The difference was even greater in terms of resistance to erythromycin with *C. coli* resistance rates increasing markedly from 2002, peaking at 40% of isolates in 2005 and remaining near this level. *C. jejuni* had consistently low rates of <5% of isolates resistant to erythromycin over this time. Again changes in sales data did not reflect changes in drug resistance.
17. Antibiotic resistance in verocytotoxigenic *E. coli* O157 isolates has remained at approx 20% since 2001. Multi-drug resistance in these organisms has generally remained low, although cases of infection associated with foreign travel are more often multi-drug resistant and this has increased over time from 31% of isolates in 2003 to 43% in 2006.
18. The question of the importance of gene exchange between commensals and foodborne pathogens was raised from the floor and the Chair explained that this would be dealt with in a subsequent presentation. The practice of testing *E. coli* O157 isolates for drug resistance was queried as infection with this organism was not generally treated with antibiotics. Professor Threlfall explained that as *E. coli* O157 was a priority organism for the HPA all isolates were characterised in detail. They were also a useful marker organism. Clarification was sought over whether the comments regarding vaccination and the decline in *S. Enteritidis* PT4 was referring to the specific *S. Enteritidis* PT4 vaccine or another vaccine.

Professor Threlfall confirmed that he was referring to the overall egg vaccination policy in the 1990's.

Presentation 3: Antimicrobial use and resistance issues in food animal production – Mr John FitzGerald (Veterinary Medicines Directorate) and Dr Nick Coldham (Veterinary Laboratories Agency)

19. The Chair invited Mr John FitzGerald and Dr Nick Coldham to outline antimicrobial use and resistance issues in food animal production.
20. Mr FitzGerald began by outlining Defra policy which starts from the premise that antimicrobials are important for animal health and welfare but should be used responsibly. They are not and should not be used as a replacement for good farm management/husbandry. Use of antimicrobial medicines and resistance in livestock production should be monitored and antimicrobial medicines should only be used under veterinary prescription.
21. Regulatory controls on veterinary medicines are set by an EC Directive. All veterinary medicines have to have a marketing authorisation and pharmaceutical companies have to prepare dossiers to international standards. The European Medicines Agency (EMA) or national authorities assess dossiers to the same standards for risk/benefit balance of safety, quality and efficacy and human regulatory authorities are involved in assessment of antimicrobials for food producing animals.
22. The Government has published a comprehensive strategy to address the issue of antibiotic resistance and a key element identified in this was the need to detail the quantity of antibiotics sold annually. This was also an ACMSF recommendation.
23. The Veterinary Medicines Directorate (VMD) has undertaken this task and produced data covering 14 years (1993-2006). Data on sales of veterinary antimicrobial products from pharmaceutical companies is now collected as a statutory requirement (EC Directive 2001/82 as amended). Eight reports have been published and these are available on the VMD website.
24. Dr Nick Coldham then gave an overview of the work undertaken by the Veterinary Laboratories Agency (VLA) for surveillance of antimicrobial resistance. Two types of surveillance are undertaken – passive, which relies on reported incidents and is useful for trend analysis and active, which comprises structured surveys designed specifically for prevalence estimation.
25. Examples of passive surveillance include collecting data from all *Salmonella* isolations as these are all reportable (clinical disease and others); *Salmonella* voluntary surveillance (e.g. Lion code for layers); diagnostic submissions to VLA reference laboratories and enhanced surveillance for hazard detection. Examples of enhanced surveillance for

hazard detection includes CTX-M ESBL producing *E. coli* and Meticillin Resistant *Staphylococcus aureus* (MRSA) where proactive provision of detection and typing for assessing risk to the food chain is undertaken.

26. Examples of active surveillance includes EU baseline surveys (*Salmonella* in layers and broilers); *Salmonella* national control plans (breeders, layers and broilers, turkeys and pigs); abattoir surveys of foodborne zoonoses and *E. coli* (cattle, sheep and pigs) and research studies (*Salmonella* in cattle). Results from the 2004/05 survey of the prevalence of *Salmonella* species on commercial laying farms in the UK showed that 76% of isolates were sensitive to all 16 drugs tested.
27. Clarification from the floor was requested regarding whether MRSA and ESBLs were actually known to be foodborne zoonoses or whether they were potentially in this category. Dr Coldham indicated that, at present, they are only considered potential foodborne zoonoses but MRSA in pigs in Europe is definitely a zoonoses and human clonal complexes have been found circulating in pigs in Canada. The Chair asked whether information was shared freely between the different human and veterinary research groups and organisations. Dr Coldham explained that there was a great deal of co-ordination with the DARC group membership covering both human and animal medicine and joint posts in the VLA and HPA. DARC produced a report covering data on antimicrobial resistance in organisms isolated from humans, animals and food in early 2007.

Presentation 4: Antimicrobial use and key resistance issues in humans - Dr Alan Johnson (Health Protection Agency).

