8 June 2009

Joint scientific report of ECDC, EFSA and EMEA on meticillin resistant *Staphylococcus aureus* (MRSA) in livestock, companion animals and food[1].

Summary of the scientific Opinion of the Panel on Biological Hazards (EFSA/BIOHAZ) on *"Assessment of the Public Health significance of meticillin resistant Staphylococcus aureus (MRSA) in animals and foods"* and the Reflection paper of the Committee for Medicinal Products for Veterinary Use (EMEA/CVMP) on *"MRSA in food producing and companion animals and in the European Union: Epidemiology and control options for human and animal health"*

The Opinion from EFSA/BIOHAZ, which includes input from ECDC, can be found at http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902408708.htm

The Reflection paper from the EMEA/CVMP can be found at http://www.emea.europa.eu/htms/vet/antimicrobial/antimicrobial.htm

[1] For citation purposes:
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1. Background to the summary paper

The European Centre for Disease Prevention and Control (ECDC, http://www.ecdc.europa.eu) is the EU agency that aims at protecting EU citizens' health from infectious diseases. ECDC serves as an information, knowledge and action centre to support and strengthen all EU institutions and countries in their work to detect, prevent and control infectious diseases. In order to achieve this mission, ECDC works in partnership with national health protection bodies across Europe to strengthen and develop continent-wide disease surveillance and early warning systems. By working with experts throughout Europe, ECDC pools Europe's health knowledge, so as to develop authoritative scientific opinions about the risks posed by current and emerging infectious diseases. Antimicrobial resistance and healthcare-associated infections are the topics of a specific priority programme at ECDC, which covers antimicrobial resistance issues in hospitalised patients as well as outpatients.

The European Food Safety Authority (EFSA, http://www.efsa.europa.eu) is the keystone of EU risk assessment regarding food and feed safety, and thereby including also antimicrobial resistance, as this has a zoonotic potential. EFSA provides independent scientific advice and communication on existing and emerging risks. The Authority aims at using the best science available to carry out its tasks. Therefore EFSA mobilizes and coordinates scientific resources throughout the EU to provide high-quality and independent scientific advice and risk assessments. In practice, this takes place via scientific panels, working groups, task forces, grants and contracting scientific work as well as in other ways of networking with scientists. Requests for scientific assessments are received from the European Commission (Commission), the European Parliament (EP) and EU Member States (MS). EFSA also undertakes scientific work on its own initiative, so-called self-tasking. The BIOHAZ Panel and its supporting Scientific Unit, within the EFSA's Risk Assessment Directorate provide scientific advice on all questions on biological hazards relating to food safety and food-borne disease, including food-borne zoonoses and transmissible spongiform encephalopathies, microbiology, food hygiene and associated waste management.

The European Medicines Agency (EMEA) is a decentralised body of the European Union. Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. The mission of the European Medicines Agency (EMEA, http://www.emea.europa.eu/) is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health. The EMEA provides independent, science-based recommendations on the safety and efficacy of medicines applying efficient and transparent evaluation procedures to help bring new medicines to the market by means of a single, EU-wide marketing authorisation granted by the European Commission, this includes issues related to antimicrobial resistance derived from the use of medicines for humans as well as for animals. The Committee for Medicinal Products for Veterinary Use (CVMP) provides the scientific recommendations and opinions on veterinary medicines when those are related to antimicrobials, the Committee is supported by its Scientific Advisory Group on Antimicrobials (SAGAM). As indicated on the CVMP strategy on antimicrobials 2006-2010, the CVMP considers maintaining the efficacy of antimicrobials and minimising the development of resistance one of the most important tasks in the field of veterinary medicine.

Following concerns on the increase of MRSA in livestock and companion animals, the EFSA, with its Panel on Biological Hazards (BIOHAZ), and the EMEA, with its Committee for Medicinal Products for Veterinary Use (CVMP), independently decided to undertake self-tasking mandates and to produce scientific reports to address the issue. ECDC was represented in this exercise through membership of the EFSA/BIOHAZ expert working group.

