ADVISORY COMMITTEE ON ANIMAL FEEDINGSTUFFS

61st Meeting of ACAF on 8 May 2013

Information Paper: Update on Antimicrobial Resistance – Work Proposed by the Advisory Committee on Microbiological Safety of Food

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Update on Antimicrobial Resistance – Work proposed by the Advisory Committee on Microbiological Safety of Food (ACMSF)

Introduction

1. I was invited to attend the 79th meeting of the Advisory Committee on the Microbiological Safety of Food (ACMSF) on 31 January 2013 in Aviation House, London. The ACMSF agenda included two items under **Antimicrobial resistance (ACM/1091 see Annexes A and B below):** First, an update on developments and emerging issues in relation to antimicrobial resistance and to which the ACMSF were asked whether to consider this issue in more detail, and second the Veterinary Medicines Directorate had been asked to give a presentation on antimicrobial resistance.

ACMSF presentation

2. Dr Paul Cook (ACMSF Secretariat) presented a synopsis of a document which had been prepared on 'Antimicrobial resistance and the food chain'. The whole document being publicly available from the ACMSF web site.

3. The first paragraph stated:

   '*The area of antimicrobial resistance is a large and complex one representing a significant threat to human health. The ACMSF has previously examined the contribution of the food chain to the problem of antimicrobial resistance and this paper updates the committee on recent developments in this area. The committee is asked to consider whether there are any particular areas where they feel further investigation is needed by ACMSF or other committees.*'

4. In brief the 29 page report covered the subject starting with early ACMSF assessments of the risks to human health from antibiotic resistant micro-organisms entering the food chain starting in 1996. A further review of the ACMSF recommendations in 2007 (ACM/868) highlighted a number of broad areas requiring further consideration. These included antimicrobial resistance in commensal bacteria in food, antimicrobial resistant bacteria in imported food and animal feed and microbiological risk assessment. The report continued to the wider need for co-ordinated Government action to control the spread of

multi-drug resistant pathogens, and to conserve the efficacy of existing antimicrobial drugs. The launch in 2001 by the European Commission for the phasing out of antibiotics for non-medical use in animals, and actions including data collection, surveillance, research and awareness-raising. The increasing interest at the European and international level of the use of antimicrobials in animal medicine, in particular food animal production and the role of the food chain contribution to the overall burden of antimicrobial resistance was recognised.

5. Topics under '*Emerging issues'*, included:

   i. Methicillin-resistant *Staphylococcus aureus* (MRSA) in milk and pigs.

   ii. Extended beta-lactamases (ESBLs), including the 2012 report by DARC[1] and ARHAI[2], '*ESBLs - A Threat to Animal and Human Health?*' with 26 recommendations and areas requiring further research.

   iii. The 2011 EFSA assessment on the potential contribution of food and food-producing animals to the public health risks posed by ESBLs (http://www.efsa.europa.eu/en/efsajournal/doc/2322.pdf). The EFSA report concluded that the use of antimicrobials in food-producing animals is a risk factor for the spread of these bacterial strains. They recommended that decreasing the overall use of antimicrobials in food-producing animals in the EU should be a priority in terms of limiting the risk to public health arising from resistance in the food chain and that an effective option would be to restrict or stop the use of cephalosporins in the treatment of food-producing animals.

   iv. The Department of Health five year (2013-2018) Strategy and action plan on antimicrobial resistance, for which the ACMSF Members had commented on the technical consultation of this strategy. It is anticipated that the strategy and action plan will be published in early 2013.

[1] DARC: Defra Antimicrobial Resistance Coordination Group

[2] ARHAI: Advisory Committee on Antimicrobial Resistance and Healthcare Acquired Infection

6. Finally, progress on ACMSF recommendations stated (para.45) that only 4 out of 48 recommendations remained outstanding since the 2007 ACMSF review. These included (quoted):

    a. Gaps in knowledge base identified with regards to the prevalence of antibiotic resistance in commensal microorganisms found in food (particularly *E. coli* and enterococci) and investigation of these recommendations (Recommendations 4.72 and 6.121 in the 1999 report).

    b. Gaps in Government funded research in antibiotic-resistance bacteria in imported food and animal feeding stuffs and secondly in the area of microbiological risk assessment (Recommendations 12.34 and 12.36).

ACAF views

7. I was asked to give the interest by ACAF into the topic, and explained that although antimicrobial agents were not used as growth promoters in animal feed, that there was still an overlap of interests between the two committees. In addition the matter was of public concern and is widely discussed in the media subsequently that there was a need for clear information from the UK perspective.

ACMSF conclusions

8. After open discussion it was decided that the ACMSF did still wish to consider the issue in more detail, and that a subgroup of members from the ACMSF should form which would include myself from ACAF. There have been no further communications on the topic since January. I believe their next meeting is 27th June.

Addendum:

On 16th May EFSA published their report 'The European Union Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2011'. http://www.efsa.europa.eu/en/efsajournal/doc/3196.pdf.

Professor Steve Forsythe

May 2013

ACM/1091

ADVISORY COMMITTEE ON THE MICROBIOLOGICAL SAFETY OF FOOD

Antimicrobial resistance and the food chain

Issue

1. The area of antimicrobial resistance is a large and complex one representing a significant threat to human health. The ACMSF has previously examined the contribution of the food chain to the problem of antimicrobial resistance and this paper updates the committee on recent developments in this area. The committee is asked to consider whether there are any particular areas where they feel further investigation is needed by ACMSF or other committees.

Introduction

2. Antimicrobials, such as antibiotics, are substances used to kill microorganisms or to stop them from multiplying. They are commonly used in human and veterinary medicine to treat a wide variety of infectious diseases. Antimicrobials used in food producing animals are frequently the same or belong to the same class as those used in human medicine.

3. Antimicrobial resistance (AMR) is a major public health concern and a food safety concern. It is a complex issue driven by a variety of interconnected factors enabling micro-organisms to withstand antimicrobial treatments to which they were once susceptible. The overuse or misuse of antibiotics has been linked to the emergence and spread of microorganisms which are resistant to them, rendering treatment ineffective and posing a risk to public health.

4. In 1996, the Advisory Committee on the Microbiological Safety of Food (ACMSF) set up a Working Group to assess the risks to humans from antibiotic resistant microorganisms entering the food chain and to consider the need to protect public health. The Committee's Report on Microbial Antibiotic Resistance in Relation to Food Safety was published in 1999 (ACMSF, 1999) and listed a series of recommendations, most of which were for Government to consider taking forward, please see Annex A.

5. Defra's Antimicrobial Resistance Coordination (DARC) Group was established in 1999 and part of its remit was to track and update the Government's response to the ACMSF report. In 2005 the DARC secretariat produced a paper (ACM/730) that summarised the actions taken by Government over the five year period since publication of the ACMSF report. Please see Annex B for copy of paper. The majority of the recommendations in the ACMSF report have been taken forward and the DARC paper

comprehensively covered progress on these. A further review of the ACMSF recommendations in 2007 (ACM/868) highlighted a number of broad areas requiring further consideration including antimicrobial resistance in commensal bacteria in food, antimicrobial resistant bacteria in imported food and animal feed and microbiological risk assessment. These areas will be addressed later in this paper. Annex C includes a copy of this paper.

6. The Advisory Committee on Animal Feedingstuffs (ACAF) was established in 1999 with a remit of advising on the safety of animal feeds and feeding practices with particular emphasis on protecting human health. Antimicrobial Resistance has been discussed at both the 19 September 2012 and 16 January 2013 ACAF meetings. Lesley Johnson (Veterinary Medicine Directorate) provided an overview of antimicrobial resistance at the September meeting and explained that the Commission is considering the issue of AMR in relation to medicated feedingstuffs. A draft proposal is expected mid-late 2013.

7. The ACAF Committee agreed that the issue of AMR was complex and it wished to explore this topic at a future meeting, where it could discuss the available evidence to support whether AMR was a current issue for animal feed.

Wider Government context

8. The emergence of a range of multi-drug resistant pathogens has highlighted the need for coordinated Government action to control their spread and to conserve the efficacy of existing antimicrobial drugs. There are a range of Government Departments, organisations, groups and individuals who are involved in antimicrobial resistance. In simplest terms, DH leads this area for human medicine whereas primary responsibility for the control and use of antimicrobial drugs in animal medicine lies with Defra and its Executive Agency, the Veterinary Medicine Directorate (VMD).

9. The FSA's role in this area is very much a complementary one to Defra. It is the FSA's responsibility to assess whether current agricultural practices may be having a deleterious effect on public health via the foodchain, and work to effect change where we consider this to be the case.

10. The FSA continues to promote the 4Cs (cleaning, avoiding cross contamination, cooking and chilling) in its food hygiene messaging to both industry and consumers. Greater awareness and practice of good hygiene by food businesses and consumers is important in protecting consumers from pathogens and other bacteria some of which may be resistant to antimicrobials. Cooking and pasteurisation will destroy bacteria irrespective of whether the organisms are resistant to antibiotics or not.