28. The Chair invited Dr Alan Johnson to provide an overview of issues relating to antimicrobial resistance in human infections.
29. Antimicrobial drug use appears to be a driving force for the emergence and spread of resistance. The majority of antimicrobial drug use in the UK is in the community, with 270 tonnes as opposed to 70 tonnes per year in hospitals. Figures from 2004 show that approximately equal amounts of antimicrobials were used in the veterinary sector (454T) as the human sector (401T). The majority of veterinary use was in food producing animals (at least 393T). There are differences between the types and quantities of antimicrobials used in human and veterinary medicines. For example tetracyclines and trimethoprim/sulphonamides are used heavily in animals but not as frequently in humans.
30. Strategies in human medicine to decrease the problems of antimicrobial resistance centre on less and better tailored use of these drugs. Continued surveillance is key to determining whether this is occurring and the effect it is having. However, while bacterial isolates from hospitalised patients are routinely tested for antimicrobial resistance, GPs do not routinely sample patients microbiologically except when treatment fails. This leads to an inherently biased sample from which the antimicrobial resistance data is derived.

31. Antimicrobial resistance surveillance therefore relies primarily on hospital data. Since 1974, hospitals in England and Wales have voluntarily reported infections to the PHLS/HPA, and since 1989, laboratories have also voluntarily reported results of routine antimicrobial susceptibility testing. Surveillance focuses on bloodstream infections.
32. MRSA is one of the key antimicrobial resistant organisms in human infections today. In the UK, the prevalence of MRSA rose markedly throughout the 1990s. In 2001 the Department of Health (DH) made it mandatory for all acute NHS trusts in England to report all cases of bacteraemia caused by *S. aureus* and the proportion of these cases that were due to MRSA. The majority of human infections in the UK are due to two epidemic strains EMRSA-15 and EMRSA-16.
33. Another key antimicrobial resistance is the emergence of increasing resistance in *E. coli* to two important drugs – fluoroquinolones and cephalosporins. Most of the increase in resistance to cephalosporins is due to CTX-M ESBL production by *E. coli*.
34. Following Dr Johnson's presentation the Chair commented that it would be challenging to try to determine how much antimicrobial resistance is foodborne. Other comments from the floor focused on the fact that data on antimicrobial resistance in the community remains a significant gap in current research. Dr Johnson agreed and added that although the majority of antimicrobial resistance is in the community there is currently no 'tapable' data source. GPs are not routinely testing patients for antimicrobial resistant bacteria due to the resource issues involved e.g. time taken for sampling and testing of samples. The resources need to be in place first before this issue can be addressed. It was pointed out that usage of sulphonamides in farm animals has decreased recently from 100 to 70 tonnes. Dr Johnson noted that it would be interesting to see whether the reduction in antimicrobial use in animals has an effect on resistance in human pathogens. The lack of regulation on prescribing antibiotics in some other EU countries was raised as in some, individuals do not need a doctor's prescription for antibiotics and can purchase them over the counter. Over time the bacteria these patients carry may develop antimicrobial resistance and this may spread to other countries when these individuals travel. Dr Johnson commented that microbiologists are aware of the misuse of antibiotics and are looking to address this. There is a distinct north/south divide in Europe regarding this.

Presentation 5: Transmission of antibiotic resistant bacteria - Professor Laura Piddock (University of Birmingham)

35. The Chair invited Prof Laura Piddock to provide an overview of issues regarding the transmission of antimicrobial resistant bacteria.

36. Prof Piddock began by explaining mechanisms of gene transfer among bacteria and explained the process of conjugation as well as the importance of genetic elements such as plasmids, transposons and integrons. The concept of pathogens and commensal microorganisms is a purely human construct – these organisms are often found in the same ecosystems and are able to share DNA. The elements within plasmids, such as transposons and integrons, are key for the development of multi-drug resistance as they allow the ‘stacking’ of resistance genes. For example integrons can incorporate genes that encode resistance to various antibiotics as well as genes that encode resistance to quaternary ammonium compounds.
37. The initial origin of antimicrobial resistance genes can be the producers of antibiotics themselves. These genes then become mobilised and end up in other organisms. Mutation of chromosomal genes is also an important source of resistance.
38. There are considerable problems tracking the worldwide spread of antimicrobial resistance as data from different countries is often not comparable. Fluoroquinolone resistant *Campylobacter* is a good example of this problem. The true numbers of infections caused by these organisms is probably underestimated due to a lack of reporting. This underestimation will vary from country to country due to different systems for collecting such data, making comparison of rates of fluoroquinolone resistant *Campylobacter* impossible.
39. Antimicrobial agents of similar chemical structure to those used in man are used in animals and this can lead to resistance problems that may be significant for man e.g. avoparcin is a growth promoter and has selected for vancomycin resistant enterococci. Although its use is not permitted in the EC it is still used elsewhere. Also, dosing with many antimicrobial drugs is not at the level of the individual animal but at the herd/flock level and this increases selection pressure e.g. fluoroquinolones used for therapy in poultry and ciprofloxacin resistant *Campylobacter*.
40. A key to the spread of resistant strains is the concept of cross-infection. This can occur on farm, in the abattoir or during food processing. Spread of resistant strains can occur among animals and to people, and by and among people. Global travel and importation of food can exacerbate this problem.
41. One approach to controlling antimicrobial resistance is to withdraw antimicrobials from use. For example, it has been shown that fluoroquinolone resistant bacteria appear when fluoroquinolone treatment is initiated and gradually decrease in frequency when the antimicrobial is removed. Such data has been used by the Food and Drug Administration (FDA) in the USA as part of the case for withdrawal of the fluoroquinolones from use in animals. Similar findings hold true for avoparcin and vancomycin resistant enterococci.