Shortly after the start of the work on the respective self-tasking mandates, the European Commission (DG SANCO) formally requested from ECDC, EFSA and EMEA a close collaboration to summarise the main outcomes of the independent assessments. From that point, the three Agencies have worked in close collaboration, and in a coordinated fashion, for the preparation of the independent reports, and have actively worked together in the integration of the major conclusions and recommendations in the

summary paper presented here. The ECDC opinion is not presented as a separate document, but has been integrated in the EFSA/BIOHAZ opinion. During the preparation of the paper the agencies carefully took into account their terms of reference to avoid addressing areas that are not within their remit.

For detailed information on the content of the scientific reports further reference should be made to each individual document. The EFSA document is based on the Opinion of its BIOHAZ Panel, which includes input from ECDC. The EMEA/CVMP document is based on the proposal of its Scientific Advisory Group on Antimicrobials (SAGAM).

The information provided below represents the overall conclusions and recommendations from the previously mentioned reports The EFSA/BIOHAZ conclusions and recommendations reflect the focus of the Authority on Risk Assessment, whilst the EMEA/CVMP conclusions and remarks reflect the Agencies' role in Risk Assessment and Risk Management. The joint publication of this summary does not imply formal adoption/endorsement of the conclusions and recommendations outside the remit of each independent agency.

A base-line study in all EU-Member States with the aim to estimate the prevalence of MRSA in swine breeding herds is currently being finalised (Decision 2008/55/EC, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:014:0010:0025:EN:PDF). The Unit on Zoonoses Data Collection in EFSA are performing the analysis of the results generated by the MSs, and will produce reports on prevalence estimates and analysis or risk factors in 2009. When this new information becomes available, the present document and its source documents may require updating.

2. Introduction

Staphylococcus aureus can be persistently or intermittently carried by healthy humans (e.g. in the nose, throat, axilla, rectum, perineum or gastrointestinal tract), being a very common cause of minor skin infections that usually do not require treatment. For patients in hospitals, it is the most common cause of hospital-acquired infections (from trivial to very severe).

Meticillin-resistant *S. aureus* or MRSA, is resistant to virtually all available beta-lactam antimicrobials. This resistance is mediated by the chromosomally located *mec*A gene. MRSA first emerged in hospitals in the 1970s, and by the 1990s increased dramatically worldwide, becoming a serious clinical problem in hospital environments. In recent years a major change in epidemiology of MRSA has been observed, with the appearance of cases in the community affecting people having no epidemiological connection with hospitals.

The hazard of animal-associated MRSA has also been recently identified. In this case, it is important to distinguish between MRSA isolated from companion animals, and MRSA from animals used in food production.

In food animals a new clone CC398 has emerged. Carriage of this clone has been found in intensively reared production animals (primarily pigs, but also cattle and poultry) in several countries around the world. CC398 can be transmitted from food producing animals to humans. Animals in food production and their products are therefore a potential source of MRSA for humans.

Since the 1990s, an increasing number of studies have reported MRSA infections in companion animal patients at veterinary clinics and hospitals. It is generally accepted that pets become colonised through contact with colonised people. MRSA can also cause clinical disease in a number of such animals (mainly dogs and horses). The majority of such clinical cases have been due to post-operative infections.

Thus there is increasing concern about the public health impact of MRSA associated with animals (food-producing and companion animals). This evolution of MRSA in different animal species demands for a critical review on the factors associated with its emergence from the veterinary and public health point of view. EFSA in collaboration with the ECDC, and EMEA have undertaken self-taking mandates according to the terms of reference indicated in the next section of this document.

3. Terms of reference (ToR)

Specifically the agencies have addressed the following different terms of reference:

3.1. EFSA/BIOHAZ and ECDC

ToR1. To assess the risk to human health posed by MRSA associated with food-producing animals.

ToR2. To assess the importance of food, food-producing animals, and companion animals in the risk of human infection and/or food-borne disease caused by MRSA in both the community and hospital settings.

ToR3. To determine which animal species (and if appropriate, foods derived there from) represent the greatest risk to humans.

ToR4. To identify which methods are best suited for the isolation and molecular typing of MRSA of animal origin.

ToR5. To indicate what control options (pre- and post-harvest) can be considered to minimize the risk of transfer of food-associated and animal-associated MRSA to humans.

3.2. EMEA/CVMP

ToR6. To provide a preliminary risk profile for animal use of antimicrobials in relation to the risk of MRSA infection and colonization in animals (livestock and companion). Specifically:

- To assess the impact of use of antimicrobials in livestock and companion animals on the risk of colonization or infection with MRSA.
- To provide advice on management options for animals related to the issue.