11. In November 2007, the FSA held a stakeholder meeting to discuss key issues concerning bacteria exhibiting antimicrobial resistance and the role of the foodchain. The meeting was attended by more than 50 external delegates representing other Government Departments and their Executive Agencies, food industry, consumer organisations and other non-governmental organisations.

12. Delegates highlighted a range of issues that they felt the Agency should address. They focussed heavily on the need to assess the degree of antimicrobial resistance in the foodchain and highlighted the lack of surveillance data in this area relating to food. They also felt there needed to be a greater emphasis on antimicrobial resistance in non-pathogenic bacteria as these organisms are more abundant than pathogens. Imported foods and animal feeds were felt to be an important area for investigation as these may play a role in the introduction of exotic antimicrobial resistant bacteria or resistance genes. Ready-to-eat foods that are minimally processed, such as salads, were felt to pose a particular risk. There was also a general view that there was a further need to look at systems of food production such as animal husbandry and particularly the use of antimicrobials. Although this responsibility primarily falls under Defra's remit, delegates felt that it was important that the FSA should be involved in this process.

13. The DARC Group has carefully considered how *Clostridium difficile* may impact on animal health and the possible consequences to human health. It concluded from the evidence currently available that there is a minimal risk associated with transmission of *C. difficile* from animals to humans via food. DARC will continue to consider the presence of *C. difficile* in animals, the environment and the foodchain to ensure that the most appropriate action is taken to ensure animal and human health. It is however noted that *C. difficile* infection is not zoonotic, i.e. a disease which is biologically adapted to and normally found in animals but which under some conditions also infects humans.

European and International context

14. There has also recently been an increasing level of interest in the issue of antimicrobial resistance in both the European Union (EU) and wider international fronts (WHO, FAO and Codex). This has increased the focus of attention on the use of antimicrobials in animal medicine, particularly in food animal production, and the role the food chain may have in contributing to the overall burden of antimicrobial resistance. The FSA keeps a watching brief over developments within the EU and internationally and responds as appropriate.

15. In 2001 the European Commission launched an EU strategy to combat the threat of antimicrobial resistance to human, animal and plant health. It

included the phasing out of antibiotics for non-medical use in animals, and covered a range of actions at EU and national level in the areas of data collection, surveillance, research and awareness-raising.

16. Directive 2003/99/EC obliges Member States (MS) to monitor and report antimicrobial resistance in *Salmonella* and *Campylobacter* isolates from animals and food, whereas the monitoring and reporting of resistance data from indicator organisms (commensal *E. coli* and enterococci) is voluntary. Directive 2003/99/EC foresees that the monitoring of antimicrobial resistance is based on the surveillance systems in place in MS which may differ in terms of origin of the isolates and laboratory testing of isolates. EU legislation for animal nutrition banned the use of antibiotics used for growth promotion in animal feed from January 2006.

17. To harmonise the monitoring of antimicrobial resistance in *Salmonella* and *Campylobacter* found in animals and food, EFSA's Biological Monitoring Unit published specifications in 2007. In 2008 EFSA's Panel on Biological Hazards issued an opinion examining how food may become a vehicle for transmitting antimicrobial resistant bacteria to humans (http://www.efsa.europa.eu/en/efsajournal/doc/765.pdf).
    It made recommendations for preventing and controlling transmission, highlighting good hygiene at all stages of the food chain as a critical prevention and control factor. Further specifications for harmonised monitoring of resistance in *E. coli* and enterococci bacteria in animals and foods were also published by EFSA.

18. The European Centre for Disease and Control (ECDC) organised the first Antibiotic Awareness Day in 2008 to raise awareness about the threat to public health of antibiotic resistance and prudent antibiotic use and now runs annually. In 2010, EFSA published the first EU Summary Reports on antimicrobial resistance in zoonotic bacteria found in animals and foods covering the years 2004-2007 (http://www.efsa.europa.eu/en/efsajournal/doc/1309.pdf). Twenty six Member States (MS) and two non-MS submitted information on the occurrence of antimicrobial resistance in zoonotic bacteria originating from poultry, pigs and cattle. The reported information covered resistance to 51 antimicrobial substances.

19. Antimicrobial resistance in *Salmonella*, *Campylobacter*, indicator *E. coli* and indicator enterococci isolates, were reported from animals and food. In this report quantitative antimicrobial resistance data reported by EU MS and non-MS deriving from different testing methods (minimum inhibitory concentration and inhibition zone diameter data) were for the first time interpreted using the same epidemiological cut-off values across the reporting countries and years. However, differences observed between the reporting countries may partly be due to real differences in the resistance situation but sometimes also because

of differences in the monitoring system in place. At MS level the occurrence of antimicrobial resistance over time remained, in most cases, relatively stable over the reporting years. However, some fluctuations in resistance were observed.

Emerging Issues

Methicillin-resistant *Staphylococcus aureus* (MRSA)

20. MRSA can be persistently or intermittently carried by healthy humans, and the major risk factor for infection is colonisation. Infection can be mild to severe and in some instances, fatal. MRSA clones have originated in at least three separate settings: human hospitals, human carriers outside of hospitals (community) and livestock animals. MRSA are now a major cause of hospital acquired infection in many European countries, with large differences in prevalence and control policies. A limited number of lineages of MRSA tend to predominate in specific geographical locations. Clonal Complex (CC)398 is the MRSA lineage most often associated with asymptomatic carriage in intensively reared food-producing animals. MRSA commonly carry enterotoxin genes but there has been only one report of food intoxication due to MRSA.

21. In 2009, EFSA published their assessment of the Public Health significance of MRSA in animals and foods: http://www.efsa.europa.eu/en/scdocs/doc/biohaz_op_993_mrsa_en.pdf.

    On the question of what was the risk to human health posed by MRSA associated with food-producing animals, the Panel concluded that "livestock-associated MRSA (LA-MRSA) represent only a small proportion of the total number of reports of MRSA infections in the EU". On the question of which animal species (and if appropriate, foods derived there from) represent the greatest risk to humans, the Panel concluded that "the primary reservoirs of CC398 in affected countries are pigs, veal calves, and broilers. CC398 has also been found in companion animals and horses on farms with colonised livestock. MRSA has now been reported from dogs, cats and horses with sporadic reports of isolation from a wide range of other companion animals. There are no specific studies which examined the relative risk of different small animals and horses as sources of infection or colonisation in humans."

MRSA in milk

22. More recently, LA-MRSA CC398 was isolated from bulk milk tanks from 5 geographically dispersed UK farms suggesting it may be established in British cattle (http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20337). This is the first description of LA-MRSA in food-producing animals in the UK. However, 5 farms out of 1500 were positive for MRSA, indicating a very low

prevalence level. The Cambridge study results and Animal Health and Veterinary Health Laboratories monitoring suggest that MRSA in cattle is infrequent.

23. In addition, a Defra study, carried out in 2011 by the University of Cambridge, isolated an MRSA containing a novel *mecA* homologue from dairy cattle and humans, the researchers isolated the organism from both milk from cows with mastitis and in 2 samples from a bulk milk tank. This study does not provide evidence that humans are being infected with MRSA from cattle; the data simply shows that the same types of MRSA can be found in both humans and cattle.

24. The majority of milk sold for human consumption is pasteurised. This process will destroy *Staphylococcus aureus* whether it is resistant to antibiotics or not. Raw drinking milk in England, Wales and NI must carry (or have displayed near point of sale) a health warning stating that the milk 'has not been heat-treated and may therefore contain organisms harmful to health'. In Wales the warning also includes 'the FSA strongly advises that raw milk should not be consumed by children, pregnant women, older people or those who are unwell or have chronic illness'.

MRSA in pigs

25. The MRSA lineage Sequence Type 398 (MRSA ST398) has recently been described as a cause of infection for people on the continent occupationally exposed to pigs, either by direct or indirect contact. MRSA ST398 can occasionally be introduced into hospitals as a result of community-acquired human infections. To assess the occurrence and the diversity of MRSA in pig primary production, a European Union-wide preliminary survey was carried out in parallel with a baseline survey on *Salmonella* spp. in holdings with breeding pigs to determine the prevalence of holdings positive for MRSA and MRSA ST398. The EU prevalence in breeding farms was 14% but in breeding/finisher or production farms was 26.9%. The UK contributed to the EFSA 2008 baseline survey of breeding pigs and the samples were all found to be negative for MRSA.

26. EFSA recommends that more information is gathered at national level on those factors that put pig holdings at risk of infection with MRSA and on the measures that can prevent its spread.

27. *Staphylococcus aureus* is routinely enumerated in a wide variety of ready-to-eat foods, as part of general microbiological safety checks. Moreover, Regulation (EC) No. 2073/2005 (on microbiological criteria in foodstuffs), specifies maximum limits for coagulase-positive staphylococci in food, to be complied with by food business operators during processing of cheese, milk powder and whey powder, and staphylococcal enterotoxins must be absent in

these products placed on the market during their shelf-life. However, the presence of MRSA in food is not routinely investigated, and data are only available from a small number of studies

ESBLs

28. Extended-Spectrum Beta-Lactamases (ESBLs) are enzymes that can be produced by bacteria making them resistant to the most widely used antibiotics in many hospitals.