42. Although this phenomenon is true for fluoroquinolones it does not hold true for all types of antimicrobials and there is good evidence that resistance to some types of antimicrobials persists even when the selective pressure is removed.
43. In conclusion, controlling antimicrobial resistant bacteria depends upon many factors including the properties of the antimicrobial, the resistance mechanism and the species of bacteria.
44. Clarification from the floor was sought over the role that the use of antibiotics at low doses plays in encouraging the transfer of antimicrobial resistance genes. Mechanisms that might be important that were raised were induction of the SOS response and transfer via phage mobilisation during this process. There was published work showing that fluoroquinolones could induce the SOS response. It is known that transfer of certain virulence genes e.g. shiga-toxins was mediated by phages. Prof Piddock explained that although the SOS response has been shown to occur in the laboratory, it does not happen at therapeutic doses of fluoroquinolones. All antibiotics have to pass the Aymes test before they are placed on the market and this would highlight if this was an issue. In addition, most antimicrobial resistance genes causing current concern are not transmitted by phages. The Chair added that there are many routes of transfer but emphasised that the risk management of these routes is the key.

Presentation 6: Emerging issues - Professor Peter Hawkey (University of Birmingham)

45. The Chair invited Prof Peter Hawkey to provide an overview of newly emerging antimicrobial resistance issues.
46. Prof Hawkey outlined that the major emerging issues in the field of antimicrobial resistance are ESBLs, transmissible fluoroquinolone resistance, carbapenemases and MRSA in animals.
47. Inactivation of penicillins and other beta-lactam antibiotics by beta-lactamase enzymes has been known since the 1960s and new beta-lactamases have been continually appearing since this time. ESBLs, which are active against third generation cephalosporins, first made their appearance in the late 1980s. These were initially variants on classical beta-lactamases but in the 1990s a new class of enzyme, CTX-M, appeared. CTX-M enzymes appear to have been mobilised from the chromosome of a commensal Enterobacteriaceae, *Kluyvera*, and spread into pathogens such as *E. coli*, *Klebsiella* and *Salmonella*. There are a range of different types of CTX-M which are delineated on the basis of differences in their gene sequences. These are named numerically.
48. These new CTX-M ESBLs have become a major problem in human clinical medicine. In the UK there was a large outbreak in the Midlands that was both hospital and community focussed in 2003-4. As discussed

by Dr Johnson, CTX-M ESBL-producing *E. coli* are now a major community and hospital pathogen and almost totally responsible for the higher rates of cephalosporin resistant *E. coli* being seen.

49. There is a worldwide pandemic of ESBL producing *E. coli* and *Klebsiella* spp. The CTX-M enzymes show geographical specificity with, for example, CTX-M-15 the only genotype found in India (accounting for 90% of isolates) whereas CTX-M-14 and to lesser extent CTX-M-3 is most common in China. In the UK CTX-M-15 is the most common type seen, followed by CTX-M-14.
50. India provides a useful case study for the prevalence and spread of CTX-M ESBL producing *E. coli*. 50-60% of hospital isolates of *E. coli* produce ESBLs and many also exhibit multi-drug resistance. In the community approximately 34% of *E. coli* isolates from urinary tract infections are ESBL producers. A similar picture is now also seen in China.
51. The link between organisms found in food animals and human ESBLs is demonstrated by a study in Hong Kong showing that CTX-M ESBL producing *E. coli* can be found in food animals and that these are the same CTX-M types, CTX-M-3 and CTX-M-14, which are predominant in human infections in the Far East.
52. A small study of raw chicken meat at retail sale in the UK found CTX-M ESBL producing *E. coli* in 13% of samples and showed that the CTX-M types found generally represented the most common type seen in human infections in the country of origin of the chicken. For example, CTX-M-2 was found in chicken from Brazil.
53. CTX-M ESBLs can also be found in *Salmonella* although the prevalence varies enormously geographically. Although they are found, they are rare in Europe. However, they are more common in Latin America, the Far East and India.
54. Another emerging issue is that of transmissible fluoroquinolone resistance. Resistance to fluoroquinolones is generally chromosomally located and due to mutations in the *gyrA* gene, which encodes the enzyme DNA gyrase (the target of the antibiotic). This type of resistance is not transmissible.
55. More recently, plasmid mediated fluoroquinolone resistance has been seen. The mechanism of resistance is different to the chromosomally mediated resistance and two types are seen. The *aac(6')* resistance type inactivates the drug whereas the *qnr* resistance type binds to DNA gyrase and prevents the fluoroquinolone from binding. Neither of these mechanisms confers clinical resistance (i.e. they don't cause treatment failure) but they probably allow bacteria to persist long enough in the presence of the drug to mutate and develop classical chromosomal resistance.