4. Conclusions

4.1. General

- There are different states of interaction between *S. aureus* (including MRSA) and its host. These can be defined as: infections, carriage or colonisation, and contamination.
- Meticillin resistant *S. aureus* (MRSA) can be persistently or intermittently carried in the nose by healthy humans, and can also be found in the throat, axilla, rectum, perineum or gastrointestinal tract. Colonisation is the major risk factor for infection.
- MRSA are now widespread in hospitals in many European countries and is a major cause of hospital acquired infection. Infection can be mild to severe and, in some instances, fatal. There are large differences in prevalence and policies to control MRSA in different MS.
- There are major lineages within *S. aureus* (including MRSA), some of which show host specificity to humans or animals. A limited number of lineages of MRSA tend to predominate in specific geographical locations.
- CC398 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. At present, CC398 has not been associated with staphylococcal foodborne intoxication.

4.2. ToR1. To assess the risk to human health posed by MRSA associated with food-producing animals

- LA-MRSA (CC398) represents only a small proportion of the total number of reports of MRSA infections in the EU. However, this proportion differs between Member States and is much higher in Denmark, The Netherlands and Belgium where active control policies are implemented.
- In some countries with low prevalence of human MRSA infection, CC398 is a major contributor to the overall MRSA burden. In countries with high overall human MRSA prevalence, CC398 is considered of less significance for public health.
- CC398 has, albeit rarely, been associated with deep-seated infections of skin and soft tissue, pneumonia and septicaemia in humans.
- Where CC398 prevalence is high in food-producing animals, people in contact with these live animals (especially farmers and veterinarians, and their families) are at greater risk of colonisation and infection than the general population.
- The risk to human health from different levels (dose response) of MRSA during carriage in animals (and in the environment) is not known.

4.3. ToR2. To assess the importance of food, food-producing animals, and companion animals in the risk of human infection and/or food-borne disease caused by MRSA in both the community and hospital settings.

- Food may be contaminated by MRSA (including CC398): eating and handling contaminated food is a potential vehicle for transmission. There is currently no evidence for increased risk of human colonisation or infection following contact or consumption of food contaminated by CC398 both in the community and in hospital.
- MRSA (including CC398) can enter the slaughterhouse in or on animals and occurs on raw meat. Although it may become part of the endemic flora of the slaughterhouse, the risk of infection to slaughterhouse workers and persons handling meat appears to be low, based on current data.
- The potential for CC398-colonised humans to contribute to the spread of MRSA in hospitals currently seem to be less than for hospital associated MRSA strains.
- MRSA infections in companion animals are increasingly reported and in almost all cases, the strains causing infection in animals are the same as those commonly occurring in hospitals in the same geographical region. Humans are likely to spread MRSA to companion animals, and these can then be a reservoir for humans both in the community and in health care facilities.
- Horses can become colonised and/or infected with MRSA from humans or from other animal sources in their environment. There are sporadic reports of human disease, usually minor skin infections, attributable to an equine source.

4.4. ToR3. To determine which animal species (and if appropriate, foods derived there from) represent the greatest risk to humans.

- 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 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.

4.5. ToR4. To identify which methods are best suited for the isolation and molecular typing of MRSA of animal origin

- There is a wide variety of methods available for the isolation of MRSA.

- MRSA can be identified using phenotypic (antimicrobial susceptibility testing) or genotypic methods.
- For diagnosis of infection, samples taken directly from a lesion, biopsy specimens or blood cultures are cultured onto non-selective and selective media.
- For detection of carriage or contamination, swabbing of noses (for individuals), dust (for herds or flocks), and sampling of food are used. Increased sensitivity is obtained when using selective liquid enrichment methods.
- *spa* typing is applicable for lineage detection in first line typing because of wide congruence with results of MLST and other typing methods.
- There are insufficient data to identify the optimal sampling and isolation methods to identify herd/flock prevalence.

4.6. ToR5. To indicate what control options (pre- and post-harvest) can be considered to minimize the risk of transfer of food-associated and animal-associated MRSA to humans.