29. The ACMSF newly-emerging pathogens working group considered CTX-M type ESBL- producing *E. coli* in 2007 and 2008 (ACM/892a and ACM/892) and in summary the Group identified the need for a holistic approach to defining and understanding the problem. ESBLs are enzymes that can be produced by bacteria, which make bacterial infections more difficult to treat. The Group recommended cross-government working to address the holistic context. It was noted that both DARC and the Department of Health's (DH) Advisory Committee on Antimicrobial Resistance and Healthcare Acquired Infection (ARHAI) were considering ESBL-producing *E. coli,* with ARHAI having a specific working group on the topic.
    The Group identified a number of outcomes (ACM/892 http://www.food.gov.uk/multimedia/pdfs/committee/acm892esbl.pdf). The FSA has representation on the DARC Group and are observers at the ARHAI committee, both of which meet on a quarterly basis.

DARC/ARHAI report on ESBLs

30. In February 2012 DARC and ARHAI published a report on the extended spectrum beta-lactamases, 'ESBLs - A Threat to Animal and Human Health?' (http://www.vmd.defra.gov.uk/pdf/ESBL_report.pdf)

31. The purpose of this report was to:

- Review the current state of knowledge with regard to the occurrence, distribution, identification and ecology of ESBL-producing bacteria;
- Consider the causation and development of the problem;
- Assess the impact on human and animal health;
- Identify 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 ESBL Producing Coliforms (ESBLPCs); and
- Provide a range of recommendations for public health and animal health.

32. The ARHAI/DARC report makes 26 recommendations which are divided into 6 sections: characterisation, transfer pathways, surveillance, therapy, control options and outcome measures and research gaps. Of the 26 recommendations, 6 are related to food:

Recommendation on transfer pathway

- 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.

Recommendations on research gaps

- The carriage of ESBLs in domestic and imported foods warrants further investigation.
- A rapid detection method for ESBLs should be explored.
- Further research into novel therapies (e.g. gamma-radiation of food and the use of vaccines) should be undertaken.
- Further research into routes of transmission and human–animal cycling should be carried out and if appropriate, further research into methodologies to minimise such transmission. The possibility of reducing ESBLs in human and animal waste prior to release into the environment should be evaluated as a control option.
- Research on the carriage patterns of resistant bacteria in animals compared to humans and the influence of the usage of various antimicrobials would be useful.

33. The need for robust methods was seen as a key gap for undertaking such surveillance and FSA funded research started in May 2011 which focuses on identifying and testing appropriate methods for the detection of ESBL-producing *E. coli* and other Enterobacteriaceae in foods (FSA Project FS241023). This is an important area of research as there is currently no standard method for the detection of ESBLs in food. Results are expected in late 2014.

34. The Department of Health is investing £700,000 for new research into antibiotic-resistant bacteria following this report. The research will focus on providing information on the prevalence of ESBLs in the general population, specific groups that might be at higher risk and the environment.

35. EFSA published an assessment on the potential contribution of food and food-producing animals to the public health risks posed by ESBLs in 2011 (http://www.efsa.europa.eu/en/efsajournal/doc/2322.pdf). EFSA concluded that the use of antimicrobials in food-producing animals is a risk factor for the spread of these bacterial strains. The experts recommend that decreasing the overall use of antimicrobials in food-producing animals in the EU should be a priority in terms of limiting the risk to public health arising from resistance in the food chain and that an effective option would be to restrict or stop the use of cephalosporins in the treatment of food-producing animals.

Carbapenems

36. Carbapenems are a powerful group of broad-spectrum beta-lactam (penicillin-related) antibiotics which, in many cases, are our last effective defence against multi-resistant bacterial infections. The spread of ESBLs has increased reliance on carbapenems in severe infections. Most ESBL producers are broadly resistant to antibiotics other than carbapenems, meaning that there are few alternatives to this strategy. What is of concern, however, is that resistance is beginning to emerge to carbapenems. Furthermore, carbapenem-destroying beta-lactamases called carbapenemases are starting to appear in Enterobacteriaceae including a few reports from food producing animals in Europe. Carbapenems are not licensed for veterinary use.

Fluoroquinolones + 3rd and 4th generation cephalosporins

37. Fluoroquinolones and the 3rd generation cephalosporins are antimicrobials classified by the World Health Organisation as *critically important* for human medicine. Their use has generally been considered to be a selective force in the emergence of ESBLs. Additionally the gradual increase in use in food producing animal production may be linked to the recent emergence of ESBLs in bacteria associated with cattle, poultry and pigs. It is thought that emergence of ESBL bacteria in food producing animals may present a risk of resistant strains being transmitted to humans through the food chain. The joint DARC/ARHAI working group published their report in 2012 and recommended:

    - A review of the practicalities of changing the amount and timing of administration of antimicrobials to animals to reduce the prevalence of ESBLPCs should be considered. The use of cephalosporin (and quinolone if appropriate) medication should be stopped or generally reduced, with other medicines being used in their place on any farm known or suspected to have ESBLs.
    - The practice of co-administration of 3rd generation cephalosporins with Mareks's disease vaccine to young chicks should stop.

38. The British Poultry Council have introduced a voluntary ban on the use of fluoroquinolones and 3rd and 4th generation cephalosporins in production from January 2012.

39. In June 2012, the EFSA opinion on poultry meat inspections (http://www.efsa.europa.eu/en/efsajournal/doc/2741.pdf) highlighted that traditional poultry meat inspection does not enable the detection of the most important hazards to public health (*Campylobacter*, *Salmonella* and ESBL/AmpC gene-carrying bacteria), and recommends improvements to the current system. The FSA published a response to EFSA's recommendations in July 2012 and these recommendations are being considered carefully by

the FSA. EFSA's views, and the views of European MS, stakeholders and international trade partners, will be considered by the Commission before proposing changes to the current regulations.

UK 5 year AMR strategy

40. The Department of Health is leading on a new UK five year Antimicrobial Resistance (AMR) strategy and action plan (2013-2018). ACMSF Members had an opportunity to comment on the technical consultation of this strategy. It is anticipated that the strategy and action plan will be published in early 2013. The strategy acknowledges that there is limited understanding of the development of antimicrobial resistance and greater emphasis will need to be given to developing the evidence base through research and surveillance activities as well as the development and discovery of effective new antimicrobials and diagnostics. Improving the evidence base and understanding of resistance mechanisms will help to strengthen interventions to prevent the development and spread of resistance.

EU Strategy and other international work

41. The Commission's 2011 action plan (http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf) against the rising threats from antimicrobial resistance contains 12 actions for implementation with EU member countries and identifies 7 areas where measures are most necessary:

- Making sure antimicrobials are used appropriately in both humans and animals.
- Preventing microbial infections and their spread.
- Developing new effective antimicrobials or alternatives for treatment.
- Cooperating with international partners to contain the risks of AMR.
- Improving monitoring and surveillance in human and animal medicine.
- Promoting research and innovation.
- Improving communication, education and training.

42. The Commission funds several antimicrobial resistance projects through its Health Programme and monitors AMR risks with the support of the European Centre for Disease Prevention and Control and the European Food Safety Authority. In 2011, the transatlantic task force on antimicrobial resistance published recommendations for future collaboration between the US and EU (http://www.cdc.gov/drugresistance/pdf/tatfar-report.pdf).

43. In 2011 Codex Alimentarius produced guidelines to provide science-based guidance on processes and methodology for risk analysis of foodborne antimicrobial resistance. The guidelines aim to assess the risk to human health associated with the presence of AMR microorganisms and

determinants in food and animal feed, including aquaculture, and the transmission through food and animal feed, to provide advice on appropriate risk management activities to reduce such risk. The guidelines will further address the risk associated with different sectors of antimicrobial agent use such as veterinary applications, plant protection or food processing.

44. The EU and United States have also created a transatlantic task force on antimicrobial resistance issues.

Progress on ACMSF recommendations

45. It is evident that the majority of recommendations from 1999 ACMSF report on Microbial Antibiotic Resistance in Relation to Food Safety have been taken forward and completed (Annex A). Only 4 out of 48 recommendations remained outstanding since the 2007 ACMSF review which was referred to at the beginning of this paper (Annex C). These include:

    a. Gaps in knowledge base identified with regards to the prevalence of antibiotic resistance in commensal microorganisms found in food (particularly *E. coli* and enterococci) and investigation of these recommendations (Recommendations 4.72 and 6.121 in the 1999 report).

    b. Gaps in Government funded research in antibiotic-resistance bacteria in imported food and animal feeding stuffs and secondly in the area of microbiological risk assessment (Recommendations 12.34 and 12.36).