56. Resistance to carbapenemases is also now a clinically significant issue in human medicine. Due to emergence of ESBL producers, treatment of Gram negative bacterial infections has become much more difficult. The last reliable treatment option for these organisms is now a group of antibiotics called the carbapenems – these are beta-lactamase antibiotics that are not susceptible to destruction by ESBLs. However, resistance to this class of antibiotic is now being seen.
57. There are a number of different mechanisms of resistance to carbapenems but the most successful is called VIM-2 and this is now appearing in *E. coli*.
58. Another mechanism, KPC, is similar to CTX-M ESBLs in that it is found on plasmids that spread easily among *E. coli* and *Klebsiella* spp. This resistance type is now common in the USA where it has caused a number of outbreaks, particularly on the east coast. It has now been found in Scotland.
59. MRSA although previously a common hospital pathogen has recently emerged as a much more common infection in humans in the community. Unlike hospital MRSA, community acquired strains are much more diverse and generally sensitive to a much greater range of antibiotics. However, a number also carry potent toxins such as the PVL toxin. In the USA a number of specific clones (known as sequence types or STs) have emerged in the community and caused disease.
60. A recent development has been the emergence of a pig-associated MRSA clone, MRSA ST398, in the Netherlands. This MRSA type is common in both pigs and people who look after them, such as farmers and veterinarians. This clone is now widespread in livestock in Europe and has also been seen in Canada. At this point transmission seems to be through close contact but the organism has also been found in foodstuffs.
61. A wide range of emerging antimicrobial resistances of clinical significance have been covered, but not all of these are or will be significant in terms of transmission via food. Transmissible fluoroquinolone resistance has not obviously driven the rise of resistant *Salmonella* and *Campylobacter* so the question of their significance in terms of food is still very open. MRSA is primarily acquired by contact and so is, at present, probably of little significance in food. However, if the expansion of animal MRSA continues and the organism becomes very common in foods this may need to be re-visited. The most concerning at present is CTX-M ESBL producing *E. coli*. The prevalence of these organisms is likely to continue to rise, and when more common, amplification of numbers could occur via the animal gut-human gut bacterial cycle. There is also the question of how far these will develop in foodborne pathogens such as *Salmonella*. Professor Hawkey finished with a final thought – with increased international movement of food should we be concerned about commensal bacteria that are multi-drug resistant?

62. An opinion on the potential significance of *Clostridium difficile* in the food chain was requested from the floor as, although it is not specifically an antimicrobial resistance issue, disease follows antimicrobial treatment. Professor Hawkey highlighted that although *C. difficile* can be found in food and food producing animals the primary issue was acquisition of the organism in hospitals and the amplifying effect that disease and contamination of the hospital environment has. However, he suggested that *C. difficile* should be flagged up as part of this meeting's horizon scanning task and that work to determine whether *C. difficile* is animal or human adaptive may be worthwhile.
63. Another issue raised from the floor was the presence and significance of the resistance gene CMY-2 in *E. coli*, particularly in the USA. Professor Hawkey commented that this gene was similar to CTX-M genes in that it is mobilised onto a plasmid and is seen in bacteria from both cattle and human infections. This resistance is known to be a clinically significant problem in the USA, but is largely under recognised in the UK. It is also known to be a problem in countries such as India. A number of countries may have similar problems with CYM-2 but many of these are not entitled to export meat or meat products to the EU. However, they may export dry products (such as spices, cereals or pulses) to the EU and these may be contaminated due to cross-contamination.

Structured discussion

64. The Chair introduced the afternoon session of the meeting. He reminded those attending that the purpose of this session was to provide a summary of the current issues in antimicrobial resistance and to provide a forum for discussion and stakeholder views. This would provide a mechanism for feeding these views into the development of a strategy paper by the FSA.

Discussion Topic 1: What do consumers and other stakeholders think about antibiotic resistant bacteria in food?

65. Views expressed from the floor were as follows:
- Delegates indicated that antimicrobial resistance issues and the role of the food chain were of concern to them. However, it was felt that among consumers there was a general lack of awareness of antimicrobial resistance and how it relates to the food chain. This could be due to the complex nature of the subject area, which is difficult for the consumer to absorb. Consumer perception was felt to be largely formed by the media on this issue and delegates expressed the view that the quality of media reporting was often very poor. Hence the nature of the message was sporadic and the issues were often poorly explained. To help inform the consumer, messages on antimicrobial resistance need to be clear and should focus on what would have a big impact.

- A recent survey conducted on antimicrobial resistance issues by the Special Advisory Committee on Antimicrobial Resistance (SACAR) indicated that consumer knowledge on antimicrobial resistance was very low with only 10 to 15% of individuals aware of the issues surrounding this subject. A sustainable well financed antimicrobial resistance campaign is required to raise awareness. A survey by the Institute of Grocery Distribution asked 1,000 consumers what they considered to be the priorities in terms of food. Animal health and welfare was flagged up as a high priority whilst the use of medicines in farm animals was considered to be a low priority.
- Part of the reason for the low-level of awareness of antimicrobial resistance issues and the food chain could be due to the lack of specific food surveys on this subject. If these were undertaken it may raise awareness but the question of whether industry would be happy with this approach was raised. It was suggested that if a structured antimicrobial resistance survey was undertaken the survey should try to determine and put into perspective the risk to humans and cover the international situation (imported foods).
- It was felt that lowering levels of antimicrobial resistant organisms could only be beneficial and it was suggested that this may be easier to achieve in animals than humans. As veterinarians make part of their income from prescribing antimicrobials, changing this may reduce antimicrobial use and hence antimicrobial resistance in animals. However, it was pointed out that veterinarians could not adopt the same approach used by GPs in giving less antibiotics to farm animals as the numbers involved in intensive farming (poultry and pigs) are huge and without changing the farming systems large reductions in antimicrobial use were unlikely.
- There is a lack of information on infections in humans and antimicrobial resistance in food and how this links together. It was suggested that the FSA has a role in addressing this.
- It was pointed out that antimicrobial resistance is not generally a direct food safety issue - rather the food chain may act as a conveyor of resistance. This would indicate that the issue is broader than the FSA's remit and clarity of the FSA's role is needed.
- Antimicrobial resistance can be transferred directly to humans by other routes, such as manure spreading on land.
- Emerging issues in the food chain is an area which is developing very quickly. It was pointed out that a small unpublished survey carried out by Dutch scientists showed that MRSA ST398 was present in 20% of pork products, 20% of poultry products and 3% of beef products tested. It was felt that if a similar trend is seen in the UK, people would become more concerned with handling meat with MRSA. Professor Dik Mevius, from the Netherlands pointed out that the bacterial numbers of MRSA in food were very low and that the case-control study carried out by the Dutch did not make a link with food but with direct animal contact. The Dutch opinion is that the food chain currently has a minimal role in the spread of MRSA ST398. Defra commented that both the FSA and Defra are working closely with stakeholders, through the DARC committee, to get a better understanding of new and emerging issues such as MRSA and ESBLs.