- Monitoring and surveillance are not control options as such, however these processes are essential for determining control strategies and for the evaluation of their effectiveness.
    - Surveillance of MRSA in humans, including *spa* typing of a representative number of isolates is necessary in order to monitor the occurrence of different strains of MRSA including CC398 in people.
- Animal movement and contact between animals is likely to be an important factor for transmission of MRSA. In the absence of specific studies on the spread and persistence of MRSA, general control options on farms, in slaughterhouses and in food production areas are likely to be the same for MSSA as well as MRSA, and include good husbandry practices, HACCP, GHP and GMP. Monitoring and subsequent restrictions on movement may reduce transmission.
- Since the most important routes of transmission to humans are through direct contact with live animals and their environments, the most effective control options will be at pre-harvest.
- LA-MRSA carriers in hospital and other healthcare settings can be managed in the same way as HA- and CA-MRSA carriers in both staff and patients by screening and infection control measures. Strategies for screening (together with actions taken following their results) vary considerably between different MSs. Search and destroy policy seems to be the most effective, however its implementation is difficult when MRSA is already prevalent.
- Transfer of MRSA to humans from companion animals and horses is difficult to control. Basic hygiene measures are key, especially hand washing before and after contact, and if possible, avoiding direct contact with nasal secretions, saliva and wounds.

4.7. ToR6. To provide a preliminary risk profile for animal use of antimicrobials in relation to the risk of MRSA infection and colonization in animals (livestock and companion) [2].

4.7.1. Impact of use of antimicrobials in livestock and companion animals on the risk of colonization or infection with MRSA.

4.7.1.1. Livestock

- As with human medicine, antimicrobial consumption is considered a driving force in the emergence and spread of CC398.
- Molecular studies support the hypothesis that co-selection by non beta-lactam agents probably contributes to the high prevalence of CC398.

[2] ***Conclusions overlapping with the above EFSA terms of reference were deleted; in case of doubt reference should be made to the EMEA/CVMP reflection paper.***

- Monitoring of antimicrobial consumption in veterinary medicine is lacking in most countries. Such monitoring is required to provide additional evidence for the causal relationship with the occurrence of MRSA CC398.

4.7.1.2. Horses

- Case studies suggest equine hospitals to be at a high risk, and postsurgical infections can lead to epidemics within such settings.
- Studies indicate that antimicrobial use is a risk factor for MRSA carriage in horses, which agrees with the evidence from MRSA epidemiology in human medicine.

4.7.1.3. Companion animals

- MRSA contamination can lead to colonisation, to infection especially after surgery, and to cross-transmission between owners, veterinary personnel and other companion animals.
- Studies indicate that antimicrobial use is a risk factor for MRSA carriage in companion animals, which agrees with the evidence from MRSA epidemiology in human medicine.

4.7.2. Conclusion on management options for animals

4.7.2.1. General

- Based upon extrapolations from human medicine, biosecurity and reduction of antimicrobial selection pressure are cornerstones in constraining the spread of MRSA in animal husbandry.
- Hygiene measures such as hand disinfection and adequate wound management are essential.
- For surveillance purposes, records for antimicrobial consumption need to be detailed, including e.g. information of the animal species and regimen applied (e.g. dose and route of administration), to evaluate the compliance to and effect of antibiotic policies.
- Limitation of veterinary use of critical and new agents for MRSA infections in humans needs to be considered. No MRLs are set for such substances[3] and they cannot be used for food producing animals. Their use in companion animals and non-food producing horses is also questionable, due to the risk for development of resistance against these agents and subsequent spread of resistant bacteria to humans.
- Studies have to document the long-term carriage of MRSA, and find efficient ways to decolonize animals and to clear different animal husbandry settings.

4.7.2.2. Livestock

- The extensive use of antimicrobials for prevention of disease appears to be an important risk factor for the spread of MRSA although data are still sparse.
- Taking into account the occurrence of CC398 in different Member States the multi-faceted approach is advisable whereby infection control strategies and surveillance are integrated.
- Biosecurity measures that disrupt the spread to, within and between farms need to be documented and investigated for their efficacy and long term effect. A focus on avoiding transmission via trade is advisable.

4.7.2.3. Horses and companion animals

- Well controlled hygiene and quarantine measures are needed to clear animal hospital epidemics.
- Strategies that effectively reduce the risk of hospital acquired infections, including MRSA, need to be applied. One component of such strategies would be to limit the prophylactic use of antimicrobials related to surgery.