46. To address these knowledge gaps since 2007 the FSA has contributed to a European research project which examined the zoonotic aspects of ESBL-positive commensal *E. coli* strains and their mobile genetic elements in food-producing animals, as well as animal products as a source of introduction of the resistant genes into foodborne pathogens, commensals and pathogens in the community and healthcare settings (Safefood Era Project). This project has now been completed and the final report is expected to be published in 2013. As described previously the FSA also has a research project (FSA 241023) which focuses on identifying and testing appropriate methods for the detection of ESBL-producing *E. coli* and other Enterobacteriaceae in foods. This is an important area of research as there is currently no standard method for the detection of ESBLs in food. Results are expected in late 2014. We are considering funding additional work on ESBLs.

47. Defra has funded a project in collaboration with Health Protection Agency and Veterinary Laboratory Agency. The aim of the project was to formulate an informed qualitative risk assessment of the likelihood of the development of antimicrobial resistance in zoonotic salmonellas in relation to the veterinary use of antimicrobials in the UK and in countries outside the UK which regularly import animal food products. This research was completed at the

end of 2009 (http://randd.defra.gov.uk/Default.aspx?Location=None&Module=FilterSearchNewLook&Completed=0 project number VM02209).

48. To our knowledge these are the only areas of work that have been publically funded covering these recommendations. We will discuss these recommendations with DARC with a view to updating these areas.

Food surveillance

49. The FSA has included testing for antimicrobial resistance as part of its retail food surveys for major foodborne pathogens. For example, in the red meat survey (http://www.foodbase.org.uk//admintools/reportdocuments/548-1-956_B18018_final.pdf) and retail chicken survey (http://www.food.gov.uk/science/research/surveillance/fsisbranch2009/fsis0409) all isolates of *Salmonella* and *Campylobacter* were tested for resistance to a wide range of antibiotics.

50. Both the HPA and FSA undertake screening of bacteria for antimicrobial resistance as part of food surveillance activities. New technologies such as whole genome sequencing could enhance our ability to investigate isolates in more detail including those involving antimicrobial resistant strains.

Conclusions

51. AMR is a complex area and requires a comprehensive range of activities including surveillance, prevention and control, research and product development. Cross-government, European and international co-operation is required to address this issue as it cannot be tackled in isolation.

52. The Committee is invited to:

- Comment on progress in understanding the issue in relation to the food chain since the committee produced its report in 1999 and subsequent reviews in 2005 and 2007.
- Identify the key risks to the food chain which may have consequences for human health
- Highlight key research or surveillance gaps in relation to the food chain

Secretariat
January 2013

Annex B

ACM/730

ADVISORY COMMITTEE ON THE MICROBIOLOGICAL SAFETY OF FOOD

REPORT FROM THE DEFRA ANTIMICROBIAL RESISTANCE COORDINATION GROUP (DARC)

1. The Defra Antimicrobial Resistance Coordination Group has prepared the attached paper summarising the actions taken to address the recommendations in the ACMSF 1999 Report on Microbial Antibiotic Resistance in Relation to Food Safety. Members may wish to read this paper in conjunction with the recommendations and Government's response paper which has been circulated as an Information Paper (ACM/736) for this meeting.

Secretariat

March 2005

Report on the Government's Actions to address the Recommendations of the ACMSF report on Microbial Antibiotic Resistance In Relation To Food Safety

1 Introduction

1.1 During 1995 the Advisory Committee on the Microbiological Safety of Food (ACMSF) took stock of the position in relation to antibiotic resistance in enteric bacteria infecting animals and man. This was with a view to deciding whether the Committee needed to involve itself further in assessing the situation, given the work already being undertaken in the area by other bodies and agencies. Following these considerations the Committee decided to embark upon an in-depth review of the role of the food chain in transferring microbial antibiotic resistance. A Working Group was set up to assess the risks to humans from antibiotic resistant micro-organisms entering the food chain and to consider the need for any action to protect public health. The committee's report was published in 1999 and listed a series of recommendations most of which were for the Government to consider taking forward.

1.2 The Defra Antimicrobial Resistance Coordination (DARC) Group was established in 1999, and part of its remit was to track and update the Government's response to the ACMSF Report. The DARC Group secretariat has summarised below the actions taken over the last five years to address the ACMSF recommendations. For ease of reference, the summary provided below is arranged according to the order of chapters in the ACMSF Report. The paper has not considered the recommendations made by the ACMSF in Chapter 12 of their report on research, as this was not the remit of the DARC Group. The recommendations from the ACMSF Report are not included in the summary and Members should consult the original report or the Government response, which is included with this paper for information.

2 Progress to meet recommendations made in Chapter 3: Patterns of antibiotics resistance in bacteria isolated from food animals

2.1 Surveys have been carried out by the Veterinary Laboratories Agency (VLA), Department of Agriculture and Rural Development in Northern Ireland (DARDNI), and Scottish Agricultural College (SAC) to determine the prevalence, subtypes and antimicrobial resistance of foodborne pathogens including *Salmonella*, *Campylobacter* and *E. coli* O157. The results of the GB surveys have been published on the Defra web site and were released at Open Meetings in February 2002 and January 2005, held at the National Agricultural Centre Stoneleigh. These surveys included collection of data

on the prevalence of resistant *Escherichia coli* and resistance in key anaerobes. Follow up surveys to this work are planned.

2.2 Health Protection Agency (HPA) and VLA have organised harmonisation ring trials of methods to test for antimicrobial resistance in *Salmonella* and *Campylobacter* to determine if the methods used showed any regional differences. Thirteen human and veterinary laboratories from across the UK participated in the trials. Results from the trials will be published independently.

2.3 Research has been funded which examined the emergence and disappearance of multi-resistant strains of *Salmonella* and others on antimicrobial resistance in *Campylobacter*. Details about all projects are available from the Defra we site at http://www2.defra.gov.uk/research/project_data/Default.asp and the VMD web site at www.vmd.gov.uk. The Food Standards Agency (FSA) has funded the HPA to provide typing, antimicrobial resistance testing and archiving of pathogens and other organisms isolated during FSA food surveys.

2.4 The Government has developed and published a Strategy for developing and implementing a programme of surveillance for Antimicrobial Resistance in animals in England and Wales to address how data are collected. This report is available from the VMD website at www.vmd.gov.uk. This strategy is in line with similar documents prepared for Scotland and Northern Ireland.

2.5 A paper jointly co-authored by the HPA and VLA, comparing and contrasting drug-resistant strains of *Salmonella* from cases of human infection and from food-producing animals has been published.

2.6 The DARC Group are leading a cross-Departmental and cross-Agency Working Group to consider how to develop the current individual reports on antimicrobial resistance issues across the UK, into a single UK-wide report covering all aspects of veterinary and human antimicrobial resistance issues and antimicrobial resistance in the food chain.

3 Progress to meet recommendations made in Chapter 4: Patterns of antibiotic resistance in bacteria isolated from foodstuffs

3.1 The FSA priorities for national food surveys have been eggs and poultry. Results from FSA surveys, which include information on subtypes and antimicrobial resistance are available from the FSA website at www.food.gov.uk. National food surveys covering a wider range of foods

have also been undertaken by HPA / LACORS and the findings published in the literature.

3.2 The FSA recognises there are a paucity of data on antimicrobial resistance of *E. coli* isolates from food and will include work to address this in future food surveys where appropriate.

3.3 The HPA has developed an archive of foodborne pathogens that were isolated from food as part of FSA food surveys. These have been sub-typed and screened for antimicrobial resistance.

3.4 The committee recommended to research funding organisations, that studies be undertaken to assess the effects of food processing, storage conditions and food preparation on antimicrobial resistant microflora of foods and transfer of resistance between food bacteria. The FSA does not consider this to be a current priority but will review the situation when deciding future research requirements and in the light of work commissioned by other funders.

3.5 The DARC Group are leading a cross-Departmental and cross-Agency Working group to consider how to develop the current individual reports on antimicrobial resistance issues across the UK, into a single UK-wide report covering all aspects of veterinary and human antimicrobial resistance issues and antimicrobial resistance in the food chain.

4 Progress to meet recommendations made in Chapter 5: Human infections associated with antibiotic resistance foodborne pathogens

4.1 R&D has been funded which examined the emergence and disappearance of multi-resistant strains of *Salmonella* and others on antimicrobial resistance in *Campylobacter*. Details about all projects are available from the Defra we site at http://www2.defra.gov.uk/research/project_data/Default.asp and the VMD web site at www.vmd.gov.uk.

4.2 The HPA and VLA have organised and participated in a harmonisation ring trial of methods to test for antimicrobial resistance in *Salmonella* and *Campylobacter* to determine if the methods used showed any regional differences. Thirteen laboratories from across the UK were involved in the trial. Results from the trial will be published independently. HPA and VLA

are involved in developing and participating in an EU-wide trial to standardise antimicrobial testing methods.