- It was suggested that focusing on eliminating pathogens, such as *Campylobacter* and *Salmonella* in foods should be given priority as achieving these targets would also address many of the problems with antimicrobial resistant organisms. It was pointed out that in certain sectors e.g. the pig industry, controlling pathogens in breeding stocks was difficult and a more appropriate control point would be the slaughterhouse. Focusing at the slaughterhouse level should contribute towards reducing both food poisoning and antimicrobial resistance problems. The Chair pointed out that although the *Salmonella* vaccination policy had controlled *Salmonella* in poultry, this has not controlled the bacterial load at slaughter.

The Chair summarised the key points from the discussions within this section:

66. There is not widespread consumer concern about antimicrobial resistance and food in the UK but this is likely to be due to ignorance of the issue rather than lack of concern.
67. There is a need to assess the degree of antimicrobial resistance in the food chain and look for the antimicrobial resistance genes rather than for pathogens. There should be greater emphasis on non-pathogenic bacteria as these organisms are more abundant than pathogenic microorganisms.
68. It was suggested that research could focus on using HACCP to limit the transmission of antimicrobial resistant bacteria. However, at present, HACCP will only control/reduce pathogens and will not necessarily impact on other bacteria.

Discussion Topic 2: What is the risk to consumers from antibiotic resistant organisms in the food chain?

69. Views expressed from the floor were as follows:
 - The risk to the consumer will vary according to their health status and one standard would not apply to all. Vulnerable groups, hospital inpatients and individuals in the community would all have different levels of risk. It was also pointed out that there was more to the food chain than just food and farm animals. The issue of antibiotic resistance in the environment due to food production also needed to be taken into account.
 - It was recognised that the risk to consumers was difficult to quantify due to significant data gaps. Prof Hawkey suggested that antimicrobial resistance in commensals remains a significant research gap and that further research is also required to determine the factors that are influencing the rise of antimicrobial resistance. Commissioning a broad epidemiological study would be beneficial to determine the sources of antimicrobial resistance. Prof O'Brien agreed there is a lack of data on the distribution of antimicrobial resistance in the community and in the food chain and the link between the two. There is some evidence, from

studies in both the USA and Denmark, to suggest that people with antimicrobial resistant infections have worse clinical outcomes. In the UK, surveys of *Campylobacter* infection found no evidence of increased severity if the bacteria was resistant to antimicrobials but outbreak investigations showed that patients with multi-drug resistant *Salmonella* infections fared considerably worse. The issue of antimicrobial resistance and enhanced virulence was discussed at a recent scientific meeting and it was concluded that more emphasis was needed in this area and in particular on the status of the host e.g. "at risk groups" such as the young or elderly. It was also suggested that it would be useful to investigate whether antimicrobial resistance gene transfer from animal plasmids to humans occurs in the human gut, although the difficulties (e.g. ethics) in carrying out such a study were acknowledged.

- It was pointed out that the first report on antimicrobial resistance (the Netherthorpe report) was published 1962 and since then there has been 45 years of research, reports and committees. However the prevalence of antimicrobial resistance and the risks associated with it had continued to rise. Some delegates expressed the view that we were past the point of discussing what to do and instead should actually be doing something.
- There was a recognition that resistance genes are now widely distributed and may penetrate into populations of organisms that can cause severe disease. It was suggested that a holistic approach to investigating this was needed. As antimicrobial resistant bacteria come from a variety of sources a co-ordinated effort is required. The view that there is a tendency for the medical side to push the focus of antimicrobial resistance to the food chain and vice versa was expressed. The research effort should focus on both the medical and domestic arena along with the food chain.
- It was suggested that stopping antibiotic use in animals would not have the desired effect of eliminating antimicrobial resistant bacteria as these are already present and in many cases have been shown to persist even in the absence of antimicrobial selective pressure. Following up this point it was pointed out that there are differences in antimicrobial resistance profiles between human diagnostic data, farm animal data, slaughterhouse data and retail meat data. A recommendation for reducing exposure of consumers to these organisms was to irradiate foods.
- Discussion moved onto the risk to consumers of MRSA in the food chain. As *S. aureus* is a human adapted organism reservations about the importance of food as a source of MRSA were expressed. In general, the contribution of the food chain to the spread of MRSA was felt to be minimal and the majority of delegates agreed with this opinion. The Chair emphasised the need to get the balance of a precautionary approach and a proportional approach right.
- The risk posed to consumers by antimicrobial resistant bacteria in imported foods was raised. It was pointed out that today's consumers tend to eat more salad, fruit and vegetables and a considerable amount of these ready-to-eat foods are imported into the UK to meet the growing demand. This is a possible route for introducing antimicrobial resistance genes into the UK population. This is a global issue and there is a need to look at all populations in the gene pool.