[3] As mentioned in the report

4.7.2.4. People in contact with live animals

- Close collaboration between human and veterinary experts, coupled with appropriate education is necessary to develop adequate management guidelines
- Risk mitigation measures to limit spread of MRSA between animals needs to consider humans in contact with animals.

5. Recommendations

5.1. Recommendations from ToRs 1 to 5

- It is recommended that periodic monitoring of intensively reared animals is carried out. This would provide trends in the development of this epidemic in all Member States. Data that would be comparable with the ongoing on-farm base-line study in breeding pigs would be useful in countries where the problem already exists, and may be extended to fattening pigs, veal calves and poultry. The preferred sampling method would be the collection of dust samples. In countries with a low or zero prevalence, studies at the abattoir level may be sufficient to detect the emergence of LA-MRSA. Although the preferred sampling method at the abattoir level has not yet been established, nasal swabs of pigs and cattle should be considered.
- In order to identify trends in the spread and evolution of zoonotically acquired MRSA, systematic surveillance and monitoring of MRSA in humans and food producing animals is recommended in all Member States. Harmonised data, including information on risk factors, as well as analysis of a representative sample of isolates for susceptibility to multiple antimicrobial agents, virulence associated traits, and lineage determination, should be available from a single location.
- In order to evaluate the effectiveness of control measures to reduce the carriage of CC398 in livestock, intervention studies should be carried out. Such studies should be longitudinal over consecutive production cycles.
- Further work should be performed on harmonising methods for sampling, detection and quantification of MRSA during carriage in both humans and animals, as well as for detection of MRSA as a contaminant of food, and in the environment including from dust both in air and on surfaces.
- The factors responsible for host specificity, persistence in different environments, transmission routes (including airborne transmission) and vectors, should be investigated.
- In order to evaluate the effectiveness of control measures to reduce the carriage of MRSA in companion animals and horses and their human contacts, intervention studies should be carried out.
- On the base of already existing recommendations for prevention of MRSA infections in some MSs, protocols for screening at admission to hospitals should be expanded to include humans exposed to intensively reared livestock.

5.2. Recommendations from ToR 6

- Due to the multiresistant character of MRSA, there are several antimicrobial classes that may increase the risk of spread of MRSA. Therefore, to be effective to control the emergence of MRSA, measures to reduce the use of antimicrobials cannot be limited to any specific class but routine use of antimicrobials is to be regarded as a risk factor. Any measures to be taken should consider all antimicrobials with the aim to eliminate unnecessary use or replace use with other strategies. Thus adherence to the principles of prudent use remains a key measure to manage risks for spread of MRSA as discussed in the CVMP strategy on antimicrobials 2006-2010 and status report on activities on antimicrobials (EMEA/CVMP/353297/2005[4]) remains crucial. Special consideration should be given to improving controls related to group and flock medication of food

[4] http://www.emea.europa.eu/pdfs/vet/swp/35329705.pdf

producing animals and routine perioperative treatment of companion animals and horses when implementing these guidelines.

- Development of non-antimicrobial control measures should be encouraged. Further studies are required to document the long-term carriage of MRSA, and to find effective ways to decolonize animals and to clear the organism from different animal husbandry settings. The clonal nature of the Livestock Associated MRSA (LA-MRSA) theoretically presents opportunities for vaccine development but further research would be required. Use of antimicrobials for decolonisation seems to be of limited value.
- Appropriate wound management without antimicrobials will be sufficient for many MRSA infections. If antimicrobial treatment is necessary, based on the severity of the infection, there is a need to manage the risk of emergence of further resistance in the strain of MRSA infecting the animals to avoid subsequent spread of resistance to animals and humans. Due to the multiresistant nature of MRSA it may be difficult to find approved veterinary medicinal products for the condition. Last resort human medicines for MRSA treatment such as e.g. glycopeptides, oxazolidones, tigecycline and streptogramins have no maximum residue limit (MRL) and therefore they are not allowed to be used in animals intended for food production (Council Regulation (EEC) No 2377/90). Any use of such molecules in companion animals and horses should take into account the public health risk involved and should therefore involve discussions with public health practitioners.
- Monitoring of the consumption of antimicrobials in the EU is needed to identify and target action towards sources of unnecessary use of antimicrobials. This will also allow for evaluation of the effectiveness of measures taken in this respect.