4.3 The Strategy for developing and implementing a programme of surveillance for Antimicrobial Resistance in animals in England and Wales also details the work to harmonise antimicrobial resistance methods internationally.

4.4 The DARC Group are leading a cross-Departmental and cross-Agency Working group to consider how to develop the current individual reports on antimicrobial resistance issues across the UK, into a single UK-wide report covering all aspects of veterinary and human antimicrobial resistance issues and antimicrobial resistance in the food chain.

5 Progress to meet recommendations made in Chapter 6: Evidence of the food chain contributing to human infections with antibiotic-resistance microorganisms

5.1 The annual veterinary antimicrobial sales data collected by the VMD illustrates that 1- 2 tonnes of fluoroquinolones are sold for use each year in animals. This confirms a reasonably stable use of fluoroquinolones in the veterinary field over the last six years. Data for 2003 sales of veterinary antimicrobials have recently been published and show that 1.39 tonnes of fluoroquinolones were sold for use in that year. This report is available from the VMD website at www.vmd.gov.uk.

5.2 Guidelines on the Responsible Use of Antimicrobials in Food Producing Species have been published by the Responsible Use of Medicines in Agriculture (RUMA) Alliance and are supported by Government. A Code of Practice on the Responsible Use of Animal Medicines on the Farm has been published by VMD. All of these documents are available from the VMD web site at www.vmd.gov.uk.

5.3 On the relative contribution of different foods as vehicles for antibiotic-resistant enterococci, the FSA will consider including these microorganisms when planning any future surveys of meats, dairy products, raw vegetables and fruits.

5.4 Bacitracin zinc, spiramycin, tylosin and virginamycin were all phased-out across the EU in 1999 and remain banned from use. All remaining antibiotic growth promoters (avilamycin, monensin, flavophospholipol and salinomycin) will be banned from sale or use across the EU from 1 January

2006 on a precautionary basis. To date no new antibiotic growth promoting ingredients have been developed.

6 Progress to meet recommendations made in Chapter 7: Approval, prescribing and control measures relating to veterinary medicines

6.1 The supply of data derived from the testing of the antimicrobial concerned for antimicrobial resistance in the target animal species, under the intended conditions of use, is a standard requirement of the application process for veterinary medicinal products across the EU.

6.2 Full details of all post-marketing surveillance in relation to antimicrobial resistance are published to make them available to the veterinary and medical professions.

6.3 The VMD publish an annual report that details the amounts of veterinary antimicrobials sold for use in the UK, to inform others about the amounts of antimicrobials used in UK food animals. The report breaks down the sales into the categories suggested by the ACMSF, but also in additional ways to take on board comments from Stakeholders. These reports are all available from the VMD web site at www.vmd.gov.uk.

7 Progress to meet recommendations made in Chapter 8: The use of antibiotics in farm animals

7.1 The Government has developed and published its Animal Health and Welfare Strategy which includes medicines record keeping and encourages Herd Health Planning as part of a provision to provide more information on the prevalence of disease on farms and how to prevent it. One of the key aims of the Strategy is to encourage disease prevention rather than disease treatment.

7.2 Guidelines on the Responsible Use of Antimicrobials in Food Producing Species have been published by the Responsible Use of Medicines in Agriculture (RUMA) Alliance and are supported by Government. A Code of Practice on the Responsible Use of Animal Medicines on the Farm has been published by VMD. All of these documents are available from the VMD web site at www.vmd.gov.uk.

7.3 Defra has funded an R&D project entitled “Proactive Health Management and the influence of Antibiotic usage in Pigs”. Details of the project findings were released in open meetings around the UK during 2004. Details about the project are available from the Defra website at

http://www2.defra.gov.uk/research/project_data/Default.asp and the VMD web site at www.vmd.gov.uk.

7.4 In accordance with EU legislation, all antimicrobial veterinary medicinal products are Prescription Only Medicines (POM). Prescribing is permitted only by veterinarians for animals under their care. Vets who use antimicrobials under the prescribing cascade system have to keep detailed records. (The prescribing cascade is a decision tree to allow vets to use other products where there is no authorised product for the disease and species they are treating). The UK is supporting the re-classification of coccidiostats as veterinary medicinal products under EU legislation. This would bring coccidiostats into the POM category.

7.5 The British Veterinary Association have run courses for veterinary practitioners on veterinary pharmacy to better inform veterinary prescribing and use of antibiotics. All Veterinary Schools have been approached and have reviewed their syllabuses to further take antibiotic prescribing into account. The Royal College of Veterinary Surgeons has also been approached and the Education Committee is reviewing the position.

7.6 The importance of record keeping has been retained in revised EU legislation and will be included in new National Legislation. Enforcement issues are being reviewed as part of the arrangements for establishing the State Veterinary Service as an Agency of Defra. HACCP principles are already largely covered by legislation requirements to record the use of antimicrobials on farms. The proposed new hygiene regulations will assist with the production of new codes.

8 Progress to meet recommendations made in Chapter 9: Medicated animal feedingstuffs

8.1 All feed mills are inspected on a regular basis and the adequacy of the current arrangements is being reviewed. All on farm mixers using medicinal additives and intermediate medicated feedingstuffs are all registered and inspected on a regular basis. Government is further considering, as part of the review of the enforcement arrangements, whether feed manufacturers who do not comply with United Kingdom Agricultural Supply Trade Association's (UKASTA) Feed Assurance Scheme should be suitable for registration by the enforcement authorities.

8.2 Government recognises the importance of an appropriate balance between the disposal or controlled use of surplus medicated feed additives to ensure human and animal safety, animal welfare and environmental accumulation are safeguarded. Introduction of quality assurance schemes permit the use of surplus materials only at levels that cannot be detected by current

analytical methods. Government has taken no steps to amend these arrangements as it considers that the current arrangements are appropriate and address known risks.

9 Progress to meet recommendations made in Chapter 10: The use of antibiotics as growth promoters in food animal production

9.1 Bacitracin zinc, spiramycin, tylosin and virginamycin were all phased-out across the EU in 1999 and remain banned from use. All remaining antibiotic growth promoters (avilamycin, monensin, flavophospholipol and salinomycin) will be banned from use across the EU from 1 January 2006 on a precautionary basis. No new antibiotic growth promoting ingredients have been developed.

9.2 The UK Government is supporting the re-classification of coccidiostats as veterinary medicinal products under EU legislation. This would bring coccidiostats into the POM category.

10 Progress to meet recommendations made in Chapter 11: Aquaculture

10.1 Under revisions to EU legislation, all marketing authorisations have to be renewed once after 5 years and after renewal, remain valid indefinitely. It would not be possible for the UK to only authorise fish antibiotics for as short a period as possible and remain within the bounds of EU legislation.

10.2 Government are in agreement with the Ornamental Aquatic Trade Association Guidelines, which are primarily aimed at traders, on public advice warnings of the potential transfer of antibiotic resistant bacteria through direct contact with ornamental fish.

11 Progress to meet recommendations made in Chapter 12: Research on antibiotic resistance in relation to food safety

11.1 The ACMSF report included a substantial number of research recommendations and the majority of these are included in chapter 12. Since the report was published research funders have commissioned a significant amount of work in the area of microbial antibiotic resistance some of which is now being reviewed. In December 2004 Defra held a 3-day review of its funded research in this area and the meeting included presentations by other funders. A report on the Defra review is expected to be published later this year on the Defra website.

Annex C

ACM/868

ADVISORY COMMITTEE ON THE MICROBIOLOGICAL SAFETY OF FOOD

UPDATE ON THE GOVERNMENT'S ACTIONS TO ADDRESS THE RECOMMENDATIONS OF THE 1999 ACMSF REPORT ON MICROBIAL ANTIBIOTIC RESISTANCE IN RELATION TO FOOD SAFETY

1. In response to a previous request from ACMSF the attached paper updates the actions taken to address the recommendations in the ACMSF 1999 Report on Microbial Antibiotic Resistance in Relation to Food Safety. Members may wish to read this paper in conjunction with initial update presented to the Committee in 2005 by the Defra Antimicrobial Resistance Coordination Group (ACM/730).

Secretariat
September 2007

Update on the Government's Actions to address the Recommendations of the 1999 ACMSF Report on Microbial Antibiotic Resistance in Relation to Food Safety

1. Introduction

1.1 In 1996 the Advisory Committee on the Microbiological Safety of Food (ACMSF) set up a Working Group to assess the risks to humans from antibiotic resistant microorganisms entering the food chain and to consider the need to protect public health. The Committee's Report on Microbial Antibiotic Resistance in Relation to Food Safety was published in 1999 (ACMSF, 1999) and listed a series of recommendations, most of which were for Government to consider taking forward.

1.2 The Defra Antimicrobial Resistance Coordination (DARC) Group was established in 1999 and part of its remit was to track and update the Government's response to the ACMSF report. In 2005 the DARC secretariat produced a paper (ACM/730) that summarised the actions taken by Government over the five year period since publication of the ACMSF report to address its recommendations. The majority of the recommendations in the ACMSF report had been taken forward and the DARC paper comprehensively covered progress on these. However, progress on some recommendations was at an early stage and would now benefit from a further update. Also, the recommendations of Chapter 12 of the ACMSF report (Research on Antibiotic Resistance in Relation to Food Safety) were not addressed by DARC.