The Chair summarised the key points from the discussions within this section as:

70. All delegates agreed that antimicrobial resistance was a serious issue. However, risk via the food chain was difficult to quantify in isolation.
71. There needs to be a holistic approach to tackling the problem. We need to quantify the gene pool and the role the food chain plays.
72. There is a need to consider other non-food antimicrobial resistance transmission routes.
73. There are parts of the food chain where improvements could influence the amount of antimicrobial resistance and this should be discussed and focussed on.
74. In terms of risk, the food chain is not currently considered to be a significant risk in terms of MRSA

Discussion Topic 3: How important is the international dimension?

75. The Chair began discussions by asking the audience to consider whether importing more foods into the UK is changing the risk of acquisition of antimicrobial resistance via these foods and if so, what could be done about this.
76. Views expressed from the floor were as follows:
 - Prof Piddock agreed that there is a link between imported foods and antimicrobial resistance. She highlighted that in the past there had been good FSA campaigns on food hygiene but despite this, food poisoning levels were still high. She pointed out that the last barrier to infection with foodborne pathogens was often consumer handling in the home, and interventions here would also limit the risk of acquisition of antimicrobial resistant bacteria. Hence interventions could be more targeted at personal hygiene standards.
 - Imported chicken was suggested to be a particular source of problems in this area. It was suggested that the EU should be promoting higher standards, such as those employed by the Swedish and Finnish poultry industry, and applying them to 3rd country producers. Mr FitzGerald pointed out that usage of medical drugs in foods exported to the EU has to comply with EU regulations. However, compliance is determined by residue testing and no testing for antimicrobial resistant bacteria is carried out. Prof John Threlfall pointed out that raw chicken products were not the problem –large outbreaks had been associated with foods that are brought into the UK requiring little or no cooking. This includes for example, salads, cooked meats and eggs. Other delegates suggested that work on salads from EU and non-EU sources could be undertaken

and that issues such as whether these were grown in compost made from animal faeces or water from open water courses should also be looked at.

- There was a question from the floor relating to the recent outbreak of Avian Influenza (AI) in turkeys in Norfolk. Turkeys from Hungary were transported in a raw state to the UK and it was suggested that this posed a real danger. The enquirer wished to know who was responsible for protecting the UK consumers from this risk? Dr Hilton pointed out that Defra are the Enforcement Agency and that measures are in place to protect the consumer when an AI outbreak occurs. These include setting up protection and surveillance zones surrounding the source of the outbreak and restrictions on movement of chicken from other countries that have been implicated in an AI outbreak.
- It was pointed out that the persistence of antimicrobial resistance following withdrawal of an antimicrobial differs according to the antimicrobial in question and that this was not taken into account when setting withdrawal periods for these drugs. It was felt that this could have a global impact and was not addressed by residue testing. Mr FitzGerald confirmed that residue testing looks for residues of the medicine and not for antimicrobial resistance. The difficulty of attempting to use antimicrobial resistance markers as a withdrawal criterion was highlighted from the floor. For example, which organisms do you target to examine – commensals or pathogens, particular serotypes etc?
- The Chair questioned whether imported animal feeds pose a risk of importing antimicrobial resistant bacteria. Contributions from the floor suggested that this was potentially an issue but that very little data on this was available. It was noted, for example, that the UK poultry industry does import animal feeds although these should be heavily processed, which should reduce the risk. However, it was felt that there was even less data on other potential sources such as animal manures and sludges. It was pointed out that many organisms found in these types of materials were not cultivatable and more modern molecular methods should be employed to examine materials for them. Professor Threlfall added that the VLA has collected data on *Salmonella* in animal feeds and this information has been published in the UK Zoonoses report.
- The lack of data on the pool of resistant bacteria in our gut and the mechanisms by which they colonise and persist were highlighted. This was suggested as an important area for research.

The Chair summarised the key points from the discussions within this section as:

77. Exotic antimicrobial resistance genes and new diseases can be introduced into the UK through people returning from holidays abroad and importing of food and animal feeds, so there is a need to determine the portion of antimicrobial resistance that comes from these routes.
78. Ready-to-eat foods that are minimally processed, such as salads, pose a particular risk.

79. There appears to be a lack of information on the types and levels of antimicrobial resistance existing in many countries that we source food from.

Discussion Topic 4: What do you think the role of the FSA is on antimicrobial resistance and where specifically should the FSA target issues?

80. The Chair began by asking the audience for their views on the role that the FSA should play in combating antimicrobial resistance, bearing in mind that the Agency's remit is to protect the consumer in relation to food and other food issues.