1.3 This paper provides an update on recommendations that were outstanding and those where further substantial progress has been made since 2005. It does not cover all the ACMSF recommendations as the majority were covered by the DARC report (ACM/730) and do not require further updating. Also outlined is the research commissioned in relation to the recommendations laid out in Chapter 12.

2. Progress on non-research recommendations

2.1 Chapters 3, 4 and 5 of the ACMSF report (ACMSF, 1999) reviewed patterns of antibiotic resistance in bacteria isolated from food animals, foodstuffs and human infections associated with antibiotic-resistant foodborne pathogens. A common recommendation that spanned these chapters was the requirement to bring data covering antimicrobial resistance in organisms from human clinical, veterinary and food sources from different regions across the UK together in a coherent document. This has been addressed by the publication

of the Overview of Antimicrobial Usage and Bacterial Resistance in Selected Human and Animal Pathogens in the UK:2004 (VMD, 2007).

2.2 Recommendations from Chapters 3 and 5 suggested that comparisons of isolates of *Salmonella* from different regions of the UK and the human and animal sectors using appropriate methodologies should be made. DARC reported to ACMSF on a ring trial that was conducted by the Health Protection Agency (HPA) and Veterinary Laboratories Agency (VLA) to meet these recommendations. The results of the trial were published in 2003 (Threlfall *et al*., 2003). Further work, resulting from this ring trial, involving molecular comparison of the antibiotic resistance determinants in *Salmonella* isolates from humans and food-producing animals has recently been published (Hopkins *et al*., 2007).

2.3 A recommendation from Chapter 3 (3.134) suggested that Government should initiate studies to identify the key factors that lead to the emergence and disappearance of multi-resistant clones of *Salmonella* Typhimurium. There is currently a Defra funded project and a Med-Vet-Net project on this underway. Additionally, an industry funded study conducted by the HPA was published in 2004 (Hopkins and Threlfall, 2004).

2.4 Chapter 6 of the ACMSF report reviewed the evidence of the foodchain contributing to human infections with antibiotic-resistant microorganisms. Gaps in the knowledge base were identified with regards to the prevalence of antibiotic resistance in commensal microorganisms found in food (particularly *E. coli* and enterococci) and investigation of these was recommended (Recommendations 4.72 and 6.121). To our knowledge no work has been commissioned by Government specifically to meet these recommendations.

2.5 Sections 8.34 and 8.35 of the ACMSF report reviewed the training arrangements for veterinarians in the UK regarding antibiotic prescribing and antimicrobial resistance. Recommendation 8.51 suggested that veterinary schools and colleges should review their existing courses to ensure that microbial resistance was given a suitably high profile in undergraduate courses. In 2005 DARC reported that the Royal College of Veterinary Surgeons was approached and was reviewing the situation. The Veterinary Medicines Directorate recently wrote to the Universities offering undergraduate degrees in veterinary medicine to confirm that these topics had been incorporated into the degrees and are satisfied that this has been done.

2.6 Chapter 9 of the ACMSF report reviewed the use of medicated animal feedingstuffs. Recommendation 9.25 suggested that manufacturers who failed to comply with UKASTA's (United Kingdom Agricultural Supply Trade Association Ltd.) Feed Assurance Scheme should not be considered as

suitable for registration by the enforcement authorities. At the time of the DARC report to the ACMSF in 2005 a review of enforcement arrangements for feed manufacture was being undertaken and this led to new legislation to regulate this sector. The Veterinary Medicines Regulations (2006) state that manufacturers and distributors of premixtures and feedingstuffs containing veterinary medicinal products and premixtures and feedingstuffs containing specified feed additives must be approved. The statutory inspection and approval of these premises is carried out by the Veterinary Medicine's Directorate (VMD) Animal Medicines Inspectorate and is more thorough than the assurance scheme discussed by industry. In light of these developments the industry assurance scheme was not taken forward.

3. Progress to meet recommendations made in Chapter 12: Research on antibiotic resistance in relation to food safety

3.1 A large body of research has been conducted since 1999 to meet the recommendations made in Chapter 12 of the ACMSF report. The Microbiological Safety of Food Funders Group (MSFFG) recently published a detailed report on UK publicly funded research on microbial antibiotic resistance in relation to the safety of food that was presented to the ACMSF in March 2007 (MSFFG, 2007).

3.2 A summary of how the research covered in the MSFFG report relates to the ACMSF recommendations from Chapter 12 can be found in Table 1. It is important to note that research covering a number of recommendations has been carried out in other countries or funded within the UK by other bodies. Hence, the appearance of gaps in Table 1 does not necessarily represent a lack of scientific evidence relating to a particular recommendation.

3.3 Reviewing the recommendations it is apparent that there are two key areas where there may be gaps in Government funded research. Firstly, the occurrence of antibiotic-resistant bacteria in imported food and animal feedingstuffs and, secondly, in the area of microbiological risk assessment.

3.4 Government funded surveys specifically testing for antibiotic-resistant bacteria in imported foods only are rare. However, FSA surveys on microbiological contamination in various foodstuffs are designed to allow detection of microbiological contamination (and test for antimicrobial resistance) in particular products available to the consumer at the point of sale. As such, samples taken during these surveys will usually comprise a mixture of home-produced and imported products. Specific surveys of the microbiological contamination of imported foods have been carried out by the FSA only when a significant issue relating to imported foods has emerged (e.g. *Salmonella* contamination of eggs).

3.5 The presence of antibiotic-resistant bacteria in imported animal feedstuffs has not yet been investigated but is currently being considered by Defra.

3.6 To date, meaningful microbiological risk assessment relating to antibiotic-resistant bacteria has been difficult to carry out due to a lack of data to support the assessment. FSA funded Project B10004 (Assessment of, relative to other pathways, the contribution made by the foodchain to the problem of quinolone resistance in microorganisms causing human infections) is the only project that addresses recommendation 12.36 in it's entirety. However, the vast body of research carried out in the last eight years should now allow this work to be undertaken in a more comprehensive manner.

3.7 To determine the extent to which the research questions underlying the recommendations of this Chapter have been answered research undertaken in the UK and elsewhere will be further reviewed. This process will contribute to the development of an FSA strategy on antimicrobial resistance in the foodchain.

4. Conclusions

4.1 It is evident that the majority of recommendations from the 1999 ACMSF Report on Microbial Antibiotic Resistance in Relation to Food Safety have been taken forward and completed.

4.2 Areas that have been highlighted for further consideration by this review of the ACMSF recommendations include antibiotic resistance in commensal microorganisms in food, antibiotic-resistant microoganisms in imported food and animal feed and Microbiological Risk Assessment.

4.3 The FSA intends to hold a stakeholder meeting on Antimicrobial resistance in the food chain in November 2007. The topics listed above, as well as issues which have emerged since the publication of the report (such as ESBL-producing *E. coli* and MRSA in pigs), will be considered during this stakeholder meeting. The results of the stakeholder meeting are intended to inform work on an FSA strategy on antimicrobial resistance in the food chain.

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http://www.vmd.gov.uk/Publications/Antibiotic/antimicrob120707.pdf

Table 1: Recommendations from Chapter 12 and corresponding research projects

Recommendation	Relevant Research Projects
12.33 Research should be undertaken to: • Undertake integrated local surveillance studies to examine prevalence of antibiotic resistance associated with Campylobacter, Salmonella and commensal bacteria throughout slaughter and processing • Assess the prevalence of antibiotic resistance in wild animals, including birds, and food animals on farms in relation to the usage of antibiotics, particularly a) growth promoters and b) fluoroquinolones	Defra funded project FZ2009 (Abattoir Survey of Foodborne Pathogens in Cattle, Sheep & Pigs in Great Britain 2003) Defra funded projects OD2009, OD2003, OZ0501, VM02100, VM02101, VM02200 Scottish Executive funded project SAC/147/97
12.34 Research should be funded to: • Identify risk factors for acquiring an infection with an antibiotic resistant pathogen. Such studies need to be conducted in both humans and, where appropriate, animals • Assess the extent of infection in travellers caused by antibiotic-resistant strains and the contribution these make to the burden of IID and antibiotic resistance in the UK • Assess the importance of imported food and animal feed as a source of antibiotic-resistant bacteria • Determine the contribution made by microorganisms of human origin to microbial antibiotic resistance in animals and food • Model current patterns and predict future trends in antibiotic resistance of foodborne pathogens in humans and animals • Determine the socioeconomic costs attributable to antibiotic-resistant foodborne pathogens in humans, above the costs attributable to antibiotic sensitive foodborne	FSA funded project B14001 FSA funded projects B10004, B14001 FSA funded surveys B18002, B18012, B18017, B18018, B18022, B18024, B18025 Scottish Executive funded projectsSAC/254/00 FSA funded project B10004

pathogens	
12.35 Research should be funded to: • Develop methods which will characterise the origins of resistance in foodborne pathogens and commensal microorganisms, so as to improve identification of sources and routes of transfer of resistant organisms from farm through food to humans	BBRSC funded project 4311218 Defra funded projects OD2011, OD2014, OD2020, OZ0132, VM02100, VM02105, VM02136 FSA funded project B10001 MRC funded projects G0501415, G0300020
12.36 In relation to microbiological risk assessment (MRA), research should be funded to: • Undertake structured MRA to assess the risk of infectious intestinal disease from antibiotic-resistant foodborne pathogens and commensal bacteria in food animals, foods and the environment • Use MRA to quantify the magnitude of the key pathways by which microbial antibiotic resistance can transfer from food animals to humans via the food chain and environment • Undertake MRA to assess links between a) use of growth promoters and b) fluoroquinolones in food animals and the development of antibiotic-resistant infections in humans	FSA funded project B10004
12.37 To facilitate a reduction in the usage of antibiotics, research should be funded to: • Underpin effective antibiotic management policies in animals, aimed at optimising administration practices to minimise the risk of development of resistance. This will include investigations of the persistence of antibiotic-resistant bacteria in the gastrointestinal tract of food animals after antibiotic withdrawal • Further investigate how particular hygiene practices and interventions can bring about a real reduction in the need for antibiotics in food animal production, without jeopardising animal	Defra funded projects OD2003, OD2007, OD2014, OD2015, OZ0501, OZ0502, VM0292, VM02201 Scottish Executive funded projects SAC/137/97, SAC/147/97

welfare • Evaluate the potential of vaccines, probiotics and competitive exclusion to reduce the usage of antibiotics and the level of resistance in microorganisms in food	Scottish Executive funded projects SAC/137/97 and SAC/147/97
12.38 Research should be conducted to: • Determine the relationship between antibiotic resistance and virulence in foodborne pathogens in humans and, where appropriate, animals • Review the clinical picture (duration, severity, treatment and outcome) of cases of IID involving antibiotic-resistant foodborne pathogens as opposed to cases infected with sensitive isolates, and assess whether there are any longterm implications of these infections for the patient	FSA funded project B14001
12.39 Research should be funded to: • Examine the antibiotic-resistant pathogens and commensal organisms from animals an humans to determine their survival characteristics in the environment compared to non-resistant strains • Examine the effect of antibiotic selection pressure on the survival and persistence of antibiotic-resistant strains, both in vitro and in vivo • Examine the transfer of resistance determinants between foodborne pathogens and commensal flora of humans and animals in a) foods and b) the environment	BBSRC funded projects 772, 4311218, D15925 Defra funded projects OD2002, OD2005, OD2008 SEERAD funded project RRI/743/01 BBSRC funded projects 772, 4311218, D15925 SEERAD funded project RRI/743/01

Summary of recommendations

Subject	Chapter	Paragraph	Recommendation	Immediate (Imm) or medium/ long-term (M/L) effect
Patterns of antibiotic resistance in bacteria isolated from food animals	3	3.134	The Government should initiate studies to identify the key factors that lead to the emergence and disappearance of multiresistant clones of *Salmonella typhimurium.*	M/L
		3.135	The Government should ensure that isolates of salmonellas from animals in England and Wales, Scotland and Northern Ireland are compared, using appropriate methodologies, to see whether there are any regional differences in antibiotic susceptibilities.	M/L
		3.136	The Government should consider how the monitoring of pathogens in food animals could be improved, with a view to obtaining data on the prevalence, subtypes and antibiotic resistance of important foodborne pathogens, and publishing this information on a regular basis. Reference laboratories should establish the relationship between antibiotic resistance and subtype of animal isolates of *Campylobacter*, to aid further studies aimed at identifying the sources of antibiotic-resistant strains. Government should ensure that those organisations directing or undertaking surveillance of organisms isolated from animals should work together with organisations monitoring resistance in bacteria from food and humans to produce an annual UK report summarising antibiotic resistance in the food chain. Surveys of UK veterinary laboratories should be carried out to ascertain current practices with regard to antibiotic resistance testing of microorganisms important in the food chain, with a view to improving comparability between animal, food and human data.	M/L
		3.137	The Veterinary Laboratories Agency should consider including *Escherichia coli* in any surveillance of antibiotic resistance in "healthy" food animals.	M/L
		3.138	The Veterinary Laboratories Agency should collate and publish its data on resistance in anaerobes at the earliest opportunity.	M/L
Patterns of antibiotic resistance in bacteria isolated from foodstuffs	4	4.67	There should be enhanced national and international surveillance for antibiotic resistance of microorganisms isolated from foods. Surveys should be conducted where the primary aim is to gather information on antibiotic resistance and, in planning future food microbiological surveys, consideration should be given to the screening of foodborne pathogens and other microorganisms for antibiotic resistance using appropriate methodologies.	M/L

Subject	Chapter	Paragraph	Recommendation	Immediate (Imm) or medium/ long-term (M/L) effect
Patterns of antibiotic resistance in bacteria isolated from foodstuffs	4	4.68	Studies should be carried out to : • gather further information on antibiotic resistance in campylobacters in the UK; and • explore the variability in the isolation of resistant campylobacters from retail poultry observed in several studies.	M/L
		4.69	All microbiological reference laboratories for enteric pathogens in the UK should consider screening these and other microorgansisms isolated from routine food samples for antibiotic resistance and publishing their data on a regular basis.	M/L
		4.70	Reference laboratories should carefully examine the relationship between antibiotic resistance and subtype of food isolates of *Campylobacter* to aid further studies aimed at identifying the sources of antibiotic-resistant strains. Government should ensure that those organisations directing or undertaking surveillance of organisms isolated from food should work together with organisations monitoring resistance in bacteria from animals and humans to produce an annual UK report summarising antibiotic resistance in the food chain. Surveys should be carried out of UK food laboratories to ascertain current practices with regard to antibiotic resistance testing of microorganisms important in the food chain with a view to improving comparability between animal, food and human data.	M/L
		4.71	Research funding organisations should undertake studies to assess the effect of food processing, storage conditions and food preparation on the antibiotic-resistant microflora of foods and the transfer of resistance between food bacteria.	M/L
		4.72	Using appropriate methodologies, *Escherichia coli* isolates from foodstuffs should be screened for antibiotic resistance to provide a more sensitive indication of differences between food commodities and changes in resistance over time.	M/L
Human infections associated with antibiotic-resistant foodborne pathogens	5	5.80	Funding organisations should commission research to establish why certain *Salmonella* serotypes (eg. *S. hadar*, *S. typhimurium*, *S. virchow*) develop antibiotic resistance and multiresistance, whereas others (eg. *S. enteritidis*) have remained largely sensitive.	M/L
	5	5.81	The Government should investigate the basis for regional differences in fluoroquinolone (eg. ciprofloxacin) resistance in salmonellas in the UK.	M/L

Subject	Chapter	Paragraph	Recommendation	Immediate (Imm) or medium/ long-term (M/L) effect
Human infections associated with antibiotic-resistant foodborne pathogens		5.82	The reference laboratories should carefully examine the relationship between antibiotic resistance and subtype of human isolates of *Campylobacter* to aid further studies aimed at identifying the sources of antibiotic-resistant strains.	M/L
			The Government should take steps to ensure that those organisations directing or undertaking surveillance of organisms isolated from humans should work together with organisations monitoring resistance in bacteria from animals and food to produce an annual UK report summarising antibiotic resistance in the food chain.	
			Surveys of UK clinical laboratories should be carried out to ascertain current practices with regard to antibiotic resistance testing of microorganisms important in the food chain, with a view to improving comparability between animal, food and human data.	
		5.83	The Government should seek ways of achieving further standardisation of antibiotic resistance testing across Europe and internationally.	M/L
Evidence of the food chain contributing to human infections with antibiotic-resistant micro-organisms	6	6.120	We endorse the recommendation made by the House of Lords in their report on resistance to antibiotics that the veterinary profession must address the problem of the over-use of fluoroquinolones and feel that targeted codes of practice on prescribing should be introduced as soon as possible.	Imm
		6.121	The relative contribution of meats, dairy products, raw vegetables and fruits as vehicles for antibiotic-resistant enterococci should be clarified.	M/L
		6.122	There should be continual surveillance and assessment of the risks to humans associated with the use of those growth promoters still authorised in the EU and we make appropriate recommendations in Chapter 10.	M/L
Approval, prescribing and control measures relating to veterinary medicines	7	7.22	The Government, in association with the other Member States of the European Union, should require applicants applying for marketing authorisations for antibiotics for veterinary use to supply data derived from the testing of the antibiotic concerned for microbial resistance in target animal species under intended conditions of use. Such data should be made publicly available in support of licensing decisions.	Imm