81. Views expressed from the floor were as follows:

- Professor Threlfall highlighted that the FDA has a very active surveillance programme of food for the presence of antimicrobial resistant bacteria and suggested that the FSA should promote a similar survey to inform the debate. There was support for this from the floor.
- There was a query from the floor as to the priorities of the FSA and whether it was possible to comment on the role of the FSA without understanding this. The Chair clarified that the purpose of this meeting was to determine what stakeholders would like the FSA to do and suggestions should not be constrained by FSA budgets or priorities.
- It was suggested that the FSA should use its influence to improve the quality of research in this area. How research questions are formulated and studies designed is key to moving understanding forward in the area.
- The need to take control of meat production and meat hygiene was raised, in regard to the attempt to reduce *Campylobacter* levels. It was suggested that this should be the number one priority for the FSA and that this would contribute to reducing antimicrobial resistance in the food chain. Dr Hilton explained that the Agency has a *Campylobacter* strategy and work is currently underway to try and reduce carcass contamination.
- The relevance of the "farm to fork" slogan of the FSA was raised in that the "farm" aspect required further investigation, particularly the importance of keeping animals fit and healthy. The Chair clarified that animal welfare, husbandry and health falls under the remit of Defra but that the FSA could feed into Defra policy in this area.
- The view was expressed that the issue of farming practices remains a grey area for the FSA. Antimicrobial usage is higher in intensive systems and it was suggested that it would be preferable to move the industry away from these. There was also the issue that if this occurred, food production would be more expensive and it was important to ensure that cheaper imports (with the same antimicrobial resistance issues) did not come to dominate the market. It was suggested that there was a role for the FSA in disseminating these messages to the public. The Chair questioned whether greater use of Farm Assurance schemes could be made in this regard. However, some delegates felt that informing and educating the consumer was key.

- It was highlighted that the House of Lords Science and Technology committee had previously taken evidence from the Food industry. During this process it had emerged that many companies were working with suppliers outside the EU to ensure that the same standards were applied as within the EU. This included one case where antibiotic usage was controlled via a commercial agreement. It was suggested that this was a possible route to controlling antimicrobial resistance issues in imported foods and that the FSA may have a role in promoting this approach.
- Responsibility for implementation of the recommendation arising from the ACMSF report on antimicrobial resistance (1999) that the Government should have a coherent strategy for reducing antimicrobial use on farms was queried. The ACMSF is the responsibility of the FSA but many of the recommendations were aimed at the animal production sector, which is a Defra responsibility so lines of responsibility did not appear clear. The Chair explained that the implementation of the recommendations made in the ACMSF report had been taken forward by the DARC group. An update on these recommendations was considered by the ACMSF in September 2007.
- The view was expressed that the Defra strategy for reducing antimicrobial use in animals had not been particularly successful. Also, the format that antimicrobial sales data is produced in was queried and it was suggested that it would be more useful if this could be broken down by species and class. Mr FitzGerald (VMD) commented that this was difficult due to issues of commercial confidentiality and that the UK was producing more data in this field than most other EU Member States. In terms of decreasing antibiotic usage, it is not the policy of the VMD to interfere with veterinarians' clinical judgements. The Chair commented that one way forward would be to improve the education and training of veterinarians on the issue antimicrobial resistance and the importance of prudent prescribing.
- Concerns were expressed that a recent Veterinary Record survey showed that veterinarians were not always noting and using appropriate withdrawal periods for veterinary drugs. Mr FitzGerald commented that antibiotic residue levels in animal products were not elevated, with 99.8% of samples compliant with legal limits.
- Concerns about the decline in the number of food scientists, food microbiologists, and technicians was expressed and it was suggested that there should be more focus in promoting scientific subjects in schools. This would in turn produce more educated consumers. The E-bug programme, involving the HPA, which aims to educate children across the EU about antimicrobial resistance issues was cited as a good example of intervention at school level.
- Tobin Robinson (EFSA) revealed that the EFSA Biohazards panel is in the process of producing an opinion on food as a route of transmission for antibiotic resistance and it is envisaged that this will be published in January/February 2008. The majority of the issues raised at this meeting should be addressed by this document. Antimicrobial resistance is a very important issue at the European level and a European strategy is being developed. He highlighted that the EU-wide baseline study on *Salmonella* in pigs had been modified to include looking for MRSA in light

of the emergence of MRSA ST398 in pigs in the Netherlands. He also highlighted that the EU commission was developing a holistic strategy on antimicrobial resistance. These comments were welcomed by delegates.

- The view was expressed that as the FSA was close to consumers it was imperative that the Agency took the initiative and worked closely with Defra and DH in this field. Co-operation of all relevant institutions was highlighted as a key and it was suggested, for example, that EFSA needs to work closely with DG Sanco.

The Chair summarised the key points from the discussions within this section as:

82. There was a general view that there is a need to look at systems of food production (animal husbandry). Although this responsibility falls under Defra's remit the FSA should feed into this process.
83. Better surveillance for antimicrobial resistant bacteria in foods should be undertaken. The USA model was held up as an example of best practice.
84. In terms of imported foods, the Agency should work with industry to promote best practice in terms of production of these foods in their countries of origin. Quality assurance outside the EU was felt to be a particularly important issue.
85. The Agency should consider the EFSA opinion on antimicrobial resistance in the food chain prior to formulating a new antimicrobial resistance strategy.
86. The Chair brought the discussion session to a close by thanking all the delegates for their useful contributions. He invited delegates to write into the Agency if they had further comments and brought the meeting to a close.