Subject	Chapter	Paragraph	Recommendation	Immediate (Imm) or medium/ long-term (M/L) effect
Approval, prescribing and control measures relating to veterinary medicines	7	7.23	The Government should discuss with the veterinary profession and the pharmaceutical industry ways in which the information gathered as part of post-marketing surveillance, including that on the incidence and prevalence of resistance, could best be made available to the veterinary and medical professions. It is important that the regulatory authorities give a high degree of attention to the question of microbial antibiotic resistance, both in the initial licensing process and subsequently at the 5 year licence review stage.	Imm
		7.24	The Government should take steps to establish the amounts of antibiotics given to food animals. This information should be published at regular intervals by the Veterinary Medicines Directorate and should, at the very least, be so structured as to provide a breakdown by compound, class, medical equivalent (where appropriate) and target species.	Imm
Use of antibiotics in farm animals	8	8.47	The Government should coordinate the development of a coherent strategy aimed at reducing the veterinary use of antibiotics.	Imm
		8.48	More specifically, the Government should take all possible measures to ensure that :- • all antibiotics used for purposes other than growth promotion are prescription only medicines (POM); • all prescribing by veterinarians is for animals under their care; and • detailed written justification is provided by veterinarians using cascade medicines.	Imm
		8.49	The Government should bring together the relevant bodies to produce and publish without delay:- • Codes of Practice aimed at reducing the use of antibiotics; • appropriate dosage strategies; • detailed preventative medicine programmes for all livestock-based food production enterprises covering routine medication (including the use of anticoccidials and growth promoters), the length of treatment regimes, competitive exclusion and probiotic treatments and vaccines; and • policies and protocols for the use, storage and disposal of antibiotics.	Imm
		8.50	The BVA and the other relevant professional representative bodies, in cooperation with the veterinary schools and colleges, the farming industry and others, should develop appropriate courses to better inform veterinary prescribing and use of antibiotics and to draw attention to the potential dangers of resistance.	Imm

Subject	Chapter	Paragraph	Recommendation	Immediate (Imm) or medium/ long-term (M/L) effect
Use of antibiotics in farm animals	8	8.51	The veterinary schools and colleges should review their existing courses to ensure that microbial antibiotic resistance is given a suitably high profile in undergraduate training.	Imm
		8.52	The Government should mount regular campaigns to remind the livestock industry of its statutory obligations in respect of the maintenance of farm medication records, to improve enforcement, and to greatly enhance current performance levels.	Imm
		8.53	The Government should carry out regular, statistically-robust, compliance surveys and should review existing arrangements to ensure that effective follow up action can be taken where non-compliance is identified	M/L
		8.54	The Government should encourage the use of HACCP principles as a tool for improving farm practice and as a means of ensuring the responsible use of antibiotics, thus tackling the problem of microbial antibiotic resistance.	Imm
		8.55	The Government should encourage regular veterinary visits to all livestock farms or production units to audit animal disease profiles and general performance indicators, to accumulate and scrutinise mortality, morbidity and general health data, and to record antibiotic resistance patterns so that antibiotic prescribing can be adjusted accordingly.	Imm
Medicated animal feedingstuffs	9	9.23	The Government should:- • require regular, on-going surveillance of a representative cross-section of commercial feed compounders, integrated poultry producers and on-farm mixers to test compliance with the law and to oversee the guidelines for ensuring that medicated animal feeds intended for food animals are manufactured, stored and distributed in a safe and professional manner; and • review the adequacy of the current frequency of inspections by the enforcement bodies.	Imm
		9.24	On-farm mixers using medicinal additives and intermediate medicated feedingstuffs in any manner should be required to register with the RPSGB or DANI.	Imm
		9.25	Manufacturers who fail to comply with UKASTA's Feed Assurance Scheme should not be regarded as suitable for registration by the enforcement authorities. In addition, all those engaged in the manufacture of medicated animal feedingstuffs are strongly encouraged to apply Hazard Analysis Critical Control Point (HACCP) principles to their operations. This means not only commercial feed compounders and the integrated poultry producers but the on-farm mixers too.	Imm

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Medicated animal feedingstuffs	9	9.26	The Government should review the arrangements under which discarded and surplus medicinal additives may be re-used in medicated feed and medicated pre-mixes, with a view to phasing out this practice in favour of appropriate disposal as waste material at the earliest opportunity.	Imm
Use of antibiotics as growth promoters in food animal production	10	10.25	The use of spiramycin, tylosin phosphate and virginiamycin as growth promoters should be phased out at the earliest opportunity.	Imm
		10.26	The use of those antibiotics where there is currently no medical equivalent, or where their medical use is rare – avilamycin, bambermycin, bacitracin zinc, monensin sodium and salinomycin – should be kept under close review, and if any evidence becomes available of medical equivalents being developed for clinical use, then their use as growth promoters should be phased out. We are particularly concerned about possible developments in the use of avilamycin and bacitracin zinc for clinical use.	Imm
		10.27	No new growth promoters should be developed which utilise substances which have possible applications in human clinical treatment.	Imm
Aquaculture	11	11.17	The Government should licence the use of antibiotics in new fish species being developed for aquaculture for as short a period as is feasible and equitable.	Imm
		11.18	The Government should issue public advice warning of the potential risk of the transfer of antibiotic resistant bacteria through direct contact exposure to ornamental fish.	M/L
Research on microbial antibiotic resistance in relation to food safety	12	12.33	Research should be funded to:– • undertake integrated local surveillance studies to examine the prevalence of antibiotic resistance associated with *Campylobacter, Salmonella* and commensal bacteria in red meat and poultry throughout slaughter and processing; • assess the prevalence of antibiotic resistance in wild animals, including birds, and food animals on farms in relation to the usage of antibiotics, particularly a) growth promoters and, b) fluoroquinolones.	M/L
		12.34	Research should be funded to:– • identify risk factors for acquiring an infection with an antibiotic resistant foodborne pathogen. Such studies need to be conducted both in humans and, where appropriate, animals;	M/L

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Research on microbial antibiotic resistance in relation to food safety	12	12.34 (cont)	• assess the extent of infection in travellers caused by antibiotic-resistant strains and the contribution these make to the burden of IID and antibiotic resistance in the UK; • assess the importance of imported food and animal feed as a source of antibiotic-resistant bacteria; • determine the contribution made by microorganisms of human origin to microbial antibiotic resistance in animals and food; • model current patterns and predict future trends in antibiotic resistance of foodborne pathogens in humans and animals; • determine the socio-economic costs attributable to antibiotic-resistant foodborne pathogens in humans, above the costs attributable to antibiotic-sensitive foodborne pathogens.	M/L
		12.35	Research should be funded to develop methods which will characterise the origins of resistance in foodborne pathogens and commensal microorganisms, so as to improve identification of the sources and routes of transfer of resistant organisms from the farm through food to humans.	M/L
		12.36	In relation to microbiological risk assessment (MRA), research should be funded to :- • undertake structured MRA to assess the risk of infectious intestinal disease from antibiotic-resistant foodborne pathogens and commensal bacteria in food animals, foods and the environment; • use MRA to quantify the magnitude of the key pathways by which microbial antibiotic resistance can transfer from food animals to humans via the food chain and the environment; • undertake MRA to assess the links between a) use of growth promoters and b) fluoroquinolones in food animals and the development of antibiotic-resistant infections in humans.	M/L
		12.37	To facilitate a reduction in the usage of antibiotics, research should be funded to :- • underpin effective antibiotic management policies in animals, aimed at optimising administration practices to minimise the risk of development of resistance. This will include investigations of the persistence of antibiotic-resistant bacteria in the gastrointestinal tract of food animals after antibiotic withdrawal; • further investigate how particular hygiene practices and interventions can bring about a reduction in the need for antibiotics in food animal production, without jeopardising animal welfare;	M/L

Subject	Chapter	Paragraph	Recommendation	Immediate (Imm) or medium/ long-term (M/L) effect
Research on microbial antibiotic resistance in relation to food safety	12	12.37 (cont)	• evaluate the potential of vaccines, probiotics and competitive exclusion to reduce the usage of antibiotics and the level of resistance in microorganisms in food animals.	
		12.38	Research should be conducted to :- • determine the relationship between antibiotic resistance and virulence in foodborne pathogens in humans and, where appropriate, animals; • review the clinical picture (duration, severity, treatment and outcome) of cases of IID involving antibiotic-resistant foodborne pathogens, as opposed to cases infected with sensitive isolates, and assess whether there are any longer-term consequences of these infections for the patient.	M/L
		12.39	Research should be funded to :- • examine antibiotic-resistant pathogens and commensal organisms from animals and humans to determine their survival characteristics in the environment, compared to non-resistant strains; • examine the effect of antibiotic selection pressure on the survival and persistence of antibiotic-resistant strains, both *in vitro* and *in vivo*; • examine the transfer of resistance determinants between foodborne pathogens and the commensal flora of humans and animals in a) foods and b) the environment.	M/L