Annex A: Government Reports on Antimicrobial Resistance and the Food Chain cited in the meeting report

1. Netherthorpe. 1962. Report of the Joint Committee on Antibiotics in Animal Feeding. Agriculture Research Council and Medical Research Council. HMSO, London
2. Swann, M. 1969. Report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine. HMSO, London.
3. Lamming E. 1992. The Report of the Expert Group on Animal Feedingstuffs. HMSO, London
4. ACMSF (1999). Report on Microbial Antibiotic Resistance in Relation to Food Safety. The Stationary Office, London

Annex B: Delegates

Stakeholders

Dr Bob Adak	Health Protection Agency
Tony Andrews	Responsible Use of Medicines in Agriculture Alliance
Theresa Baldwin	National Council of Women
David Burch	British Veterinary Association
Prof Eric Bolton	Health Protection Agency
David Briggs	British Retail Consortium
Dr Robin Bywater	National Office of Animal Health
Dr Nick Coldham	Veterinary Laboratories Agency
Andrew Curtis	Food and Drink Federation
Dr Susan Dawson	University of Liverpool
Clare Druce	Farm Animal Welfare Network
Dr Vicky Enne	University of Bristol
Dr Merion Evans	National Public Health Service for Wales
Dr Sarah Evans	Veterinary Laboratories Agency
John FitzGerald	Veterinary Medicines Directorate
Andrew Frost	Department for Environment Food and Rural Affairs
Barbara Gallani	British Retail Consortium
Dr Will Gaze	University of Warwick
Dr Janet Gibson	Department of Health
Dr John Godfrey	Foodaware
Dr Kay Goodyear	Veterinary Medicines Directorate
Kevin Hardman	Association of Port Health Authorities
Tim Hampton	Milk link
Dr Richard Holliman	St George's Hospital Medical School
Prof Peter Hawkey	University of Birmingham
Dr Rowena Jecock	Department of Health
Dr Alan Johnson	Health Protection Agency
Samantha Kirk	British Retail Consortium
Leslie Larkin	Department for Environment Food and Rural Affairs
Dr Jodi Lindsay	St George's Hospital Medical School
Jeanette Longfield	Sustain
Neil Lynford	British Retail Consortium
Jane Mani-Saada	Health Protection Agency
Dr Stanley McDowell	Agri-Food & Biosciences Institute
Paul McMullin	British Veterinary Poultry Association
Adrian Mockette	British Veterinary Poultry Association
Dr Robert Morley	Health Protection Agency
Prof Dianne Newell	Veterinary Laboratories Agency
Coilin Nunan	Soil Association
Prof Sarah O'Brien	Advisory Committee on the Microbiological Safety of Food
Andrea Patterson	Department for Environment Food and Rural

	Affairs
Prof Laura Piddock	University of Birmingham
Dr Nick Renn	Veterinary Medicines Directorate
Dr Tobin Robinson	European Food Safety Authority
Prof Peter Silley	MB Consult Limited
Dr David Stead	Central Science Laboratory
Prof John Threlfall	Health Protection Agency
Dr David Tompkins	Health Protection Agency
Dr Sheila Voas	Scottish Executive Environment and Rural Affairs Department
Dr John Walters	National Office of Animal Health
Dr Nicola Williams	University of Liverpool
Dr Caroline Willis	Health Protection Agency
Prof Richard Wise	British Society for Antimicrobial Chemotherapy
Richard Young	Soil Association

Food Standards Agency

Shanoor Ali	Microbiological Safety Division
Jaswinder Bangar	Communications Division
Dr Paul Cook	Microbiological Safety Division
Ms Louise Farmer	Microbiological Safety Division
Grace Money	Communications Division
Dr Judith Hilton	Microbiological Safety Division
Bobby Kainth	Microbiological Safety Division
Heather Lewis	FSA Wales
Daniel Lovell Diaz	Microbiological Safety Division
Micah McGuire	Communications Division
Gael O'Neill	Microbiological Safety Division
Chris Pratt	Primary Production Division
Milorad Radokovic	Meat Hygiene and Veterinary Division
Prof Bill Reilly	FSA Board Member
Gavin Shears	Primary Production Division

Annex C: Abbreviations

ACMSF	Advisory Committee on the Microbiological Safety of Food
AI	Avian Influenza
<i>C. coli</i>	<i>Campylobacter coli</i>
<i>C. difficile</i>	<i>Clostridium difficile</i>
<i>C. jejuni</i>	<i>Campylobacter jejuni</i>
DARC	Defra Antimicrobial Resistance Coordination group
Defra	Department for the Environment, Food and Rural Affairs
DG Sanco	Directorate General for Health and Consumer Affairs
DH	Department of Health
DNA	Deoxyribonucleic acid
DT	Determinative type
EC	European Community
<i>E. coli</i>	<i>Escherichia coli</i>
EFSA	European Food Safety Authority
EMA	European Medicines Agency
ESBL	Extended Spectrum Beta-lactamase
EU	European Union
FDA	Food and Drug Administration
FSA	Food Standards Agency
GI	Gastrointestinal
GP	General Practitioner
HPA	Health Protection Agency
MRSA	Meticillin Resistant <i>Staphylococcus aureus</i>
NHS	National Health Service
PHLS	Public Health Laboratory Service
PT	Phage Type
PVL	Panton-Valentin Leukocidin
SACAR	Specialist Advisory Committee on Antimicrobial Resistance
SOS response	a post-replication DNA repair system that allows DNA replication to bypass lesions or errors in the DNA
ST	Sequence type
UK	United Kingdom
VLA	Veterinary Laboratories Agency
VMD	Veterinary Medicines Directorate